CLERK'S OFFICE U.S. DIST. COURT
AT ABINGDON, VA
FILED
MAY 07 2012
JULIA C. DUDLEY, CLERK
BY: DEPUTY CLERK

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
ABINGDON DIVISION

UNITED STATES	:	
	:	
v.	:	**Criminal No.** 1:12CR26
	:	
ABBOTT LABORATORIES	:	

PLEA AGREEMENT

ABBOTT LABORATORIES (EIN: 36-0698440) ("ABBOTT") has entered into a Plea Agreement with the United States of America, by counsel, pursuant to Rule 11(c)(1)(C) of the Federal Rules of Criminal Procedure ("Fed. R. Crim. P."). The terms and conditions of this agreement are as follows:

1. CHARGE TO WHICH ABBOTT IS PLEADING GUILTY AND WAIVER OF RIGHTS

ABBOTT will enter a plea of guilty to Count One of the Information charging it with violating Title 21, United States Code, Sections 331(a), 333(a)(1), 352(a) and 352(f)(1) by introducing and delivering for introduction into interstate commerce and causing the introduction and delivery for introduction into interstate commerce from Illinois and Puerto Rico to various locations throughout the United States, including the Western District of Virginia, of Depakote, Depakote ER and Depakote Sprinkle that were misbranded.

The parties agree and stipulate that the maximum statutory penalty is a fine of $800,000,000.00 (twice the gross gain), pursuant to Title 18, United States Code, Section 3571(d), plus a period of probation of up to five years, pursuant to Title 18, United States Code, Section 3561(c)(2). In addition, ABBOTT's assets may be subject to forfeiture. ABBOTT understands that fees may be imposed to pay for probation and that there will be a $125 special assessment for Count One, pursuant to Title 18, United States Code, Section 3013(a)(1)(B)(iii). ABBOTT's attorneys have informed it of the nature of the charge and the elements of the charge that must be proved by the United States beyond a reasonable doubt before ABBOTT could be found guilty as charged.

ABBOTT acknowledges that ABBOTT has had all of its rights explained to it. ABBOTT expressly recognizes that, as a corporation, ABBOTT may have the following constitutional rights and that by voluntarily pleading guilty ABBOTT knowingly waives and gives up these valuable constitutional rights:

The right to plead not guilty and persist in that plea.
The right to a speedy and public jury trial.
The right to assistance of counsel at that trial and in any subsequent appeal.
The right to remain silent at trial.
The right to testify at trial.
The right to confront and cross-examine witnesses.

The right to present evidence and witnesses.
The right to compulsory process of the court.
The right to compel the attendance of witnesses at trial.
The right to be presumed innocent.
The right to a unanimous guilty verdict.
The right to appeal a guilty verdict.

ABBOTT is pleading guilty as described above because ABBOTT is in fact guilty and because ABBOTT believes it is in its best interest to do so and not because of any threats or promises, other than the terms of the Plea Agreement, described herein, in exchange for its plea of guilty. ABBOTT agrees that all of the matters set forth in the Information are true and correct.

ABBOTT understands that the plea is being entered in accordance with Fed. R. Crim. P. 11(c)(1)(C).

2. SENTENCING PROVISIONS

Based upon the evidence currently known to the United States, the parties agree that the 2011 version of the United States Sentencing Commission Guidelines Manual is the appropriate Guidelines Manual to utilize. According to U.S.S.G. § 8C2.1, the organizational fine provisions do not apply to the count of conviction in this case, which is a misdemeanor under 21 U.S.C. § 333(a)(1).

The parties agree that the fine shall be $500,000,000.00 (five hundred million dollars).

The parties agree and stipulate that a term of probation for five years will be imposed subject to modification as set forth in the section of this Plea Agreement titled "SUCCESSION ISSUES." ABBOTT understands and agrees that if its probation is revoked, it may be resentenced and a total aggregate fine up to the statutory maximum of $800,000,000.00 (eight hundred million dollars) may be imposed.

The parties agree that if the Court refuses to accept the Plea Agreement with the agreed-upon sentence, this Plea Agreement will be null and void, and ABBOTT will be free to withdraw this guilty plea. In the event the Court refuses to accept the Plea Agreement with the agreed-upon sentence and ABBOTT withdraws this guilty plea, nothing in this Plea Agreement shall be deemed a waiver of the provisions of Federal Rule of Evidence ("Fed. R. Evid.") 410 and the United States will move to dismiss the Information without prejudice to the United States' right to proceed criminally against ABBOTT or any other entity or individual on any charge.

3. FINANCIAL OBLIGATIONS

The parties agree and understand that any of the money paid pursuant to this Plea Agreement will be returned if, and only if, the Court refuses to accept the Plea Agreement with the agreed-upon sentence and, as a result, ABBOTT withdraws its guilty plea. If the Court rejects the plea agreement, the United States will return all money paid by ABBOTT, without interest, not more than 3 days after ABBOTT withdraws its guilty plea and notifies the United States Attorney's Office for the Western District of Virginia, in writing, that it wishes to have the money returned.

a. Criminal Resolution Payments

Not more than 3 days after the entry of ABBOTT's guilty plea, ABBOTT will make the following disbursements:

(1) $125.00 (one hundred twenty-five dollars) to the Clerk, U.S. District Court, Abingdon, Virginia, as payment of the special assessment;

(2) $500,000,000.00 (five hundred million dollars) to the Clerk, U.S. District Court, Abingdon, Virginia, as payment of the fine;

(3) $1,500,000.00 (one million five hundred thousand dollars) to the Virginia Medicaid Fraud Control Unit's Program Income Fund; and

(4) $198,500,000.00 (one hundred ninety-eight million five hundred thousand dollars), made payable to the United States Department of the Treasury, as directed by the United States Attorney's Office as payment of a forfeiture.

b. Forfeiture

ABBOTT agrees to forfeit $198,500,000.00 (one hundred ninety-eight million five hundred thousand dollars), and agrees to sign any documentation necessary to accomplish the forfeiture. ABBOTT agrees to forfeit all interest in these funds and to take whatever steps are necessary to pass clear title of this sum to the United States. These steps include but are not limited to making the sum available to the United States, as directed by the United States. ABBOTT agrees not to file a claim in any forfeiture proceeding or to contest, in any manner, the forfeiture of said assets. ABBOTT understands and agrees that forfeiture of this property is proportionate to the degree and nature of the offense. ABBOTT freely and knowingly waives any and all constitutional and statutory challenges to any forfeiture carried out in accordance with this Plea Agreement on any grounds, including that the forfeiture constitutes an excessive fine or punishment. ABBOTT further understands and agrees that this forfeiture is separate and distinct from, and is not in the nature of, or in lieu of, any monetary penalty that may be imposed by the court.

c. Restitution

The parties agree and stipulate, pursuant to 18 U.S.C. § 3663(a)(1)(B)(ii), that no restitution should be ordered.

4. ADDITIONAL OBLIGATIONS

Unless the Court rejects this Plea Agreement and, as a result, ABBOTT withdraws its plea, ABBOTT agrees to: (1) accept responsibility for its conduct; (2) not attempt to withdraw its guilty plea; (3) not deny that it committed the crimes to which it has pled guilty; (4) not make or adopt any arguments or objections to the presentence investigation report that are inconsistent

with this Plea Agreement; (5) comply with its obligations under the Civil Settlement Agreement (attached as Attachment D); and (6) enter into a Corporate Integrity Agreement (attached as Attachment E).

ABBOTT will not (1) make any public statement or (2) make any statement or take any position in litigation in which any United States department or agency is a party, contradicting any statement of fact set forth in the Agreed Statement of Facts (attached as Attachment B). If ABBOTT makes a public statement that in whole or in part contradicts a statement of fact contained in the Agreed Statement of Facts, ABBOTT may avoid being in violation of this Plea Agreement by promptly publicly repudiating such statement. For the purposes of this paragraph, the term "public statement" means any statement made or authorized by ABBOTT's directors, officers, management employees, or attorneys and includes, but is not limited to, a statement in (1) a press release, (2) public relations material, or (3) ABBOTT website. Notwithstanding the above, any ABBOTT entity may avail itself of any legal or factual arguments available to it (1) in defending litigation brought by a party other than the United States or (2) in any investigation or proceeding brought by a state entity or by the United States Congress. This paragraph does not apply to any statement made by any individual in the course of any actual or contemplated criminal, regulatory, administrative or civil case initiated by any governmental or private party against such individual.

5. WAIVER OF RIGHT TO APPEAL AND COLLATERALLY ATTACK THE JUDGMENT AND SENTENCE IMPOSED BY THE COURT

If the Court accepts this Plea Agreement, ABBOTT agrees that ABBOTT will not appeal the conviction or sentence imposed. ABBOTT is knowingly and voluntarily waiving any right to appeal and is voluntarily willing to rely on the Court in sentencing it, pursuant to the terms of Fed. R. Crim. P. 11(c)(1)(C). ABBOTT expressly waives its right to appeal as to any and all issues in this matter and waives any right it may have to collaterally attack, in any future proceeding, any order issued in this matter, unless such appeal or collateral attack cannot be waived, by law. ABBOTT understands the United States expressly reserves all of its rights to appeal, but if the United States initiates a direct appeal of the sentence imposed, ABBOTT may file a cross-appeal of that same sentence. ABBOTT agrees and understands if it files any court document (except for an appeal or collateral attack based on an issue that cannot be waived, by law) seeking to disturb, in any way, any order imposed in the case such action shall constitute a failure to comply with a provision of this agreement.

6. REMEDIES FOR FAILURE TO COMPLY WITH ANY PROVISION OF THE PLEA AGREEMENT OR OVERALL RESOLUTION

ABBOTT understands that if: (1) ABBOTT attempts to withdraw its plea (in the absence of the Court refusing to accept the Plea Agreement) or fails to comply with any provision of this Plea Agreement prior to the completion of the term of probation; (2) ABBOTT's conviction is set aside, for any reason; (3) ABBOTT fails to execute all required paperwork prior to the imposition of judgment; and/or (4) ABBOTT fails to comply with its obligations under the Civil Settlement Agreement (attached as Attachment D) the United States may, at its election, pursue any or all of the following remedies: (a) declare this Plea Agreement void; (b) file, by

indictment or information, any charges which were filed and/or could have been filed concerning the matters involved in the instant investigation; (c) refuse to abide by any stipulations and/or recommendations contained in this Plea Agreement; (d) not be bound by any obligation of the United States set forth in this Plea Agreement, including, but not limited to, those obligations set forth in the section of this Plea Agreement titled "COMPLETION OF PROSECUTION;" and (e) take any other action provided for under this Plea Agreement or by statute, regulation or court rule.

The remedies set forth above are cumulative and not mutually exclusive. If the United States pursues any of its permissible remedies as set forth in this Plea Agreement, ABBOTT will still be bound by its obligations under this Plea Agreement. ABBOTT hereby waives its right under Fed. R. Crim. P. 7 to be proceeded against by indictment and consents to the filing of an information against it concerning any charges filed pursuant to this section of the Plea Agreement. ABBOTT hereby waives any statute of limitations argument as to any such charges.

7. INFORMATION ACCESS WAIVER

ABBOTT agrees to waive all rights, whether asserted directly or by a representative, to request or receive from any department or agency of the United States any records pertaining to the investigation or prosecution of this case, including without limitation any records that may be sought under the Freedom of Information Act, 5 U.S.C. § 552, or the Privacy Act of 1974, 5 U.S.C. § 552a.

8. DESTRUCTION OF ITEMS OBTAINED BY LAW ENFORCEMENT

By signing this Plea Agreement, ABBOTT consents to the destruction of all items obtained by law enforcement agents during the course of the investigation. However, ABBOTT expressly agrees that, within 30 days of being informed by the United States Attorney's Office that records and/or other items obtained from ABBOTT are available for removal, it will remove, at its cost, all such records and/or other items from the premises designated by the United States Attorney's Office.

9. ATTORNEY CLIENT PRIVILEGE

Nothing in this Plea Agreement shall be construed to require ABBOTT to waive any attorney-client privilege or work-product protection.

10. COMPLETION OF PROSECUTION

Pursuant to Fed. R. Crim. P. 11(c)(l)(A), so long as ABBOTT complies with all of its obligations under the Plea Agreement, the United States agrees that, other than the charge in the attached Information, it shall not further prosecute ABBOTT or its present or former parents, affiliates, divisions, or subsidiaries or their predecessors, successors, or assigns for: (a) any additional federal criminal charges or forfeiture action with respect to the conduct covered by the Information; or (b) any violations of law that were the subject matter of the investigation by the United States Attorney's Office for the Western District of Virginia and the United States

Department of Justice Consumer Protection Branch or based on facts currently known to the United States Attorney's Office for the Western District of Virginia and the United States Department of Justice Consumer Protection Branch regarding the sale, promotion, or marketing of Depakote, Depakote ER, Depakote Sprinkle, Depacon or Depakene in the United States occurring on or before May 7, 2012.

Nothing in this Plea Agreement affects the administrative, civil, criminal, or other tax liability of any entity or individual and this Plea Agreement does not bind the Internal Revenue Service of the Department of Treasury, the Tax Division of the United States Department of Justice, or any other government agency with respect to the resolution of any tax issue.

The non-prosecution provisions in this Plea Agreement are not binding on the United States with respect to any investigations of ABBOTT, its subsidiaries, affiliates, or parent that are or may be conducted in the future by the Fraud Section of the Criminal Division of the United States Department of Justice regarding possible violations of the Foreign Corrupt Practices Act and related offenses.

11. LIMITATION OF AGREEMENT

This Plea Agreement is limited to the United States Department of Justice and does not bind any other federal, state or local authority.

12. EFFECTIVE REPRESENTATION

ABBOTT has discussed the terms of the foregoing Plea Agreement and all matters pertaining to the charges against it with its attorneys and is fully satisfied with its attorneys and its attorneys' advice. At this time, ABBOTT has no dissatisfaction or complaint with its attorneys' representation. ABBOTT agrees to make known to the Court no later than at the time of sentencing any dissatisfaction or complaint ABBOTT may have with its attorneys' representation.

13. SUCCESSION ISSUES

ABBOTT has publicly announced and represents to the Court that it plans to separate into two publicly traded companies, one a diversified medical products company, which may retain the ABBOTT name, ("Diversified Company") and the other a research-based pharmaceutical company ("Pharmaceutical Company") which will not be a subsidiary or corporate affiliate of ABBOTT (this separation is hereinafter referred to as the "Transaction" and the "Effective Time" shall be the date and time that the Transaction becomes effective). The conduct for which ABBOTT was investigated and that led to this Plea Agreement relates solely to ABBOTT's research-based pharmaceutical products business and not to its diversified medical products business. Upon completion of the Transaction, the assets of ABBOTT's research-based pharmaceutical products business will be transferred, conveyed and/or assigned by it to the Pharmaceutical Company and ABBOTT shall no longer be involved in the marketing or promotion of research-based pharmaceutical products in the United States. As part of the Transaction, ABBOTT agrees that it will include the following in a contract or agreement with the Pharmaceutical Company relating to the transfer, conveyance or assignment of the assets of

the research-based pharmaceutical products business to the Pharmaceutical Company: (a) a provision stating that the Pharmaceutical Company agrees that the conditions of probation and all other provisions of this Plea Agreement are fully binding on the Pharmaceutical Company and (b) a provision stating that the Pharmaceutical Company will be deemed to carry a prior conviction for purposes of Title 21, United States Code, Section 333(a)(2), and waives any right it may have to argue that it does not have such prior conviction.

In the event the Transaction takes place and the Pharmaceutical Company agrees to (a) and (b) in the last sentence of the preceding paragraph, the United States Department of Justice and ABBOTT agree to the following:

A. The Pharmaceutical Company will be deemed the successor in interest, for purposes of this Plea Agreement, and all of ABBOTT's obligations under this Plea Agreement, including any and all conditions of probation, will become obligations of the Pharmaceutical Company as of the Effective Time of the Transaction. The term of probation shall be modified to three years from the Effective Time. As of the Effective Time, neither ABBOTT nor the Diversified Company will have any further obligations under this Plea Agreement. The Pharmaceutical Company will be the only entity that will have any further obligations under this Plea Agreement, including any and all conditions of probation, which will be terminated with respect to ABBOTT. Any violation of this Plea Agreement or any term of probation that occurs after the Effective Time shall not be a basis to impose any sanction on ABBOTT, the Diversified Company, or any of their subsidiaries after the Effective Time. After the Effective Time, all releases that run to the benefit of ABBOTT, including those set forth in the section of this Plea Agreement titled "COMPLETION OF PROSECUTION," will continue to apply fully to ABBOTT, the Diversified Company, the Pharmaceutical Company and their subsidiaries;

B. ABBOTT will be deemed to no longer carry a conviction by the United States Department of Justice and the United States Department of Justice agrees it will not use the conviction of ABBOTT pursuant to this plea agreement:

   1. In any future calculation of the Criminal History Category under the United States Sentencing Guidelines in any future sentencing of ABBOTT or the Diversified Company; or
   2. As a prior conviction for purposes of 21 U.S.C. §§ 331 and 333(a)(2) in any future criminal case against ABBOTT or the Diversified Company. The United States Department of Justice waives any right it might have to argue that either ABBOTT or the Diversified Company has such a conviction for such purposes.

C. The Pharmaceutical Company's certification, resolution, and reporting requirements will cover ABBOTT's conduct for any time period for which ABBOTT did not submit a certificate, resolution or report because the Effective Time occurred prior to the due date of the certificate, resolution or report.

For purposes of this Plea Agreement and the conditions of probation, the term "Responsible Entity" refers to the corporate entity that bears the obligations of this Plea Agreement, including the conditions of probation. ABBOTT shall be the Responsible Entity until the Effective Time and Pharmaceutical Company shall be the Responsible Entity after the Effective Time.

14. CONDITIONS OF PROBATION

The parties agree that the following will be included as the only conditions of probation:

A. All definitions set forth in the Plea Agreement shall be incorporated by reference and are included in the conditions of probation.

B. The Responsible Entity shall make the following reports to the probation office:

1. Annual Chief Executive Officer ("CEO") Certification: On an annual basis, the Responsible Entity's CEO shall conduct a review of the effectiveness of the Responsible Entity's Compliance Program as it relates to the marketing, promotion, and sale of pharmaceutical products during the preceding twelve-month period. The review shall consist of a review of updates and reports by the Responsible Entity's Chief Compliance Officer and/or a representative from the Responsible Entity's U.S. Pharmaceutical Compliance Committee about the Responsible Entity's Compliance Program and the effectiveness of that program during the preceding twelve-month period. Based on the review described above, the Responsible Entity's CEO shall submit to the probation office a signed certification stating that, to the best of his or her knowledge, during the preceding twelve-month period:

a. The Responsible Entity's Compliance Program continued to include the compliance policies and procedures set forth in the section of this Plea Agreement titled "COMPLIANCE MEASURES," and

b. To the extent that a Reportable Event (as that term is defined below) has been determined to have occurred, the Responsible Entity has fully complied with the Reportable Event reporting requirements of this Plea Agreement.

The CEO's certification shall summarize the review described above that he or she conducted to provide the required certification.

2. Annual Board of Directors Resolution: On an annual basis, the Responsible Entity's Board of Directors ("Board") or a designated Committee of the Board of Directors ("Board Committee") shall conduct a review of the effectiveness of the Responsible Entity's Compliance Program as it relates to the marketing, promotion, and sale of pharmaceutical products. This review shall consist of updates and reports by the Responsible

Entity's Chief Compliance Officer and/or a representative from the Responsible Entity's U.S. Pharmaceutical Compliance Committee about the Responsible Entity's Compliance Program and the effectiveness of that program during the preceding twelve-month period. Based on the review described above, the Responsible Entity's Board shall submit to the probation office a resolution adopted by the Board stating that, to the best of its knowledge, the Responsible Entity has had in effect policies and procedures designed to prevent the Responsible Entity from violating 21 U.S.C. §§ 331(a) or (k) by directly or indirectly causing the introduction or delivery for introduction into interstate commerce of any pharmaceutical product that was misbranded within the meaning of 21 U.S.C. § 352 or by directly or indirectly causing any pharmaceutical product to be misbranded within the meaning of 21 U.S.C. § 352 while such product was held for sale after shipment of it or any of its components in interstate commerce. The Board's resolution shall summarize the review described above that it, or the Board Committee, conducted to provide the required statement. If the Board is unable to provide this statement, it shall submit a resolution explaining the reasons why it is unable to provide this statement about the effectiveness of the Responsible Entity's Compliance Program.

3. *Reportable Events: Fifteen days after the end of each calendar quarter (that is, by January 15 for the calendar quarter ending December 31, April 15 for the calendar quarter ending March 31, July 15 for the calendar quarter ending June 30, and October 15 for the calendar quarter ending September 30) and 10 days prior to the termination of probation ("Final Report"), the Responsible Entity shall submit a report to the probation office in writing stating whether any Reportable Events have been determined to have occurred during the preceding calendar quarter (or, in the case of the Final Report, during the period since the calendar quarter last covered by a regular quarterly report) and providing updated information about Reportable Events that occurred during any prior calendar quarters. A Reportable Event is any matter that a reasonable person would consider a probable violation of the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 331(a) or (k), related to the misbranding of a pharmaceutical product within the meaning of 21 U.S.C. § 352. A Reportable Event may be the result of an isolated event or a series of occurrences. The reporting of a Reportable Event shall not be considered by the Probation Officer as a per se violation of the terms of probation. Instead, other factors will be taken into account, including, but not limited to, whether the Reportable Event violated policies the company has adopted, whether the company provided training*

addressing the subject matter of the Reportable Event, whether the Reportable Event was an isolated or systemic occurrence, the company's response to the Reportable Event, and any remedial actions taken after the company learned of the Reportable Event. Any Reportable Event determined to have occurred by the Responsible Entity shall be promptly reported to the Responsible Entity's Chief Executive Officer.

4. *The first set of annual certifications and reports shall be submitted not more than 350 days after the Responsible Entity is sentenced and shall cover the period of time commencing one month prior to the date of sentencing to the date of submission of the certification and report. Each subsequent set of annual reports and certifications shall be due one year thereafter and cover the one year period that follows the year covered in the prior annual reports and certifications.*

5. *The probation office may share any information it receives from the Responsible Entity with the United States Attorney's Office.*

6. *For the purpose of this Plea Agreement and the conditions of probation, the following terms shall have the following meaning:*

   a. *The term "Chief Compliance Officer" refers to the person at the Responsible Entity with ultimate responsibility for developing and implementing policies, procedures, and practices designed to ensure compliance with the FDCA and FDA's regulations and guidance documents relating to the marketing, promotion, and sale of pharmaceutical products. During the term of probation, the Chief Compliance Officer shall be a member of the Responsible Entity's senior management and the Responsible Entity's U.S. Pharmaceutical Compliance Committee. Not more than thirty (30) days from the imposition of sentence in this matter, the Responsible Entity shall notify the probation office in writing of the name of the Responsible Entity's Chief Compliance Officer and provide a written description of that person's responsibilities with respect to complying with the FDCA and FDA's regulations and guidance documents relating to the marketing, promotion, and sale of pharmaceutical products. The Responsible Entity shall, in writing, report to the probation office any changes in the identity of or any material changes in the position and responsibilities of the Chief Compliance Officer. This report shall be provided within fifteen (15) days after such a change.*

   b. *The term "U.S. Pharmaceutical Compliance Committee" refers to the committee established or to be established by the Responsible Entity to, in conjunction with the Chief*

Compliance Officer, assist in the implementation and enhancement of the Compliance Program's policies and procedures relating to compliance with the FDCA and FDA's regulations and guidance documents concerning the marketing, promotion, and sale of pharmaceutical products. During the term of probation, this committee shall, at a minimum, include the Responsible Entity's Chief Compliance Officer and other members of the Responsible Entity's senior management with responsibilities concerning the marketing, promotion, and sale of the Responsible Entity's pharmaceutical products. Not more than thirty (30) days from the imposition of sentence in this matter, the Responsible Entity shall notify the probation office in writing of the names of the Responsible Entity's senior managers on the U.S. Pharmaceutical Compliance Committee and provide a written description of their responsibilities with respect to complying with the FDCA and FDA's regulations and guidance documents relating to the marketing, promotion, and sale of pharmaceutical products. The Responsible Entity shall, in writing, report to the probation office any changes in the identity of or any material changes in the position and responsibilities of these senior managers. This report shall be provided within fifteen (15) days after such a change.

c. *The term "Compliance Program" refers to the policies, procedures, practices, and other measures that the Responsible Entity has established or will establish to address regulatory compliance issues, relating to the marketing, promotion and sale of pharmaceutical products, including the Responsible Entity's compliance with FDCA and FDA regulations and guidance documents.*

d. *The term "pharmaceutical products" means drugs marketed, promoted, or sold in the United States and intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or drugs intended to affect the structure or any function of the body of humans. 21 U.S.C. § 321(g)(1)(B) & (C).*

C. *The Responsible Entity shall not commit any federal health care fraud offense, any offense under Titles 21 or 42 of the United States Code, or any felony during the term of probation. The commission of an offense shall not be considered by the Probation Officer as a per se violation of the terms of probation. Instead, other factors will be taken into account, including, but not limited to, whether the offense violated policies the company has adopted, whether the company provided training addressing the subject matter of the offense, whether the offense was an isolated or*

systemic occurrence, the company's response to the offense, and any remedial actions taken after the company learned of the offense.

D. *Within 7 days of filing, the Responsible Entity shall submit to the probation office a copy of each Securities and Exchange Commission Form 10-Q.*

15. COMPLIANCE MEASURES

ABBOTT agrees that, prior to entering its plea of guilty, as the Responsible Entity it has instituted a Compliance Program, under which policies, procedures, practices, and other measures are set forth to address, among other matters, regulatory compliance issues with respect to the marketing, promotion and sale of pharmaceutical products in the United States, including compliance with the Food, Drug and Cosmetic Act ("FDCA") and Food and Drug Administration ("FDA") regulations and guidance documents. The Responsible Entity's Compliance Program includes the policies and procedures relating to pharmaceutical products as set forth below:

A. The Responsible Entity requires that the compensation (including through salaries, bonuses, and contests) of its United States sales representatives be designed to ensure that financial incentives do not inappropriately motivate such individuals to engage in off-label marketing, promotion, and sales of the Responsible Entity's pharmaceutical products.

B. The Responsible Entity requires Continuing Medical Education ("CME") grant-making decisions to be approved by the Responsible Entity's financial or other organizations separate from sales and marketing, and requires financial support to be provided only to programs that foster increased understanding of scientific, clinical or healthcare issues. The Responsible Entity requires a third-party CME provider to maintain full responsibility for, and control over, the selection of content, faculty, educational methods, materials and venue for CME programs.

C. The Responsible Entity requires medical information letters to be accurate and unbiased. The Responsible Entity's policies and procedures prohibit the prompting of requests for medical information letters; and

D. The Responsible Entity requires clinical trials funded or controlled by the Responsible Entity to be approved by ABBOTT's medical and/or scientific organizations and that the scientific research and any resulting publications foster increased understanding of scientific, clinical or healthcare issues. The Responsible Entity's policies and procedures require that it will not approve scientific research purely for the purpose of developing an article or reprint for sales representative use. The Responsible Entity requires all investigators to disclose the Responsible Entity's support for their research and financial relationships between the Responsible Entity and investigators (including any interest in any Responsible Entity product). The Responsible Entity has a publication policy designed to ensure that the Responsible Entity develops publications in a consistent and transparent manner, reporting complete

and accurate results, presented objectively and with discussion of the strengths and limitations of the study. The Responsible Entity requires that a person can be considered an "author" only if he or she has made substantial contributions to the conception and design of the study, acquisition or analysis of data and has final approval of the version to be published. The Responsible Entity requires acknowledgement in all related scientific publications of its role as the funding source of all research and clinical trials initiated by the Responsible Entity.

The Responsible Entity agrees to maintain the policies and procedures set forth above through the completion of the term of probation.

16. EFFECT OF ABBOTT'S SIGNATURE

ABBOTT understands that its Authorized Corporate Officer's signature on this Plea Agreement constitutes a binding offer by it to enter into this Plea Agreement. ABBOTT understands that the United States has not accepted ABBOTT's offer until the authorized representative of the United States has signed the Plea Agreement.

17. GENERAL UNDERSTANDINGS

ABBOTT understands that a presentence investigation will be conducted and sentencing recommendations independent of the United States Attorney's Office will be made by the presentence preparer.

ABBOTT understands the United States and ABBOTT will be free to allocute or describe the nature of this offense and the evidence in this case.

ABBOTT understands the United States and ABBOTT retain the right, notwithstanding any provision in this Plea Agreement, to inform the Probation Office and the Court of all relevant facts, to address the Court with respect to the nature and seriousness of the offense, to respond to any questions raised by the Court, to correct any inaccuracies or inadequacies in the presentence report, if a report is prepared, and to respond to any statements made to the Court.

ABBOTT willingly stipulates that there is a sufficient factual basis for the Court to accept the plea.

ABBOTT understands that this Plea Agreement does not apply to any crimes or charges not addressed in this Plea Agreement.

ABBOTT has not been coerced, threatened, or promised anything other than the terms of this Plea Agreement, described above, in exchange for its plea of guilty. ABBOTT understands that its attorneys will be free to argue any mitigating factors on its behalf to the extent they are not inconsistent with the terms of this Plea Agreement. ABBOTT understands that ABBOTT will have an opportunity to have a representative address the Court prior to sentence being imposed.

This writing and the Agreed Statement of Facts (attached as Attachment B), Civil Settlement Agreement (attached as Attachment D), Corporate Integrity Agreement (attached as Attachment E), and Agreed Order of Forfeiture (attached as Attachment C) are the complete and only agreements between the United States and ABBOTT concerning resolution of this matter. In addition, ABBOTT has no objection to the filing of the Information (Attachment A) (which

will incorporate the Agreed Statement of Facts). The agreements and documents listed in this paragraph set forth the entire understanding between the parties and constitute the complete agreement between the United States Attorney for the Western District of Virginia and ABBOTT and no other additional terms or agreements shall be entered except and unless those other terms or agreements are in writing and signed by the parties. These agreements supersede all prior understandings, promises, agreements, or conditions, if any, between the United States and ABBOTT. ABBOTT consents to public disclosure of all of the agreements and other documents referenced in this paragraph.

ABBOTT has consulted with its attorneys and fully understands its rights. ABBOTT has read this Plea Agreement and carefully reviewed every part of it with its attorneys. ABBOTT understands this Plea Agreement and ABBOTT voluntarily agrees to it. Being aware of all of the possible consequences of its plea, ABBOTT has independently decided to enter this plea of its own free will and is affirming that agreement on this date by the signature of its Authorized Corporate Officer below.

The Authorized Corporate Officer, by her signature below, hereby certifies to the following:

(1) She is fully authorized to enter into this plea agreement on behalf of ABBOTT;

(2) She has read the entire Plea Agreement and documents referenced herein and discussed them with ABBOTT's Board of Directors;

(3) ABBOTT understands all the terms of the Plea Agreement and those terms correctly reflect the results of plea negotiations;

(4) ABBOTT is fully satisfied with ABBOTT's attorneys' representation during all phases of this case;

(5) ABBOTT is freely and voluntarily pleading guilty in this case;

(6) ABBOTT is pleading guilty as set forth in this Plea Agreement because it is guilty of the crime to which it is entering its plea; and

(7) ABBOTT understands that it is waiving its right to appeal the judgment and conviction in this case.

ABBOTT acknowledges its acceptance of this Plea Agreement by the signature of its counsel and Authorized Corporate Officer. A copy of a certification by ABBOTT's Board of Directors authorizing the Authorized Corporate Officer to execute this Plea Agreement and all other documents to resolve this matter on behalf of ABBOTT is attached.

Date: 5/7/12

Laura J. Schumacher
Executive Vice-President, General Counsel, and Secretary
of Abbott Laboratories
Authorized Corporate Officer
ABBOTT LABORATORIES

Counsel has fully explained to the Board of Directors of ABBOTT the facts and circumstances of the case; all rights with respect to the offense charged in the Information;

possible defenses to the offense charged in the Information; all rights with respect to the applicability of the Sentencing Guidelines; and the consequences of entering into this Plea Agreement and entering a guilty plea. We have reviewed the entire Plea Agreement and documents referenced herein with my client, through its Authorized Corporate Officer. In our judgment, ABBOTT understands the terms and conditions of the Plea Agreement, and we believe ABBOTT's decision to enter into the Plea Agreement is knowing and voluntary. ABBOTT's execution of and entry into the Plea Agreement is done with our consent.

Date: 5/7/12

Theodore V. Wells, Esquire
Paul, Weiss, Rifkind, Wharton & Garrison
Counsel for Abbott Laboratories

Date: 5/7/12

Mark Filip, Esquire
Kirkland & Ellis LLP
Counsel for Abbott Laboratories

Date: 5/7/12

Timothy J. Heaphy
United States Attorney
Western District of Virginia

Rick A. Mountcastle, Assistant United States Attorney
Randy Ramseyer, Assistant United States Attorney
Carol Wallack, Trial Attorney, U.S. Dept. Of Justice
Lauren Bell, Trial Attorney, U.S. Dept. Of Justice
Jill Furman, Asst. Director, Consumer Protection Branch

CERTIFICATE

I, John A. Berry, do hereby certify that I am a duly appointed and qualified Assistant Secretary of Abbott Laboratories and acting as such; that Abbott Laboratories is a corporation duly organized and validly existing under the laws of the State of Illinois with its principal office at 100 Abbott Park Road, Abbott Park, Lake County. Illinois; that I am a keeper of its books and records and its corporate seal; that the following resolution is a true, complete and correct copy of the resolution adopted at a regular meeting of its Board of Directors on April 27, 2012; that said meeting was duly called, a quorum was present there at; and that that such resolution is still in effect:

RESOLVED, that the Executive Vice President, General Counsel and Secretary is hereby authorized to enter or cause to be entered on behalf of this Corporation: the Plea Agreement, civil settlement agreements with the federal government and the coordinating states, a Corporate Integrity Agreement with the HHS Office of Inspector General, and all other documents necessary or appropriate to effectuate the settlement of all aspects of the investigation of the Corporation's sales and marketing practices for Depakote from 1998 to 2008 by the United States Department of Justice at any time on or after the date of this meeting.

IN WITNESS WHEREOF, I have affixed my name as Assistant Secretary and have caused the corporate seal of Abbott Laboratories to be hereunto affixed as of this 30th day of April, 2012.

John A. Berry
Assistant Secretary



CLERK'S OFFICE U.S. DIST. COURT
AT ABINGDON, VA
FILED
MAY 07 2012
JULIA C. DUDLEY, CLERK
BY: DEPUTY CLERK

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
ABINGDON DIVISION

UNITED STATES	:	
	:	**Criminal No.** 1:12CR26
v.	:	
	:	**Violations: 21 U.S.C. §§ 331(a), 333(a)(1),**
ABBOTT LABORATORIES	:	**352(a) & 352(f)(1)**

INFORMATION

COUNT ONE
Introduction of Misbranded Drug into Interstate Commerce
21 U.S.C. §§ 331(a), 333(a)(1), 352(a) and 352(f)(1)

The United States Attorney charges that:

1. The Agreed Statement of Facts is alleged, incorporated by reference and made a part of this Count.

2. From in or about January 1998 to in or about December 2006, ABBOTT LABORATORIES introduced and delivered for introduction into interstate commerce and caused the introduction and delivery for introduction into interstate commerce from Illinois and Puerto Rico to various locations throughout the United States, including the Western District of Virginia, quantities of Depakote (a/k/a Depakote DR), Depakote ER, and Depakote Sprinkle (hereinafter collectively referred to as "Depakote") that were misbranded.

3. From in or about January 1998 to in or about December 2006, Depakote was misbranded, within the meaning of Title 21, United States Code, Section 352(f)(1), in that the labeling lacked adequate directions for use for the control of agitation, aggression, and other behavioral symptoms exhibited by elderly patients with dementia.

4. From in or about January 2002 to in or about December 2006, Depakote was misbranded, within the meaning of Title 21, United States Code, Section 352(f)(1), in that the labeling lacked adequate directions for use for the treatment of schizophrenia.

5. From in or about December 2004 to in or about December 2006, Depakote was misbranded, within the meaning of Title 21, United States Code, Section 352(a), in that the drugs' labeling was misleading for use for the (a) control of agitation, aggression, and other behavioral symptoms exhibited by elderly patients with dementia and (b) treatment of schizophrenia.

6. All in violation of Title 21, United States Code, Sections 331(a), 333(a)(1), 352(a) and 352(f)(1).

NOTICE OF FORFEITURE

1. Upon conviction of the offense alleged in this Information, ABBOTT LABORATORIES shall forfeit to the United States quantities of Depakote, Depakote ER and Depakote Sprinkle that were misbranded when introduced into interstate commerce, pursuant to 21 U.S.C. § 334 and 28 U.S.C. § 2461.

2. Because the above-described forfeitable property, as a result of the acts of the defendant, has been transferred or sold to third parties and cannot be located upon the exercise of due diligence, it is the intent of the United States to seek forfeiture of $198,500,000.00 (one hundred ninety-eight million five hundred thousand dollars), pursuant to 21 U.S.C. § 853(p).

Date: 5/7/12

TIMOTHY J. HEAPHY
United States Attorney
Western District of Virginia

Rick A. Mountcastle, Assistant United States Attorney
Randy Ramseyer, Assistant United States Attorney
Carol Wallack, Trial Attorney, U.S. Dept. Of Justice, Consumer Protection Branch
Lauren Bell, Trial Attorney, U.S. Dept. Of Justice, Consumer Protection Branch
Jill Furman, Assistant Director, U.S. Dept. of Justice, Consumer Protection Branch

CLERK'S OFFICE U.S. DIST. COURT
AT ABINGDON, VA
FILED
MAY 07 2012
JULIA C. DUDLEY, CLERK
BY: DEPUTY CLERK

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
ABINGDON DIVISION

UNITED STATES	:	
	:	
v.	:	**Criminal No.** 1:12CR26
	:	
ABBOTT LABORATORIES	:	

AGREED STATEMENT OF FACTS

Introduction

1. Defendant ABBOTT LABORATORIES ("ABBOTT") is an Illinois corporation, headquartered in Illinois, which markets and distributes prescription drugs through its Pharmaceutical Products Division ("PPD"). ABBOTT's PPD is responsible for the unlawful conduct set forth herein. PPD's employees include sales representatives who market ABBOTT's prescription drugs throughout the United States.

2. ABBOTT markets and distributes several different forms of divalproex sodium, including Depakote (a/k/a Depakote DR), Depakote ER, and Depakote Sprinkle (hereinafter collectively referred to as "Depakote"). ABBOTT manufactures Depakote at facilities in Illinois and Puerto Rico and distributes it throughout the United States, including the Western District of Virginia.

3. Over the ten year period from 1998 to 2008, ABBOTT's gross sales of Depakote were approximately $13.8 billion.

4. From in or about 1998 to in or about December 2006, ABBOTT introduced and delivered, and caused the introduction and delivery for introduction, into interstate commerce Depakote which was misbranded in violation of the Food, Drug, and Cosmetic Act ("FDCA"),

21 U.S.C. §§ 331(a), 333(a)(1), and Section 352(f), in that the drugs' labeling lacked adequate directions for use for the control of agitation, aggression, and other behavioral symptoms exhibited by elderly patients with dementia. From in or about 2002 to December 2006, ABBOTT introduced and delivered, and caused the introduction and delivery for introduction, into interstate commerce Depakote which was misbranded in violation of the Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 331(a), 333(a)(1), and Section 352(f), in that the drugs' labeling lacked adequate directions for use for the treatment of schizophrenia. From December 2004 to December 2006, ABBOTT introduced and delivered, and caused the introduction and delivery for introduction, into interstate commerce Depakote which was misbranded in violation of the FDCA, 21 U.S.C. §§ 331(a), 333(a)(1), and Section 352(a), in that the drugs' labeling was misleading for use for the (a) control of agitation, aggression, and other behavioral symptoms exhibited by elderly patients with dementia and (b) treatment of schizophrenia..

Statutory Framework

5. The Food and Drug Administration ("FDA") is the federal agency responsible for protecting the health and safety of the public by enforcing the FDCA and ensuring, among other things, that drugs are safe and effective for each of their intended uses and that the labeling of such drugs bears true, complete, and accurate information.

6. The FDCA, 21 U.S.C. § 355, prohibits the distribution of a new drug in interstate commerce for any use proposed by the drug's manufacturer until FDA completes an intensive review of the safety and effectiveness of the drug and approves it for the proposed use(s). Under the FDCA, 21 U.S.C. §§ 331(d) and 355(b), a manufacturer seeking FDA approval to market a new drug is required to submit a New Drug Application ("NDA") that (1) identifies all of the proposed uses of the drug intended by the manufacturer; (2) includes data, generated in

randomized and well-controlled clinical trials, which demonstrates that the drug is safe and effective for each of those uses; and (3) includes proposed labeling setting forth detailed information about the drug with respect to those intended uses. The FDCA, 21 U.S.C. § 355(a), prohibits the manufacturer from introducing the new drug into interstate commerce until FDA approves the NDA and the proposed labeling after determining that the NDA provides sufficient evidence of the drug's safety and efficacy for its intended uses.

7. The FDA's approval of a drug for one use does not mean that the drug is safe and effective for another use. Uses not approved by FDA are known as "unapproved" or "off-label" uses. The FDCA requires a manufacturer seeking FDA approval for additional uses of a drug to file a new or supplemental NDA that includes the same information described in Paragraph 6 above. The manufacturer can distribute the drug for those additional uses only after FDA (1) concludes that the drug is safe and effective for those additional uses; (2) approves the new or supplemental NDA; and (3) approves revisions to the drug's labeling to describe those additional approved uses.

8. The FDCA, 21 U.S.C. §§ 331(a) and 333(a)(1), makes it unlawful for a drug manufacturer to introduce, deliver for introduction, or cause the introduction or delivery for introduction into interstate commerce of any "misbranded" drug. Under the law, 21 U.S.C. § 352(a), a misbranded drug includes a drug whose "labeling is false or misleading in any particular." The FDCA provides that determination of whether labeling is "misleading" should "take[] into account (among other things) not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling ... fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article [which includes a drug] to

which the labeling ... relates under the conditions of use prescribed in the labeling ... or under such conditions of use as are customary or usual." 21 U.S.C. § 321(n). The FDCA also defines "labeling" as "all labels and other written, printed, or graphic matter (1) upon any article [which includes a drug] or any of its containers or wrappers, or (2) accompanying such article [which includes a drug]." 21 U.S.C. § 321(m). "Labeling" does not have to be physically attached to the drug and can include various written, printed, or graphic information that describes the drug and is disseminated by or on behalf of the drug manufacturer. Thus, a manufacturer can violate the FDCA by distributing written, printed, or graphic information about the drug that is false or misleading.

Depakote's Approved Uses and FDA-Approved Labeling

9. Depakote was approved by FDA to treat certain types of epileptic seizures and bipolar mania and to prevent the onset of migraines.[1] FDA has never approved Depakote as safe and effective for the control of agitation and aggression in patients with dementia or for the treatment of schizophrenia. ABBOTT, however, promoted Depakote for these unapproved uses.

10. The FDA-approved labeling includes information about safety risks associated with use of Depakote, including three "Black Box" warnings, other warnings and precautions, and information about adverse side effects associated with use of the drug. A Black Box warning is the most serious warning that FDA can require be placed on a drug's labeling.

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[1] On March 10, 1983, FDA approved Depakote for absence seizures. On May 26, 1995, FDA approved Depakote for manic episodes associated with bipolar disorder. On March 18, 1996, FDA approved Depakote for migraine prophylaxis. On June 20, 1996, FDA approved Depakote for complex partial seizures. On September 12, 1989, FDA approved Depakote Sprinkle for absence seizures. On June 20, 1996, FDA approved Depakote Sprinkle for complex partial seizures. On August 4, 2000, FDA approved Depakote ER for migraine prophylaxis. On December 20, 2002, FDA approved Depakote ER for complex partial seizures and absence seizures. On August 14, 2003, FDA approved Depakote ER for complex partial seizures and absence seizures in pediatric patients. On December 6, 2005, FDA approved Depakote ER for acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features. Depakote, Depakote Sprinkle, and Depakote ER were never approved by FDA for any other uses.

11. In 1999, after an ABBOTT double-blind multicenter trial of valproate[2] in elderly patients with dementia (the "Dementia Study") was prematurely terminated due to serious side effects caused by Depakote, ABBOTT implemented a change to Depakote's approved labeling to include a warning about somnolence. In 2000, FDA approved the inclusion of the following warning for somnolence in the elderly as part of the approved labeling:

> In a double-blind, multicenter trial of valproate in elderly patients with dementia (mean age=83 years), doses were increased by 125 mg/day to a target dose of 20 mg/kg/day. A significantly higher proportion of valproate patients had somnolence compared to placebo, and although not statistically significant, there was a higher proportion of patients with dehydration. Discontinuations for somnolence were also significantly higher than with placebo. In some patients with somnolence (approximately one-half), there was associated reduced nutritional intake and weight loss. There was a trend for the patients who experienced these events to have lower baseline albumin concentration, lower valproate clearance, and a higher BUN. In elderly patients, dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events. Dose reductions or discontinuation of valproate should be considered in patients with decreased food or fluid intake and in patients with excessive somnolence.

The dosage and administration section was also updated to include elderly dosing information, including that: "Dosage should be increased more slowly and with regular monitoring for fluid and nutritional intake, dehydration, somnolence, and other adverse events."

Clinical Studies of the Unapproved Use of Depakote for the Control of Agitation and Aggression in Elderly Dementia Patients

12. Dementia occurs primarily in people older than 65 and arises from various causes but is most often associated with Alzheimer's disease. Dementia in the elderly often encompasses a slow, progressive decline in cognitive mental function including memory, language, thinking, judgment, and the ability to learn new information, and sometimes dementia patients became agitated and even aggressive. Dementia is a major reason why the elderly are

[2] Valproate is the active ingredient in Depakote.

admitted to nursing homes. Drugs used to control behaviors in elderly dementia patients in nursing homes are sometimes referred to as "chemical restraints."

13. In 1996, ABBOTT submitted an application to FDA to conduct a 15-patient study of Depakote to treat agitation in elderly dementia patients titled "A Double-Blind Placebo Controlled Study of Valproate in the Treatment of Behavioral Agitation Associated with Dementia" ("M96-491"). In a letter to ABBOTT dated January 28, 1997, FDA expressed its reservations about what inferences could be drawn from the study's outcome.[3] The results of the study showed that the six Depakote-treated patients demonstrated greater mean decreases in activity disturbances and aggressiveness scores over the placebo patients, although this result was not statistically significant. ABBOTT's analysis of the study noted that "No subject died or reported a serious adverse event during the study. One Depakote-treated subject had study drug prematurely discontinued due to a series of adverse events." The same analysis concluded that Depakote was "safe and well-tolerated in the sample of elderly subjects with dementia."

14. On November 18, 1997, ABBOTT submitted an application to FDA to conduct a study titled, "A Double-Blind Placebo-Controlled Study of Depakote in the Treatment of Signs and Symptoms of Mania in Elderly Patients with Dementia" (hereinafter referred to as "M97-738" or "ABBOTT's Dementia Study" or the "Dementia Study"). In a letter to Abbott dated January 15, 1998, FDA expressed reservations about Abbott obtaining FDA approval of a new or expanded use of Depakote for mania based on this study.[4]

15. ABBOTT began the Dementia Study in 1998. In March 1999, the study was suspended due to an increased incidence of adverse events in the Depakote treatment group. In

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[3] See Attachment 1.

[4] See Attachment 2.

June 1999, ABBOTT discontinued the Dementia Study. In the study, somnolence and thrombocytopenia (low blood platelet count that may cause easy or excessive bruising, superficial bleeding in the skin, prolonged bleeding from cuts, and spontaneous bleeding from the gums or nose) occurred statistically significantly more frequently with patients given Depakote than with the placebo patients. The results provided evidence that the dosing recommendations set forth in Depakote's labeling were too high and rapid for at least some elderly dementia patients. It was this evidence which resulted in the 1999 revision to the approved labeling referenced in Paragraph 11 above.

16. The results of the Dementia Study also failed to show that Depakote was effective in treating the "signs and symptoms of mania" in elderly dementia patients. ABBOTT concluded that "[t]he lack of effect on mania suggests the manic symptoms of this population may have a different basis than the manic symptoms of bipolar disorder." There were several measurement tools used as part of the Dementia Study to determine if Depakote improved any "signs or symptoms of mania." One of these tools was the Cohen-Mansfield Agitation Inventory ("CMAI"). This was the only measurement tool that showed a positive result. Improvement in the CMAI total score and its verbally agitated behavior subscore was statistically significantly greater for the Depakote treatment group than the placebo group. The data, however, indicated that this typically occurred when patients received the maximum dosage of the drug, a dosage that resulted in an increase in adverse events for many of the elderly patients. In the Clinical Study Report, ABBOTT concluded that the positive CMAI efficacy results "suggest[ed] a drug effect independent of effects of somnolence." Two years later, an associate medical director at ABBOTT expressed his opinion that "somnolence was the true 'treatment' effect for many [of

these patients]."[5] The results of the Dementia Study were published in a peer-reviewed medical journal in 2001.

17. In 2000, ABBOTT began another clinical trial – M99-082 – to evaluate Depakote's safety and effectiveness to treat agitation in elderly patients with dementia. The study protocol called for a lower dose of the drug for some patients than the dose used in the Dementia Study in part because the adverse events experienced by the patients in the Depakote treatment group in the Dementia Study were believed to be dose-related. ABBOTT started but never completed M99-082. In June 2003, ABBOTT submitted to FDA a final clinical study report that stated that the "trial was terminated for low enrollment. . . . . The study was seriously underpowered and definitive conclusions from the data were not possible." The report also stated that the two Depakote treatment groups and the placebo group all showed improvement on the primary and secondary endpoint measures. It also noted that "study drug was well tolerated by subjects in all 3 treatment groups [that is, the two Depakote treatment groups and the placebo group] and the safety profile was similar to previous Depakote studies in this population," including the Dementia Study. The data from this study was disclosed to the FDA, but it was not published in a medical journal or disseminated by ABBOTT's sales force.

18. ABBOTT never conducted another clinical trial of Depakote for the control of agitation and aggression in elderly patients with dementia and never submitted a supplemental new drug application to FDA seeking approval of Depakote for this use.

19. In two separate peer-reviewed medical journal articles in 2001 and 2003, the results of a 56-patient study called the Rochester Study were reported. The study was funded by

[5] See Attachment 3.

the Alzheimer Association, the National Institute of Aging, and an unrestricted, investigator-initiated grant from ABBOTT. According to the 2001 article, the results of the first phase of the study "suggest[ed], but did not prove" that the use of Depakote "can be associated with reduced agitation in some patients with dementia in the nursing home." The article stated that "[t]hese results support[ed] a larger, placebo-controlled trial definitively addressing the therapeutic potential of this agent." According to the 2003 article, the results of the second phase of the Rochester Study were consistent with the results of the first phase of the study "which suggested but did not prove that short-term [Depakote] therapy can result in decreased measures of agitation." It stated that the results from a study being conducted at the time by the Alzheimer's Disease Cooperative Study ("ADCS") (discussed below) would "likely further clarify the potential role of [Depakote] for treatment of" agitation in elderly patients with dementia.

20. A 153-patient, randomized, well-controlled clinical trial of the use of Depakote for the treatment of agitation in elderly patients with dementia was conducted by the ADCS from September 2000 to December 2002 ("ADCS Study"). The results of the study were published in the peer-reviewed American Journal of Geriatric Psychiatry in November 2005 and the authors concluded that "[t]reatment with [Depakote] did not show benefit over placebo in the treatment of agitation associated with possible or probable [Alzheimer's disease] in the nursing home residents included in this trial." The article also discussed the earlier studies, including ABBOTT's Dementia Study and the Rochester Study, and stated that "[n]one of the earlier placebo-controlled studies proved that [Depakote] is efficacious for agitation in dementia, and none were sufficient to define practice."

21. In May 2003, ABBOTT received an oral report of the preliminary results of the ADCS Study. According to this report, the preliminary results did not show that Depakote

reduced symptoms of agitation and aggression. However, an ABBOTT's Associate Medical Director who received these results questioned whether the study was designed properly to show efficacy, and believed the results could still prove positive for the drug if "a 'trend' for Depakote is shown, that could be seen as favorable data – especially if the safety data looks good."[6] In July 2003, ABBOTT's Associate Medical Director then included in a summary that the ADCS Study lead researcher's "verbal report of the preliminary findings [about the ADCS Study] suggest no evidence of a meaningful treatment difference between the Depakote and placebo groups."[7] In December 2004, ABBOTT received an advance copy of the to-be-published medical journal article about the ADCS Study which included the same conclusions about Depakote's lack of efficacy as well as the conclusions regarding the Dementia Study and the Rochester Study contained in the published article as described in Paragraph 20, above.

The Off-Label Promotion of Depakote for the Control of Agitation and Aggression in Elderly Dementia Patients

22. Beginning in or about 1998, and continuing until in or about December 2006, ABBOTT misbranded Depakote by marketing it for the control of agitation and aggression in elderly dementia patients. The off-label promotion of Depakote to control agitation and aggression in elderly dementia patients included:

a. In June 1997, ABBOTT developed its 1998 Strategic Marketing Plan entitled "Depakote – New Psychiatry Markets."[8]

b. In early 1998, ABBOTT created a Long Term Care ("LTC") sales force in substantial part to promote Depakote for the control of agitation and aggression in elderly

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6 See Attachment 4.

7 See Attachment 5.

8 See Attachment 6; see also Attachment 7.

dementia patients in nursing homes. ABBOTT trained its LTC sales force to promote Depakote to doctors and other healthcare providers as safe and effective for this unapproved use. For example, ABBOTT gave its LTC sales force a Dementia Backgrounder, which informed the sales force that Depakote had been shown effective in preliminary clinical trials to treat behavioral disturbances in dementia patients and that Depakote did not have some of the same side effects as antipsychotics for this unapproved use.[9]

c. ABBOTT trained the LTC sales force to promote Depakote to healthcare providers and employees of nursing homes as advantageous over atypical antipsychotics ("ATPs") for controlling agitation and aggression in elderly dementia patients because Depakote was not subject to certain provisions of the Omnibus Budget Reconciliation Act of 1987 ("OBRA") and its implementing regulations designed to prevent the use of unnecessary medications in nursing homes. See, e.g., training material titled "Maximizing the Long Term Care Market Opportunity."[10] Depakote was not subject to any specific use restrictions under OBRA Guidelines prior to December 2006. Until December 2006, ABBOTT trained the LTC sales representatives to state that, by using Depakote, nursing homes would avoid the administrative burdens and costs of complying with OBRA regulatory restrictions otherwise applicable to ATPs, namely the prohibition against giving such patients antipsychotic drugs unless indicated for a specific condition, the requirement that patients treated with ATPs should have drug holidays and gradual

[9] See Attachment 8.

[10] See Attachment 9.

dose reductions, and the requirement for behavior management rather than ATPs whenever possible.

d. ABBOTT paid its LTC sales force bonuses based on its sales of Depakote, which included sales of Depakote for the unapproved use of the drug.

e. ABBOTT provided the LTC sales force with materials to promote Depakote for the control of agitation and aggression in elderly dementia patients. For example, in 2001, ABBOTT funded via an unrestricted educational grant, a document called "A Pocket Guide to Dementia and Associated Behavioral Symptoms: Diagnosis, Assessment, and Management" (the "Guide").[11] A private entity, accredited by ACCME, designated the Guide as continuing medical education ("CME"). Physicians and other healthcare providers could earn CME credits free-of-charge by reviewing the Guide and taking a test set forth at the end of the Guide. As early as 2002, ABBOTT began providing the LTC sales representatives with copies of the Guide to promote Depakote to treat agitation and aggression in elderly dementia patients.[12] The sales representatives were instructed to become familiar with the Guide and to provide it to doctors and other healthcare providers to whom they were promoting Depakote. They were also told that the Guide would be a resource that physicians and pharmacists used to obtain additional continuing education credits. The Guide did not disclose the results of the Dementia Study. The somnolence and dosing issues identified by the Dementia Study were disclosed in the approved labeling but the approved labeling was not attached to the Guide and the Guide did not refer healthcare providers to the approved labeling. In

[11] See Attachment 10.

[12] See Attachment 11.

addition, the efficacy results of the Dementia Study were not disclosed in the approved labeling or the Guide.

f. ABBOTT funded and gave the LTC sales force funds for speaker programs promoting the use of Depakote to control agitation and aggression in elderly patients with dementia.

g. ABBOTT funded and caused the creation of educational programs and materials (such as videos and monographs) promoting the use of Depakote to control agitation and aggression in elderly patients with dementia.

h. ABBOTT entered into contracts with Long Term Care Pharmacy Providers (LTCPPs) that included provisions regarding the payment of rebates to the LTCPPs based on increases in the use of Depakote in the nursing homes serviced by the LTCPPs. Under these contracts, ABBOTT paid millions of dollars in rebates to the LTCPPs based on increases in the use of Depakote in these facilities, including the use of Depakote in the treatment of agitation and aggression in elderly dementia patients.

i. ABBOTT funded and created and caused the creation of programs and materials to train the LTCPPs' consultant pharmacists about the use of Depakote for the control of agitation and aggression in elderly dementia patients and to encourage them to recommend the drug for this unapproved use.

j. In March 2004, at the request of an LTCPP, ABBOTT sent a check in the amount of $16,250 to fund a letter sent by the LTCPP to 4,000 doctors who prescribed ATPs and 1,000 doctors who prescribed benzodiazepine medications to patients in

nursing homes.[13] ABBOTT's LTC National Account Manager ("NAM") emailed the LTC sales force stating that this LTCPP had "sent out a targeted Depakote ER mailing to the top 4,000 prescribers of [ATPs] and top 1000 prescribers of benzodiazepines within [the LTCPP's] facilities."[14] The LTC NAM further stated that "[t]he purpose of the mailing is to help increase the overall use of Depakote ER vs [ATPs] and benzodiazepines for patients with dementia related behaviors" and that the LTCPP's letter to the doctors "strongly position[ed] Depakote ER vs the [ATPs and] emphasize[d] the excellent side effect profile of Depakote ER."

k. In October 2003 ABBOTT produced its "Depakote Long Term Care – 2004 Strategic Investment Proposal," which included the strategy to market Depakote for this unapproved use in LTC facilities, including nursing homes.[15]

l. ABBOTT also promoted Depakote as effective to treat "manic-like symptoms" exhibited by elderly dementia patients based on Depakote's efficacy to treat bipolar mania.

23. In 2001, in anticipation of a review of ABBOTT's policy about the dissemination of clinical data, a staff member in ABBOTT's Regulatory Affairs office prepared a draft slide presentation which stated that ABBOTT's practice at that time did not "explicitly" address the "difference between dissemination and promotion," the "scope of data balance," or "failed studies." These draft slides also stated that ABBOTT needed to revise its practice to "clarify dissemination vs promotion," "assure that dissemination is a balanced representation of known

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[13] See Attachment 12.

[14] See Attachment 13.

[15] See Attachment 14.

information," and that the revised practice needed to "define options after failed applications/studies." This same staff member also wrote an earlier memorandum which noted that ABBOTT's then current practice and guidance documents left open several questions, including that:

> [T]here is no direction regarding how we will handle newly generated data related to indications that were the subject of failed applications or failed or disappointing studies. Responsibilities and accountability are not established in [ABBOTT's] guidance. The [guidance] document does not clearly define the difference between dissemination and promotion.

While ABBOTT continued to update and improve its compliance practices in accordance with industry practice and FDA guidance, some of the issues identified in this draft presentation and memo were not specifically addressed until after the time period relevant here.

24. ABBOTT's LTC sales representatives used reprints of medical journal articles about studies to promote the use of Depakote to control agitation and aggression in elderly patients with dementia, as set forth below:

a. ABBOTT trained its LTC sales representatives to use a reprint of an article based on a retrospective chart review of 22 nursing home patients in two nursing homes. Although this article was not based on a randomized, blinded, and controlled clinical study, ABBOTT trained its LTC sales representatives to use it to promote Depakote for this unapproved use.

b. Beginning in approximately 2001, ABBOTT made available to its LTC sales force reprints of the 2001 medical journal article about the Dementia Study and reprints of the 2001 medical journal article about the Rochester Study. ABBOTT trained its sales representatives to respond to inquiries about the Dementia Study's premature termination for safety reasons by advising healthcare providers that the dosages used in

the study were started too high and increased too fast. ABBOTT trained its sales force to promote the use of Depakote to control agitation and aggression in elderly patients with dementia at lower doses.

c. In 2003, ABBOTT made reprints of the 2003 medical journal article about the results of the second part of the Rochester Study available to its sales representatives and trained them to use the results of the study to promote the use of Depakote to control agitation and aggression in elderly patients with dementia.

25. ABBOTT continued to disseminate copies of reprints of the Rochester Study journal article to healthcare providers after receiving a report on the preliminary results of the ADCS Study in May 2003, and after receiving an advance copy of the article about the ADCS study in December 2004. ABBOTT continued to disseminate this article about the Rochester Study without disclosing the conflicting preliminary results of the ADCS Study including:

a. In or about December 2004, ABBOTT approved the continued reprinting of the 2003 Rochester Study article for its sales representatives to disseminate to healthcare providers.

b. In or about early 2006, ABBOTT provided its sales representatives with promotional materials, including the "T1 2006 Plan- O-Gram," which stated that ABBOTT's core marketing messages included telling nursing homes that Depakote had "broad-spectrum coverage," and listing among the "Core Selling Materials" for use to convey the core marketing messages a reprint of the Rochester Study article. The results of the ADCS study were not included.

c. In February 2006, for the first time, ABBOTT provided its sales force with a reprint of the ADCS Study article and marked it "For Representative Education Only."

Accordingly, under ABBOTT's policy, its sales force could not share this reprint with healthcare providers. In March 2006, ABBOTT also discontinued reprinting copies of the 2003 article about the Rochester Study. However, after March 2006, the sales force continued to obtain copies of already-existing reprints of the 2003 article about the Rochester Study from ABBOTT's supply contractor and continued to disseminate those reprints to healthcare providers because they were not directed by ABBOTT to stop distributing existing copies of the reprints.

d. ABBOTT's clinical science managers made presentations to healthcare providers about the use of Depakote for agitation and aggression in elderly dementia patients. Prior to April 2006, these presentations did not include any information about the results of the ADCS Study. In or about April 2006, Abbott revised the presentation to include two slides about the ADCS Study. The revised presentation, however, also included approximately a dozen slides about other studies, such as the Rochester Study, and slides about when healthcare providers should use Depakote to treat agitation and aggression in elderly dementia patients and how to dose Depakote for this off-label use.

e. ABBOTT sent medical information letters to healthcare providers who requested information about the use of Depakote to control agitation and aggression in elderly dementia patients. Prior to in or about January 2006, these letters did not disclose the results of the ADCS Study.

Clinical Studies of the Unapproved Use of Depakote for Schizophrenia

26. Schizophrenia is a common and serious mental disorder. FDA has approved various drugs as safe and effective to treat schizophrenia, including atypical antipsychotics ("ATPs").

27. ABBOTT conducted two clinical trials studying the safety and effectiveness of Depakote and ATPs together to treat patients with acute exacerbations of the symptoms of schizophrenia. In 1999, ABBOTT submitted an application to FDA to conduct a study (referred to as the "M99-010 Study") of the use of Depakote in combination with certain ATPs to treat acute schizophrenia. In January 2002, ABBOTT submitted the study results to FDA. The results showed that the study failed to meet its primary endpoint in that Depakote in combination with the ATPs did not result in statistically significant improvement in symptoms of psychosis associated with schizophrenia after 28 days of treatment as compared to the results for the ATPs alone. The results did show statistically significant improvement in symptoms as early as day 3 and continuing through day 21. FDA informed ABBOTT that it considered M99-010 a negative study because it failed to meet the predefined efficacy endpoint and, therefore, the results of the study could not be used to support an application for a new indication for Depakote for schizophrenia.

28. In 2003, the results of the M99-010 Study were published in a peer-reviewed medical journal article. While the article stated that the treatment difference for the primary efficacy endpoint (28 days) did not reach the level of statistical significance between Depakote combined with an ATP compared to an ATP alone, the article did state that the Depakote combination therapy was observed to show statistically significant improvement over ATP monotherapy as early as the third treatment day and persisting through day 21. A summary of a June 2002 meeting with an external consultant stated that the consultant viewed M99-010 Study to be "a positive trial (the effect size is robust)." The consultant also told ABBOTT that while the M99-010 Study "does not support combination use (as defined strictly the combination being

superior to each agent [i.e. ATP] alone), we could still argue for study 010's applicability to add-on" therapy.[16]

29. In March 2003, ABBOTT conducted another study (referred to as the "M02-547 Study") of Depakote ER combined with certain ATPs to treat acute schizophrenia. The results of the M02-547 Study, which was completed in or about August 2004, did not show a statistically significant treatment difference between Depakote ER combination therapy and the ATPs alone. The data also showed that somnolence, weight gain, and urinary incontinence were significantly higher for patients receiving Depakote ER combined with one of the ATPs than those treated with one of the ATPs alone. Patients treated with Depakote ER combination therapy also had a significant decrease in platelet counts compared to those treated with an ATP alone.

30. In August 2006, ABBOTT posted a synopsis of the M02-547 Study results on a public website (www.clinicalstudyresults.org). In December 2008, the results of the M02-547 Study were published in an article in the peer-reviewed medical journal, Neuropsychopharmacology. The article stated that there were no significant treatment differences between Depakote ER combination therapy and ATP monotherapy.

31. ABBOTT never conducted another clinical trial of the use of Depakote to treat schizophrenia and never submitted a supplemental new drug application to FDA seeking approval of Depakote for this use.

Promotion of Depakote for Off-Label Use in Schizophrenia

32. Beginning in or about 2002, and continuing until in or about December 2006, ABBOTT misbranded Depakote by marketing it for schizophrenia.

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[16] See Attachment 15.

33. ABBOTT used M99-010 Study's secondary endpoints to promote Depakote to healthcare providers as a treatment for schizophrenia. This included:

a. ABBOTT's 2001 "010 Communication Plan" set forth ABBOTT's strategies for dissemination of the results of the M99-010 Study,[17] and ABBOTT executed part of this plan by, among other things, providing the favorable results of the study to healthcare providers.

b. ABBOTT's 010 Communication Plan also included numerous meetings with healthcare providers. In 2002, ABBOTT held a "Depakote Psychosis Speaker/Faculty Development Meeting" to review with physicians the results of the M99-010 Study. The trainers for this meeting included an ABBOTT Product Manager. Physicians were paid $2,500 plus travel and lodging expenses to attend. One of the purposes of the meeting was to present the M99-010 Study data to physicians and on ABBOTT's invitation it noted "[a]fter participation in the meeting, you may be asked to present this data at various medical information programs in 2002."[18] In or about March 2002, ABBOTT provided its physician-speakers with a slide presentation regarding the M99-010 Study data for use in speaking engagements. Also in 2002, ABBOTT organized programs at an American Psychiatric Association ("APA") meeting to provide the M99-010 Study data to promote Depakote for the treatment of schizophrenia.

c. In 2002, an ABBOTT-funded message recall survey of 76 healthcare providers confirmed that a majority of those providers recalled that, during their most

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[17] See Attachment 16.

[18] See Attachment 17.

recent visit with an ABBOTT sales representative, the sales representative had discussed the off-label use of Depakote as combination therapy for the treatment of schizophrenia.

d. In 2003, ABBOTT funded and organized "Psychiatry Consultant Meetings," which were used to provide information about the results of the M99-010 Study to healthcare providers. For at least two of these meetings ABBOTT's sales force helped to target 30 and 45 psychiatrists, respectively, from around the United States. Abbott paid a $500 "honorarium" and travel expenses for each psychiatrist's attendance.

e. ABBOTT's 2003 "Schizophrenia Strategic Plan" called for the positioning of Depakote as the "ideal 1st line agent for adjunctive therapy for schizophrenia based upon proven clinical efficacy" by, among other things, generating materials or funding programs that communicated the results of the M99-010 Study to doctors; training the sales force about the dissemination of CME materials about the M99-010 Study; and developing a speakers bureau to deliver ABBOTT's message about the efficacy of the adjunctive use of Depakote to treat schizophrenia based on the data from the M99-010 Study.

f. In February 2003, ABBOTT made available to its sales representatives reprints of the published medical journal article about the M99-010 Study results, instructing its sales representatives that the reprint was approved for "dissemination only," was not for "promotional use," and they should "not discuss the reprint with physicians and customers."

34. ABBOTT decided not to conduct the two additional clinical trials required to obtain FDA approval of Depakote for schizophrenia, instead deciding to conduct one additional

study, the M02-547 Study, to generate positive data to support ABBOTT's marketing message that Depakote was safe and effective to treat schizophrenia.

a. In August 2004, ABBOTT completed the M02-547 Study. In November 2004, one of ABBOTT's vice presidents sent an email in which he stated that ABBOTT had concluded that the M02-547 Study did not show a statistically significant treatment difference between Depakote ER combination therapy and ATPs alone and in which he further explained:

> We are confident that there are no systematic [sic] issues with the study itself . . . [the] overall weight of the evidence from both studies [M99-010 and M02-547] suggest[ed] that there is not an obvious benefit of adding Depakote to ATPs in acute schizophrenia.

b. ABBOTT's January 2005 Executive Project Status Report described the M02-547 Study, stating "[t]rial completed. Results negative not confirming -010 trial." This report also described the status of ABBOTT's development of Depakote as a treatment for schizophrenia stating "[a] significant issue has been identified that most likely or definitively will negatively impact critical path, budget, or target product profile."

c. In November 2005, ABBOTT approved another reprint of the M99-010 medical journal article and made copies available to the sales force for dissemination to doctors and other customers, but ABBOTT failed to include any information about the results of the M02-547 Study.

d. ABBOTT's T1 2006 Plan-O-Gram issued in early 2006 included the reprint of the M99-010 journal article among the "CORE SELLING MATERIALS –

psychiatric resources available to all representatives," without any information about the M02-547 Study.

e. In or about August 2006, ABBOTT gave its sales representatives a Depakote ER T3/06 Plan-O-Gram which again included the reprint of the M99-010 medical journal article as an available sales resource, but without any information about the M02-547 Study.

f. In or about August 2006, ABBOTT posted a synopsis of the M02-547 Study on the public website clinicalstudyresults.org. The synopsis stated that "Depakote ER in combination with atypical antipsychotic therapy was as well tolerated as therapy with [certain ATPs] alone," despite the fact that the incidence of somnolence in the combination group of patients treated with an ATP and Depakote was more than twice as high as in the ATP monotherapy group and that this difference was statistically significant.

g. In or about August 2006, after it posted the results of the M02-547 Study on the public website, ABBOTT notified its sales force of this posting. This notification was the first time ABBOTT advised the sales force that the M02-547 Study had failed and its results were not consistent with the results of the M99-010 Study.[19]

35. ABBOTT sent medical information letters to healthcare providers who requested information about the off-label use of Depakote for schizophrenia. Through at least 2006, these letters disclosed the results of the M99-010 Study but not the results of the M02-547 Study.

36. The parties agree to the foregoing Agreed Statement of Facts.

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[19] See Attachment 18.

FOR THE UNITED STATES:

Date: 5/7/12

Timothy J. Heaphy
United States Attorney
Western District of Virginia

Rick A. Mountcastle, Assistant United States Attorney
Randy Ramseyer, Assistant United States Attorney
Carol Wallack, Trial Attorney, U.S. Dept. Of Justice
Lauren Bell, Trial Attorney, U.S. Dept. Of Justice
Jill Furman, Asst. Director, Consumer Protection Branch

FOR DEFENDANT ABBOTT LABORATORIES

Date: 5/7/12

Laura J. Schumacher
Executive Vice-President, General Counsel, and Secretary
of Abbott Laboratories
Authorized Corporate Officer

Date: 5/7/12

Ted Wells, Esquire
Counsel for Abbott Laboratories

Date: 5/7/12

Mark Filip, Esquire
Counsel for Abbott Laboratories

REDACTED

Public Health Service

Food and Drug Administration
Rockville MD 20857

(3)

IND 30,673

JAN 28 1997

Abbott Laboratories
Pharmaceutical Products Division
Attention: REDACTED, Ph.D.
REDACTED
Abbott Park, IL 60064

Dear Dr. REDACT:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug and Cosmetic Act for Depakote (divalproex sodium).

Refer also to your amendment of December 10, 1996, providing for a new study, Protocol M96-491 entitled, "A Double-Blind, Placebo-Controlled, Study of Valproate in the Treatment of Behavioral Agitation Associated with Dementia."

Although the clinical investigation you plan to conduct can reasonably be deemed to pose no unreasonable risk to any human subject who is competent to give informed consent and elects to participate in it, we are uncertain, at least at this point in time, as to what inferences can reasonably and responsibly be drawn from its outcome.

We call attention to this matter because the declared aim of your study is to assess the effects of Depakote on what you characterize as "behavioral agitation in elderly patients with dementia." There is, however, no consensus among those expert in the management of patients with dementia as to the specific phenomena that comprise this putative syndrome or symptom set, let alone agreement on the nature of the beneficial actions that a product would have to possess to be granted a claim for such an indicated use. Accordingly, an assertion that the evidence adduced in your trial supports a claim for the treatment of "behavioral agitation in elderly patients with dementia" will be arguable.

Moreover, your protocol has other problematic features. The primary outcome measure employed, the BEHAVE-AD, measures a number of diverse phenomena, some of which are only arguably legitimate targets of pharmacologic intervention. For example, some of the phenomena rated, e.g., aggressiveness and verbal outbursts, may actually represent an attempt of an individual, deprived by his/her illness of the capacity for verbal expression, to communicate needs and express complaints about the conditions (not always kind or caring) under which he/she is compelled to live.

Furthermore, there is the problem of potential "pseudospecificity" of any behavioral management claim. Every behavioral sign and symptom exhibited by a patient with Alzheimer's Disease need not be Alzheimer's related. To the contrary, patients afflicted by dementia may suffer from any number of co-morbid conditions, both physical and emotional. The anxiety, agitation, or disruptive behaviors that occur in patients with Alzheimer's Disease may be only indirectly related to their status as Alzheimer's Disease patients. To be clear, you have every right to postulate that such a

syndrome exists, but your assumptions are not a sufficient basis to support a drug related claim, especially when, as noted earlier, there is no consensus on its existence, let alone identifying features, at this point in time.

Accordingly, if you intend to pursue any sort of behavioral control claim tied to Alzheimer's Disease, much work remains to be done, in particular, in regard to the reification of the entity for which product labeling will assert Depakote is an effective and safe treatment.

If you undertake such an endeavor, we would urge you to be conservative, defining carefully and narrowly, not only the entity, but the precise nature of the therapeutic effects of Depakote on that putative condition. Importantly, a clinical trial that shows that behaviorally symptomatic demented patients randomized to Depakote do better than those randomized to placebo on some multi-item measure of behavior is unlikely to prove sufficient for such a purpose.

Again, we are not implying that restriction of the scope of therapeutic target will necessarily gain you the kind of claim you want. To the contrary, if you were, for example, to conduct a clinical study showing that Depakote relieves the signs and symptoms of mania in patients with Alzheimer's, it would be unlikely that we would view its results as doing more than confirming the claim, already established, that Depakote is an effective antimanic. We would be likely, however, to allow Depakote product labeling to be modified to include a description of the study's results insofar as they could be characterized as further evidence supporting Depakote's approved indication as an antimanic.

In sum, in light of the controversies and uncertainties extant about the "behavioral manifestations of Alzheimer's Disease," any pursuit of a claim for such an indication could prove fruitless. We trust you understand that we are in no way opposed to efforts to document the existence of a behavioral syndrome and/or to develop effective treatments for its management; indeed, we would applaud such efforts.

Should questions arise concerning these comments, please contact CDR REDACTED, R.Ph., Project Manager, at (301) REDACTE.

Sincerely yours,

REDACTED

REDACTED, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 30,673

JAN 20 [illegible]

JAN 15 1998

Abbott Laboratories
Pharmaceutical Products Division
Attention: REDACTED
100 Abbott Park Road
REDACTED
Abbott Park, IL 60064-3500

Dear Mr. REDAC:

Reference is made to your Investigational New Drug Application (IND) for Depakote[R] (divalproex sodium delayed release tablets) for bipolar disease, and your submission dated November 18, 1997.

We also refer to our January 28, 1997, letter in response to your December 10, 1996, amendment.

We have completed our review of your protocol for Study M97-738, "A Double-Blind, Placebo-Controlled Study of Depakote in the Treatment of Signs and Symptoms of Mania in Elderly Patients with Dementia", and have the following comments:

> We note that you have incorporated our recommendations regarding study design, outlined in our January 28, 1997, letter. As noted in that letter, a positive outcome for Study M97-738 could be incorporated in some way in the labeling for Depakote. We would view such an outcome more as support for a general antimanic claim, rather than as support for an expansion of the antimanic claim. The precise labeling changes that may be permitted will need to await the completion of your study and the submission of the results in a supplement.

If you should have any questions regarding these comments, please contact REDACTED, R.Ph., Project Manager, at (301) REDACTED

Sincerely yours,

REDACTED

REDACTED, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

From: REDACTED lake/pprd/abbott;ns REDACTED @abbott.com;smtp
To: REDACTED lake/pprd/abbott@abbott; REDACTED REDACTED
Bcc: lake/ppd/abbott@abbott
Cc:

Subject: more background on elderly agitation
Date: Wed Jul 09 2003 08:26:42 EDT

Another piece of background material. This is a little more along the lines of water under the bridge. Last year, marketing felt very strongly that an elderly agitation study should be monotherapy. In the email below, REDACTED was providing justification for adjunctive treatment instead of monotherapy. The email contains, however, several points related to reasons for failure of past studies and more detail on what a next study in elderly agitation should look like.

----- Forwarded by REDACTED LAKE/PPRD/ABBOTT on 07/09/2003 07:21 AM -----

REDACTED
07/08/2003 09:49 AM

To: REDACTED LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject:Re: elderly agitation

REDACTED

Copy of an email I found from one year ago which also touches on some of the questions you asked me about yesterday concerning an LTC Depakote elderly agitation proposal. I'll give a hard copy to REDACTED as well.

REDACTED

REDACTED
Associate Medical Director
Neuroscience Development
Abbott Laboratories
REDACTED
200 Abbott Park Road
Abbott Park, Illinois 60064-6148

Phone: REDACTED REDACTED
Fax: REDACTED REDACTED
E Mail: REDACTED @abbott.com

----- Forwarded by REDACTED LAKE/PPRD/ABBOTT on 07/08/2003 09:48 AM -----

REDACTED
07/24/2002 05:11 PM

To: REDACTED LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject:Re: elderly agitation

To;

Hi REDACTED. Here are my responses. Yesterday, I started to write down the "arguments" you discussed for the three studies that I am working on...So many of my bullet points are a "cut and paste" of that information, plus additional comments. Sorry if long and redundant, but figured I'd give you all that I had already done.. We certainly "could" do a monotherapy trial--that is no problem to design--, ,,, However, most feel that with Abbott's past experience in this area, as well as some other issues I mention, that concept would be less favorable. I understand your situation in dealing with commercial. We are doing our best to come up with studies we feel would be good science, but also viable, and could be done in a timely fashion.

RED ACT-

Because commercial keeps hitting me on this point, and I keep forgetting our conversations (I also need to start capturing this info for August presentations), could you send me an email with the following related to the reasons we plan to do add-on treatment with depakote in the elderly vs. monotherapy:

1.The specific experiences we have had with depakote monotherapy trials in elderly agitation and the reasons, directly attributable to the fact that the studies were of monotherapy, that these studies failed (ie carefully explain the link between monotherapy and failure).

Depakote as monotherapy has two past Abbott trials (738 and 082) that failed to “hit” on their primary efficacy measure, and both were stopped prematurely. One due to high number of AE’s, and the other due to slow enrollment. In 738, the titration of Depakote was too rapid and doses escalated too high, leading to excessive somnolence. Also the primary endpoint was focused on mania (Bech Rafaelson Mania Rating Scale)—which was a mistake. Nonetheless, a pretty decent publication was produced by Tariot et al , since the secondary measure , the Cohen-Mansfield Agitation Inventory showed a statistically significant separation from placebo. Yet, I still suspect the somnolence was the true "treatment" effect for many-- just my opinion. In 082, because of safety concerns from 738, the inclusion/exclusion criteria were overly restrictive, and at least one of the two Depakote arms (500mg) was too low a dose to expect a difference. Also, because of the low number of patients (121, but study was powered for 396) and the three arms, the results were not good due to the trial being underpowered --as well as a very big PBO response. This doesn't really address why the trials failed specifically due to monotherapy, but we have been down this road several times now, and the factors that lead to failure were multiple. Another failed monotherapy trial would really hurt us, and possibly take us out of this clinical arena. An add-on trial, even if it is not all that successful, does not negate our current position in this population
Recruitment is difficult in this population when a "true" placebo group is involved (or I should say, a "no treatment" group is involved). Families don't like it.
Combination therapy is becoming the focus in geriatric psychiatry, as a large percentage of patients are

unresponsive or partially responsive to the first line treatment. I think this is the most compelling argument for investigating Depakote ER as an "add-on" strategy. Lamotrigine has made a nice "niche" for itself in bipolar disorder doing exactly that.
Risperdal and Zyprexa are the two most common atypical antipsychotic first line treatments (some different class agents, Desyrel and Ativan still get a lot of use also). I wish I had some great market research data about actual numbers, but even looking at out own sales data, it appears Zyprexa gets about 38% and Risperdal about 28% market share (however this is market share by sales $$, and with these meds being so much more expensive it is difficult to assess true use patterns -- plus Depakote has multiple uses, so it is hard to figure how much of our 12% is for agitation, as opposed to anti-seizure ...) Depakote gets "some" use first line, but still is mainly a second line monotherapy treatment for longer term management of this clinical problem. From the speaker's bureau data upon which I used to speak, that is generally what was felt-- with some minor exceptions. It is unlikely that we will gain on those particular atypicals as a first line treatment—they cover a larger spectrum of symptoms (psychosis, more acute agitation/aggression) in this population, and have much more clinical data to support their use. Being a special “niche” type first line (i.e., for patients with mild/moderate agitation without psychosis or thought disorder), and a solid second line monotherapy treatment is “not bad” for Depakote in this population. But frankly and we should focus on combination therapy—that is clearly where the future lies.
There is another Depakote monotherapy study (Tariot's NIA-funded ADCS study) still to be completed -- Depakote 750mg sprinkles versus placebo. It is to conclude soon –this fall sometime, and that is more data for us with respect to monotherapy with DR. However recruitment was very difficult for them as well, and they will likely finish with about 70 patients per arm (less than targeted) – not really enough to likely show anything meaningful, and at 750 mg, this is probably just a bit too low a dose for most effective treatment-- from what we know now. So, I am not entirely optimistic that we’ll find something big. Perhaps we’ll get lucky though. I have broken down all the data from 738 and 082 and have done numerous analyses. It seems that the most likely “effective” dose range is 10 to 20mg/kg/day. Doses below that-- and above that-- have response curves similar to placebo, and over 20mg/kg/day, the SEs seem to significantly increase.
Combination therapy is where this field is going. Physicians want—and need—this type of study data. If established as a viable “add-on” strategy to the most common atypicals (Risperdal and Zyprexa) this would give us an even bigger place in this market—as a solid add-on, and continue as a monotherapy treatment in certain patients. Also, if we establish value as an “add-on”, you could do a follow-up trial, looking at how patients do if you eventually withdraw the atypical (an idea??).

2.If we were to do a monotherapy trial, but with a design similar to the one you have currently, what would be your new probability of success? Also, would recruitment rate change (if so, what would the recruitment rate be for a similarly designed trial, but with monotherapy rather than add on)?

In a monotherapy study (which would be easy to construct), the chances of “hitting" statistical significant against placebo would be a challenge. This is why our design –however we choose to do it—should have a placebo lead-in. Nonetheless, I would say probability of success--if were could completely enroll and finish the study --would be about 50%.
Whereas I can't really give numbers, I would think that the add-on trial would be easier to recruit as opposed to monotherapy. We know the recruitment rate for monotherapy is about 0.5 patients/site/month (that was from 738). I believe 082 was lower than that (around 0.25/site/month- we just calculated). We don't have any add-on trials to use as a reference, but our team estimated a recruitment rate for our current add-on protocol to be about 0.75/site/month.
Recruitment for a monotherapy could not really allow for subjects taking other psychotropics, which would also slow recruitment and make the add-on design more attractive. In this "add-on" protocol we allow for all other psychotropics taken prior to enrollment to continue (with very limited exceptions). Families don't like the idea that grandmother could be assigned to the "no treatment" placebo group in a monotherapy study

3.Which specific advisors did you discuss this protocol with and what were the specific opinions expressed by each opinion leader on the question of whether the trial should be monotherapy or add-

on?

Advisors – REDACTED, REDACTED and REDACTED
We didn't poll them specifically about monotherapy VERSUS combination therapy. However, REDACTED and REDACTED (especially REDACTED) felt it was a good idea to explore combination therapy, since they see it as a very common --and growing--practice. REDACTED wasn't as sure about the frequency of combination therapy being practiced. All felt that a monotherapy trial would need very strong Abbott commitment to the investment, and that it would need be powered for any chance of success, and would have to be completed--not stopped short like 082. Otherwise, don't expect good results.
REDACTED and REDACTED were less apt to commit to any "definites" about the favorability of one design over another.
REDACTED, in particular, felt this add-on study would be easier to recruit, and could get completed in a much shorter timeline. He would actually be a good person to have at the head of such a study. He's a big name, was very enthusiastic about the idea, and could get this published in a good journal.
We should show safety and possible advantages of ER in this population
We need get our name out there in this population – for future –this is a growing population and an extraordinarily common clinical problem for which physicians currently have no "great" primary treatment. They are willing to use whatever works, as long as some data is out there, and the drug shown to be safe. There are lots of partial or inadequate responders to Risperdal and Zyprexa. Availability of the ER 250mg tab should certainly expand use of Depakote ER in this population and we need a study to follow the release of that preparation

4.What did each opinion leader (include yourself and your experience) say about the current frequency of combination (depakote + atypical) vs. monotherapy (depakote alone) in the nursing home elderly agitation population?

REDACTED said approximately 60-70% of their patients in South Carolina receive combination therapy for this purpose.
REDACTED said he feels at Rochester it is about 50% or more. He also said he recently reviewed some large scale data that suggests that up to 60-70% of such patients receive combination therapy (this includes various combinations, atypical + benzo, atypical + SSRI, SSRI + Depakote, acetylcholinesterase inhibitor + atypical, etc., etc, etc)
Personally, I was a bit more conservative than these guys, and when in practice in South Bend, and more recently at The Univ. of Chicago, I would say my use of any combination therapy for this purpose was about 33%--but I treated a lot of outpatients as well as NH patients, probably bringing that number down a bit. In a controlled environment like a NH, I was more apt to use combo therapy
REDACTED didn't give an estimate, but I don't really think REDACTED treats many patients anymore. I could be wrong though
Combination therapy is a common practice which is growing, but with no great published data as to exact frequency-- nor what specific med combinations are most commonly used. Another thing that I would love some good market research on. .

.

5.What specific statistical issues make add-on design preferable to monotherapy?

The add-on protocol as written is not powered – more of a pilot (40 patients per arm, two arms, N=80). This is because of recruitment concerns, and need to generate data in the not too distant future (DNSI criteria). We are writing the protocol to use the Neuropsychiatric Inventory –Nursing Home Version, which is an interesting scale in which key "target symptoms" can be identified as those most pertinent to study, and a "core total" of those specific items are summed as the primary endpoint. It was developed by REDACTED This is advantageous since it much more closely reflects real clinical practice in this population, and you can hone in on specific med effects you want to test. This is the scale REDACTED used in its nursing home Zyprexa trials with this population (Street et al), and it is valid. However, I don't necessarily think that scale favors "add-on" versus monotherapy in any way. But, in an add-on concept (as opposed to monotherapy), we are making the endpoint only a 30% reduction in

the NPI-NH score, which would be clinically defensible since we are looking for "additional" improvement, which has meaning in this population

If we did a monotherapy study, you really couldn't accept patients who are taking other psychotropics, which is one issue that would affect enrollment.

In an add-on study we are already working with patients who are "partial responders" to atypicals, so the likelihood of placebo effect (the major problem with 082) should be less an issue. However, you can make the converse argument they may also be "harder" subjects to get any treatment effect with.

Feel free to just type in your answers below the above questions. Thanks!

From: [redacted]
[redacted]/lake/pprd/abbott;nsf;[redacted]@abbott.com;smtp
To: [redacted]/lake/ppd/abbott@abbott
Cc: [redacted]
[redacted]/lake/ppd/abbott@abbott; [redacted]
[redacted]/lake/ppd/abbott@abbott; [redacted]
[redacted]/lake/pprd/abbott@abbott
Bcc:
Subject: ADCS Sprinkle study
Date: Mon May 05 2003 13:39:00 EDT

[redacted],

Got your voice mail on the preliminary results of the ADCS Depakote Sprinkle Study. Thanks for the update. It is unfortunate the results were not as robust as hoped.

Just some reminders -- With an of N=150, I do not believe that this was a highly powered study to begin with in light of the endpoints used (BPRS as primary and CMAI as secondary, I think). Abbott estimated a need for 396 patients to detect statisically significant difference on the CMAI (80% power) with Depakote compared to placebo in a similar population in our trial, M99-082. I could be wrong about the power on the Sprinkle study, but that is perhaps one issue to ask about. If that is the case, even if a "trend" for Depakote is shown, that could be seen as favorable data--especially if the safety data looks good.

Also, with what we know now, the 750mg dose is probably a bit too low to really give Depakote the best chance. We find that for behavioral symptom control in patients with active symptoms, most need about 15 mg/kg/day (or at least around 1000mg if an average fixed dose is to be used)- - just a bit more than was prescribed in this trial.

This is a federally funded trial through the ADCS, and though we contributed some monies, it is not our study. So, I am not sure if we will be privy to any subanalyses, or what types they consider. (?)

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Bcc:
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Subject: Depakote in agitation assoc with dementia (LTC)
Date: Mon Jul 07 2003 19:48:54 EDT
Attachments: Depakote in Agitation (Long Term Care-- Summary).doc

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REDACTED put together this brief summary of Abbott sponsored and Abbott supported studies in long term care.

----- Forwarded by REDACTED LAKE/PPRD/ABBOTT on 07/07/2003 06:47 PM -----

REDACTED
07/07/2003 04:40 PM

To REDACTED LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject:Depakote in agitation assoc with dementia (LTC)

REDACTED

In helping towards PEC prep, I am attaching the summary of Depakote studies with respect to use in agitation associated with dementia.
Basically includes anything that Abbott sponsored or provided funding for that has been "significant" one way or the other.

As you can see from the results of some of these studies, the track record in this area is not great. That is why I was surprised to see it listed as a "candidate" for that meeting.

Hope it helps

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Summary of Abbott-sponsored or funded Key Studies with Depakote in Long Term Care

Abbott Study M96-491

--A Double-Blind, Placebo Controlled Study of Depakote in the Treatment of Behavioral Agitation Associated with Dementia

Three center study, 15 patients, 3 weeks

Depakote DR, 6 in treatment group, 9 in placebo group

Depakote DR started at 125mg BID, titrated by 125mg increments every 1 to 3 days to clinical response, max dose 30mg/kg/day

Range 500mg to 1500mg day for Depakote DR group

Small number of subjects so not powered to show statistical significance, however Depakote DR treated patients demonstrated greater mean decreases (improvement) at each evaluation in the total BEHAVE-AD, YMRS, CGI and OAS

Rochester study (supported by Abbott funding)

-- Placebo-Controlled Study of Divalproex Sodium for Agitation in Dementia (published Am J Psychiatry 2001, Porsteinsson and Tariot)

Study duration was 6 weeks, n=56, avg. dose = 826mg/day, mean VPA level = 45.4

Key results; 68% of Depakote patients showed reduced agitation on the CGI versus 52% placebo (p=0.06)

This was an investigator trial that was supported by funding from Abbott

-- Open Valproate Treatment Following a Double-Blind Trial for Agitation (poster presented at The 8th (2002) International Conference on Alzheimer's Disease and Related Disorders in Stockholm, Abstract 440, Porsteinsson and Tariot)

45 of the 56 patients in the above Rochester study completed a 6-week open extension (mean dose was 851 mg/day)

Key results; 86% of subjects showed improvement on the CGI ($p < 0.001$)
Subjects showed a decreased mean BPRS, and BPRS agitation factor ($p < 0.002$ for both)

Abbott Study M97-738 (published in Current Therapeutic Research, Jan 2001, Tariot and Schneider

-- A Randomized , Double Blind, Placebo Controlled Multicenter Study Looking at Safety and Efficacy of Depakote in Reducing Signs and Symptoms of Mania Associated with Dementia in Elderly Nursing Home Patients

6 week trial, 172 subjects, 87 Depakote group, 85 in placebo group

Depakote DR titrated in 125 increments every day until 20mg/kg/day

No improvements in mania scale (Bech-Rafaelsen Mania Scale), MMSE or BPRS

CMAI scores showed significant improvement in comparison to placebo

Common adverse effects –somnolence and thrombocytopenia

Study stopped on recommendation of DSMB on 3/12/99 because of higher rate of AE's and reductions in albumin and cholesterol thought to possibly reflect decreased nutrition in Depakote group.

Critiques of the study;

1) **Depakote was dosed much too aggressively, titration was too rapid for this elderly population, and led to the significant tolerability issues in the trial and it's premature stoppage by the Data Safety Monitoring Board.**

1) **Primary efficacy measure, in retrospect, was a poor choice, since a mania rating scale (Bech-Rafaelsen) was used to evaluate behavior disturbance in an elderly population with dementia. These patients were not bipolar, and likely not experiencing true "mania", but rather the disinhibited behavioral problems seen in such nursing home patients with dementia.**

Abbott Study M98-817

--An Open-Label, Non-Comparative, Multicenter Extension of Study M97-738

93 patients enrolled, 12 week safety study

Results similar to M97-738; somnolence was the most common adverse event. The majority of patients who discontinued for adverse events reached doses over 21mg/kg/day

Lead to notion that doses up to 15mg/kg/day (approximately 1000mg/day) should be well tolerated and avoid somnolence and difficulty maintaining adequate oral intake.

Abbott Study M99-082

--A Double Blind, Placebo Controlled Study of Depakote in the Treatment of Behavioral Agitation in Elderly Patients with Dementia

Phase III, original target of 390 patients

Three arms; Compared Placebo to 500mg, and 1000mg of Depakote DR

Company decision to stop at 121 patients due to poor enrollment

Primary efficacy parameter: CMAI
Secondary: CGI, BPRS

Findings showed better safety profile than M97-738 due to slower, more cautious titration, however efficacy data was not impressive for Depakote.

In fact, the placebo group was numerically superior to both Depakote groups, and statistically more efficacious than the Depakote 500mg group. Interpretation of the data was hampered due to the low power of the study (study was powered at 390 patients, and only 121 were randomized).

Enrollment was very slow and main reason cited for prematurely stopping this trial

Critiques of the study;

1) **500mg dose group was unlikely to show efficacy over placebo as this final dose is probably too low for most patients to experience any medication benefit.**
2) **Because of all the safety concerns stemming from M97-738, the inclusion/exclusion criteria were seen as overly "stringent" by many, and not reflective of the elderly nursing home population with dementia, thus making enrollment very challenging**
3) **Also due to the previous safety concerns in M97-738, patients received more interpersonal attention from the staff in this trial and it is felt this may have contributed to the very large placebo response.**

NIA funded studies (through ADCS--Alzheimer's Disease Cooperative Study)

--- *A Randomized, Double Blind, Placebo Controlled Trial to Evaluate the Safety and Efficacy of Divalproex Sodium Therapy for Agitation in Nursing Home Residents with*

Dementia

Phase II trial , 6 weeks, patients in NH's with MMSE between 4 - 24

Target of 150 patients ; 75 subjects receiving placebo versus 75 subjects treated with a fixed dose of 750mg of Depakote sprinkle capsules

Enrollment has been completed, but detailed data not seen by Abbott. Dr. Tariot's verbal report of the preliminary findings suggest no evidence of a meaningful treatment difference between the Depakote and placebo groups.

Abbott provided drug, and supplemental funding

Primary efficacy parameter;	BPRS
Secondary:	ADCS clinical Global Impression of change (CGIC) modified, focus on agitation
	CMAI
	MMSE
	PSMS (Physical Self Maintenance Scale)

Director; Pierre Tariot, MD, NIA/ADCS Study 012

---*ADCS Project 6 -- A Clinical Trial of Valproate to Attenuate the Progression of AD*

Double blind, placebo controlled, 2 year study of 300 Alzheimer's patients with mild to moderate dementia (MMSE 10-20).

Looking at outpatients (not NH residents) who have no baseline behavioral disturbance. Want to assess if Depakote treatment leads to delay of the emergence of behavioral disturbance and if it delays course of cognitive decline.

Biological markers are being taken (b-catenin and Bcl-2) to correlate with neuroprotective properties.

Dose of Depakote ER to be determined

Abbott is providing medication, as well as supplemental funding for neuroimaging studies and genomic/proteomics. The National Institute on Aging (NIA) is funding the large majority of this trial.

Study would help establish efficacy and safety of chronic Depakote therapy in this elderly population Also, it could establish Depakote as a drug beneficial for neuroprotection and delay of onset of behavioral disturbances associated with Alzheimer's dementia

Project Director – Pierre Tariot, MD

Depakote®
New Psychiatry Markets
1998 Strategic Marketing Plan

REDACTED
REDACTED
REDACTED

June, 1997

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Depakote®

New Psychiatry Markets

1998 Strategic Marketing Plan- Table of Contents

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Appendix

I. Situation Analysis Support
II. Other Market Opportunities
  A. Patient Population Breakdown & Market Size/Potential by Disease State

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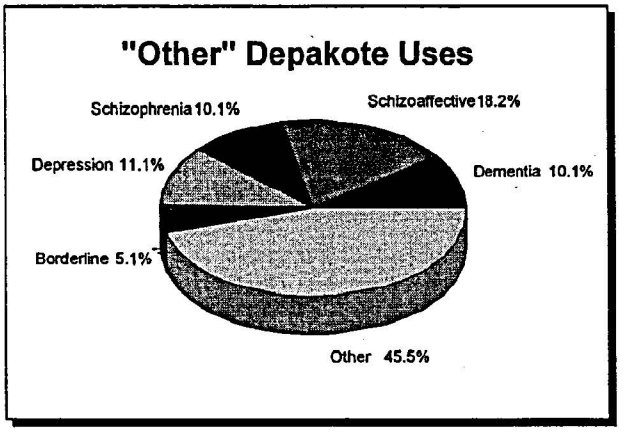
I. Executive Summary

Depakote reached several significant milestones in the past 3 years. It received FDA indications for the treatment of bipolar disorder, migraine prophylaxis, complex partial seizures, and the approval of the intravenous formulation. The opportunities continue with the expected submission of Depakote CR later this year, and the potential to become a major player in 6 other disease states before the end of the millennium.

Abbott has made significant progress in the psychiatric market, establishing Depakote as the drug of choice in 2 out of 3 bipolar patient types. Depakote achieved about 30% of all new bipolar prescriptions in only 18 months post-FDA approval.

While Depakote gained clinical success among psychiatrists for bipolar disorder, psychiatrists began to utilize Depakote in patients with diagnoses which had no standard for treatment.

Recent data indicate that now more than 20% of all Depakote use is for "other" diagnoses. These diagnoses include: Behavior Disturbances Associated with Dementia, Schizoaffective Disorder, Depression, Substance Abuse, Schizophrenia, Borderline Personality Disorder, and Post-Traumatic Stress Disorder. These markets could add substantial commercial value to the brand and significantly improve the quality of life for many under served patient groups.



Clinical data suggest Depakote to be efficacious and well tolerated by patients in these various markets. In addition, these markets may assist in the introduction and long-term use of Abbott's new antipsychotic, Serlect™, as it may create a synergistic relationship with Depakote in several markets.

Estimated annual revenue just from the top four "other" uses of Depakote range from an additional $400MM (base case) to $900MM (upside) by year 2003. There is also a significant upside potential in defining and creating these "new" markets as they are significantly less risky than developing a new drug. Fortunately, Abbott will continue to enjoy Depakote patent protection through January, 2008.

Timing is of the essence. Competitive intelligence has indicated that several other pharmaceutical companies are aggressively pursuing these other markets. Early establishment of clinical efficacy may create standard treatment regimens in the absence of FDA approved pharmacotherapy.

Although opportunities exist in each of the new markets, this plan will focus on the two most promising markets- Behavior Disturbances Associated with Dementia and Schizoaffective Disorder.

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II. Situation Analysis- *Dementia with Behavioral Disturbance*

- By the year 2000, 35% of the population will be 65+ years of age and over 5 million people will be 85+ years of age. There are currently 15,600 nursing homes in the United States, with over 1.77 million beds and 1.6 million patients.

- The nursing home market is currently a $1.8 billion drug market with an average of $1,200 a bed spent on pharmaceuticals a year. Eight nursing home pharmacy providers control more than 60% of all nursing home beds. The typical nursing home patient is 75-80 years of age, takes 7-8 medications and will spend 180 days in the nursing home. Fifty-eight percent of all nursing home beds currently are controlled by chains.

- *Dementia* is characterized by the development of multiple cognitive deficits, including memory impairment plus disturbance in at least one other area such as aphasia, apraxia, agnosia, etc. Approximately 6% of people over the age of 65 manifest severe dementia, while an additional 10-15% are found to have mild to moderate cognitive impairment. Prevalence rates in nursing home populations have been reported at 30% for severe dementia and 80% for at least mild impairment. Alzheimer's disease is the most common type of dementia (45%) and multi-infarct or vascular dementia was the most second most common type (8-34%).

- *Agitation Associated with Dementia* is a common clinical problem. Of the 4.1 million patients with dementia in the United States, 2.9 million (70%) will have some form of behavioral disturbance. The prevalence has been reported in the literature to range from 43-93% of those with dementia. Only 2/3 of these patients will actually receive medication for the aggression/agitation. No medication is approved by the US Food and Drug Administration for the treatment of dementia-related behavioral disturbance. Nonetheless, the treatment of dementia-related behavioral disturbance usually includes psychotropic medications.

- Antipsychotics (39%) and benzodiazepines (10%) are the most commonly used agents, but beta-blockers, antidepressants (15%), lithium, Depakote (3%) and carbamazepine are also used. Only about 1/3 of patients will respond dramatically to the antipsychotics which are known to have a narrow therapeutic window between efficacy and adverse effects.

- Depakote use in this market has been growing consistently over the last three years to it's current market share of 2.9%. The total market opportunity in Depakote dollars is $204MM. Open label studies and case reports have concluded that Depakote is safe and effective for the aggressive/agitated behavior associated with dementia. The use of Depakote in this market is growing due to it's broad spectrum of use across mood disorders, relatively benign side effect profile and few drug-drug interactions.

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III. Key Objectives

A. *Penetrate the Long-Term Care Market to Drive Depakote Share*

- Market share for Depakote is lower in the Long-Term Care (LTC) setting than it is in the private sectors for all approved indications. In epilepsy, Dilantin currently has a 54% market share, Tergretol has a 17 % market share and Depakote has a 6% share (vs. 18% in the retail market). In bipolar, lithium has 68% of the market, Tegretol and Depakote both have a 10.4% share (vs. 32% in the retail market). Depakene/VPA have a 4.1% share in the epilepsy market and a 10.4% share in the bipolar market, which are also higher than in the private sector.

- Education of key decision makers and focused detailing efforts can significantly increase Depakote usage for all indications as well as decrease the rapidly increasing use of Depakene and generic valproic acid.

- New indications for Depakote in mania, complex partial seizures, migraine propyhlaxis and new formulations including the controlled release formulation, and Depacon IV need to be promoted aggressively in the LTC market. The physicians, consultant pharmacists and nurses need to be educated about the correct dosing/monitoring , pharmacokinetics, pharmacodynamics as well as the adverse events profile of Depakote.

- Clinical data that demonstrate Depakote's effectiveness in treating aggression/agitation in elderly patients with dementia must be published. Competitive comparisons of other medications used in aggression/agitation need to be made to highlight Depakote's advantages.

B. *Obtain an FDA Indication for Dementia with Behavioral Disturbance*

- Conducting the clinical trials necessary to receive an NDA for Depakote in this market will result in both short-term and long-term sales growth for Depakote. Preliminary market research has shown that if Depakote were to achieve a 20% share of this market, fifth year sales could potentially reach $100MM.

- The most commonly used drugs for aggression/agitation are the antipsychotics which are known to have numerous cognitive, sedative and EPS side effects. Due to its relatively benign side effect profile and few drug-drug interactions, Depakote can capitalize on the broad spectrum of efficacy in mood disorders to become positioned as a first-line choice for patients with dementia with behavioral disturbance.

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C. *Capitalize on OBRA Restrictions to Position Depakote as the Drug of Choice*

- Depakote has a competitive advantage over neuroleptics, the most commonly prescribed drug for agitation/aggression in the elderly. In order for a patient to receive a neuroleptic in a nursing home:
  - ✓ Use of neurolpetic drugs must be documented as appropriate for the diagnosis.
  - ✓ Dose reduction and elimination of neuroleptic drugs must be attempted every six months.
  - ✓ Any drug must be used for the appropriate indication, dose, and duration.
  - ✓ Use must be adjusted based upon adverse events or drug interactions.

- Depakote can be prescribed without the above inconvenient and costly restrictions/guidelines that are an additional cost to the institution and provider.

D. *Contract With Major LTC Pharmacy Providers to Drive Depakote Growth*

- LTC Pharmacy Providers have the ability to influence therapy for the treatment of aggression/agitation in the elderly through formulary control and treatment protocols. By establishing relationships and agreements with these providers, Abbott can effectively drive market share of Depakote. Agreements can be forged by providing unrestricted educational grants to the providers in support of initiatives to educate pharmacists, physicians and nurses.

- Abbott also has the opportunity to guide the future treatment of this often ill-defined disorder by providing unrestricted grants for the development of consensus guidelines on the diagnosis and treatment of this disorder. Grants can be made to individual pharmacy providers or to various associations.

IV. Overall Positioning/Strategy/Message

- *Positioning*
  - ✓ Depakote will be positioned as the first-line choice for dementia with behavioral disturbance.

- *Core Strategy*
  - ✓ Establish Depakote as the first-line choice for dementia with behavioral disturbance due to its broad spectrum of efficacy, patient tolerability, lack of OBRA restrictions, convenient dosing, and a demonstrated 14 year track record.
  - ✓ Target education to high potential geriatric psychiatrists, medical directors, and other key customers.
  - ✓ Expand the number and scope of clinical studies to solidify Depakote's clinical role.
  - ✓ Establish Depakote as first-line treatment in practice guidelines of key

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pharmacy providers and managed care plans.

✓ Reinforce competitive advantages versus antipsychotics and benzodiazepines.

V. Key Strategic Issues

A. *The Market is Dominated by the Use of Neuroleptics/Antipsychotics*

- The major issue facing Depakote in this market is that it is dominated by antipsychotics, which currently have a 45% share of the market (approaching 20% for Risperdal). Physicians and pharmacists have used these drugs since the mid 1950's when they were first introduced. The key decision makers are comfortable with these medications. The traditional antipsychotics are now all generically available and thus, very inexpensive. Many patients with dementia are on the lower end of the socioeconomic scale and by virtue of their condition, lack insight, direction and resources to access newer drugs. Generically available drugs represent an affordable option.

- Risperdal has experienced rapid growth in the LTC market and continues to invest a significant amount of resources in promotional efforts, medical education and clinical trials. A new oral liquid was approved in late 1996 which potentially has broad applications for this market.

- Zyprexa will attempt to penetrate this market through significant investing of resources directed to clinical trials, medical education, journal advertising and focused detailing efforts. There is some question among thought leaders as to whether Zyprexa and the other novel antipsychotics will be classified by the OBRA guidelines, due to their perceived safety advantages over the traditional antipsychotics. REDACTED will also try to capitalize on a new indication for bipolar disorder expected in 1998.

B. *Abbott PPD has not Been a Major Player in the LTC Market*

- Historically, Abbott has not invested a significant amount of resources in the LTC market. Other companies such as REDACTED, REDACTED and REDACTED have been very active in this market. REDACTED has been extremely active in the LTC market with Zoloft and now with the December FDA approval of Aricept (only the second drug to be approved for dementia associated with Alzheimer's disease). REDACTED is also conducting studies in the elderly with Ziprasidone, a new antipsychotic, expected to be approved in 1998.

- Abbott PPD has devoted a limited amount of managed health care resources to the LTC market, and has not developed the key relationships our competitors have.

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Ross has established relationships with most of the key organizations in LTC, and were one of the founders of the American Medical Directors Association fifteen years ago.

C. *Depakote Market Share in the LTC Setting is Lower in all Therapeutic Segments Than it is in the Overall Market*

- The market share for Depakote is significantly lower in the LTC market for bipolar disorder and epilepsy than it is in the private sector. The market leaders, Dilantin and lithium, are older drugs that physicians and pharmacists are more comfortable with. The high prescribers in this setting tend to be primary care doctors that have not taken part in medical education initiatives in this arena. Safety concerns, specifically hepatotoxicity, are issues which have not been addressed adequately with this target audience.

- The main competitors in the aggression/agitation market are the traditional antipsychotics which physicians have used since the 1950's. REDACTED also has spent considerable amounts of funding to educate the target audience on the product profile of Risperdal.

- Lack of education, safety concerns and questions about proper dosing and drug interactions are hindering the use of Depakote for dementia with behavioral disturbance.

D. *Key Decision Makers in the LTC Setting are not Familiar with Depakote*

- Consultant pharmacists, key decision makers in the LTC market have not been targeted in the past with information or educational materials about Depakote. Relationships with the American Society of Consultant Pharmacists have been initiated but not developed to a great extent.

- Geriatric psychiatrists have not been targeted in the past with medical education about the broad spectrum of Depakote's efficacy in mood disorders.

- Medical directors of nursing homes have not been targets for medical education initiatives by Abbott on Depakote and are consequently more comfortable prescribing the older medications for aggression/agitation in the elderly.

- High anticonvulsant prescribing GP/FP/IM physicians are now beginning to be called on by NSRs on a limited basis. These physicians are being detailed by both REDACTED and REDACTED on the use of Risperdal and Zyprexa in aggression/agitation in the elderly.

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E. *FDA Obstacles May Exist to Pursuing an Indication for Aggression/Agitation*

- REDACTED M.D., Director, Division of Neuropharmacological Drug Products, FDA, has written a letter to Abbott dated January 28, in response to an Investigational New Drug Application (IND) submitted by Abbott in regards to the protocol for M96-491, "A Double-Blind, Placebo-Controlled, Study of Valproate in the Treatment of Behavioral Agitation Associated with Dementia." The letter clearly states that aggression/agitation will not be an approvable indication for divalproex. He also explains that at this time there is no diagnostic validity (except for dementia, of which agitation is one of the symptoms) and that there is no agreed therapeutic target or measure for aggression/agitation in the elderly. However, the FDA did recommend the feasibility of extending the existing antimanic claim to the elderly.

- Per discussions with several opinion leaders, competitors in this market are aggressively moving forward to conduct the studies necessary to get an indication for this market with the expectation that the FDA may alter its position towards a potential approval.

VI. Strategies to Address Key Issues

A. *The Market is Dominated by Neuroleptics/Antipsychotics*

- Drive home the Depakote message to key decision makers.

- Foster the need to improve compliance to medication through Depakote usage. Depakote's side effect profile is clearly superior to all of the traditional antipsychotics and does not have the EPS side effects of Risperdal and Zyprexa.

- Ensure that Depakote achieves competitive share of voice; focus on key customer segments, including high prescribers (psychiatry and primary care), pharmacy providers, consultant pharmacists and nurses.

- Utilize publication and education efforts to drive home the superior efficacy and safety of Depakote versus antipsychotics and benzodiazepines.

- Establish Depakote as more cost-effective than the antipsychotics in the overall disease management approach of treating aggression/agitation.

- Develop treatment algorithms for dementia with behavioral disturbance.

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B. *Abbott PPD Has Not Been a Major Player in the LTC Market*

- Abbott has begun the initial step by dedicating a National Manager for LTC as well as a product manager focusing on a potential indication for dementia with behavioral disturbance for Depakote.

- PPD can capitalize on the expertise and influence that Ross has with the major players in this market to expand awareness of Depakote.

- Provide educational grants to key organizations in this market to develop relationships/guidelines (AMDA, AAGP, ASCP).

- Dedicate focused detailing on top LTC targets.

C. *Depakote's Market Share is Lower than it is in the Community in all Therapeutic Categories*

- Drive home Depakote message to key decision makers including consultant pharmacists, medical directors of nursing homes, and geriatric psychiatrists.

- Medical education initiatives

- Focus on the broad spectrum of Depakote in mood disorders

- Develop opinion leaders in the LTC market. This is essential in facilitating rapid market share growth for Depakote. Abbott has established strong relationships with many key national psychiatric thought leaders, but needs to increase it to include both national and regional experts across specialties of primary care physicians, consultant pharmacists and directors of nursing in LTC.
  - ✓ Expand relationships through NMLs, sales and marketing management
  - ✓ Support involvement in marketing and venture funded clinical trials
  - ✓ Support medical education opportunities

- Improve the diagnosis of dementia with behavioral disturbance

D. *Key Decision Makers in the LTC Market are not Familiar with Depakote*

- Identify and target the high prescribing primary care physicians to disseminate and communicate Depakote product information.

- For each of the key decision makers (medical directors, consultant pharmacists and high prescribing GP/FP/IM)
  - ✓ Identify their role in the treatment decision
  - ✓ Utilize geropsychiatrists, consultant pharmacists, medical directors in developing CME initiatives outlining the diagnosis and treatment of dementia with behavioral disturbance.

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- ✓ Establish non-personal initiatives outlining the core message for Depakote to these key individuals/organizations.

- Capitalize on other indications for Depakote by pooling resources for medical education initiatives

E. *Regulatory Obstacles May Exist to Pursuing an FDA Indication for Aggression/Agitation*

- Meet with the FDA to discuss concerns and issues related to an approval for aggression/agitation

- Establish support from opinion leaders as to the need for consensus guidelines on the diagnostic criteria, targets and measures for a potential aggression/agitation claim.

- Conduct a clinical trial in elderly patients with mania to file for a claim extension for mania and include a large percentage of patients with dementia.

- Clinically examine if Depakote may improve cognition in Alzheimer patients as an alternative strategy for a potential FDA indication.

I. Situation Analysis- *Schizoaffective Disorder*

- Approximately 1% of the U.S. population, or 2.6MM people, suffer from schizoaffective disorder. At most, 50% of schizoaffective patients, or 1.3MM people, currently receive treatment.

- Based on 1996 NDTI data for drug uses, antipsychotics dominated the relevant market with a 43% share. This includes risperidone with 9.4%, Haldol with 3.5%, and olanzepine with 1.4% in only three months. Anticonvulsants consisted of 13% of total drug uses, led by Depakote with a 7.9% share, and followed by klonopin with 2.7% and carbamazepine with 2.6%. Lithium consisted of 8.6% of all drug uses. Other classes of drugs used to treat schizoaffective disorder include SSRIs (11%), anti-Parkinson agents (5.9%), tri/tetracyclics (4.2%), and benzodiazepines (3.5%). The total market is estimated to be worth approximately $200MM in Depakote dollars.

- Because schizoaffective disorder consists of both schizophrenic and bipolar symptoms, products in both these areas are relevant for treating the disease and are often administered concurrently.

- The availability of clearly defined diagnostic criteria for schizoaffective disorder

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has allowed significant improvement in the reliability of its diagnosis in recent years. In two studies which used such specific operational criteria to assess its diagnostic reliability, diagnostic agreement for schizoaffective disorder was comparable with that for bipolar disorder and schizophrenia.

- According to DSM-IV, schizoaffective disorder consists of an uninterrupted period of illness during which there is either a major depressive episode, a manic episode, or a mixed episode concurrent with symptoms for schizophrenia, such as delusions or hallucinations. Approximately half of those affected suffer from the bipolar subtype where the disturbance includes a manic or mixed episode (schizoaffective mania), while the remainder suffer from the depressive subtype where the disturbance only includes major depressive episodes.

II. Key Objectives

A. Obtain an FDA Approval for the Treatment of Schizoaffective Disorder

- Conducting the clinical trials either to receive an NDA for Depakote in this indication or to publish results citing Depakote's efficacy will result in both short-term and long-term sales growth for Depakote. Preliminary market research has shown that if Depakote were to achieve a 25% share of this market, fifth year sales could reach more than $100MM.

- In recent studies, depakote improved psychotic symptoms in bipolar patients and preliminary data supports depakote's efficacy in both schizoaffective disorder and schizophrenia. Depakote could be positioned as a monotherapy for schizoaffective disorder.

B. Educate Psychiatrists Regarding Depakote's Efficacy

- Currently, psychiatrists have not been systematically informed or educated on the benefits of using Depakote to treat schizoaffective disorder. Doing so through education initiatives or the publication of articles/studies in relevant journals will contribute to short-term and long-term growth for Depakote.

- Additionally, as psychiatrists become more aware of Depakote as a treatment for schizoaffective disorder, they will be more comfortable in diagnosing patients who may otherwise be diagnosed with schizophrenia or a mood disorder and prescribing Depakote as the treatment of choice.

III. Overall Positioning/Strategy/Message

- *Positioning*
  - ✓ Depakote will eventually be positioned as the first-line choice for schizoaffective disorder.

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- *Core Strategy*
  - ✓ Eventually establish Depakote as the first-line choice for schizoaffective disorder due to it's broad spectrum of efficacy, patient tolerability, lack of side effects associated with antipsychotics, convenient dosing, and a demonstrated 14 year track record.
  - ✓ Target aggressive education to high potential psychiatrists, and other key customers.
  - ✓ Establish Depakote as first-line treatment in practice guidelines
  - ✓ Reinforce competitive advantages versus lithium, Tegretol and other new mood stabilizers.

IV. Key Strategic Issues

A. Lack of Market Research

- Currently, primary and secondary data for the schizoaffective market is not readily available to track Depakote Rx's or to precisely analyze the marketplace.

B. Credibility in the Diagnosis of Schizoaffective Disorder is Building

- Traditionally, schizoaffective disorder frequently was viewed as a temporary condition as a sufferer progressed either into schizophrenia or bipolar disorder. Relatively recent research has shown that schizoaffective disorder is not part of a continuum, but rather an independent disease state with a unique clinical course and outcome. This notion is building among psychiatrists, but the traditional view is still held by many practitioners.

V. Strategies to Address Key Strategic Issues

A. Lack of Market Research

- Coordinate efforts with the Market Research department to investigate methods to track Depakote Rx's in schizoaffective disorder as well as the historic, current, and future competitive environment. Conduct primary research to understand the perceptions of psychiatrists, pharmacists, patients, and other key players for use in making better marketing decisions regarding segmentation and positioning.

B. Credibility in the Diagnosis of Schizoaffective Disorder is Building

- Work with opinion leaders and other relevant constituencies to build credibility in schizoaffective disorder as an independent disease with specific symptoms and treatments. Teach psychiatrists and other practitioners how to use the standard operational diagnostic criteria that now exist.

- Develop treatment algorithms for schizoaffective disorder and explore the possibility of eventually co-promoting Depakote with an atypical antipsychotic, preferably Serlect, but perhaps Risperdal (REDACTED) or Zyprexa (REDACTED).

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Appendix I:
Situation Analysis Support
Dementia with Behavioral Disturbance
Schizoaffective Disorder

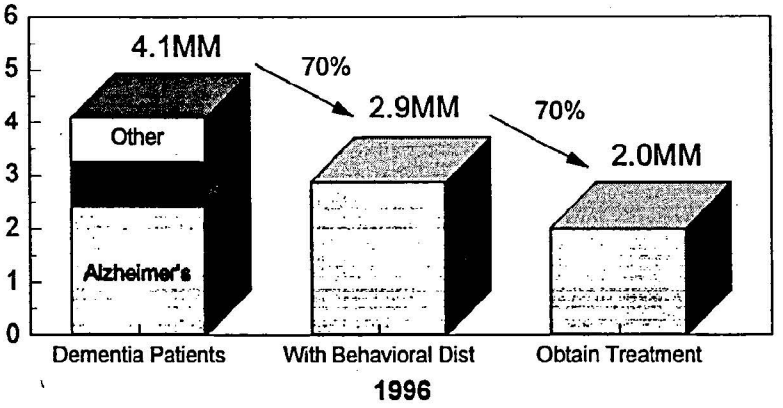
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Dementia with Behavioral Disturbance

Patient Population

10-15% of the U.S. Population Over Age 65 Has Dementia

MM



Source: Population Profile of the U.S., relevant literature.

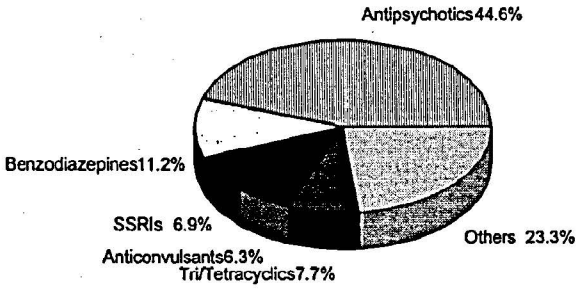
Competitive Situation

Dementia with Behavioral Disturbance

% Drug Use by Type

June 1995 thru May 1996

Total Market in Depakote Dollars: $203.6MM



Source: NDTI.

Current Depakote Market Share: 2.9%

Drug Uses = 1,915,000

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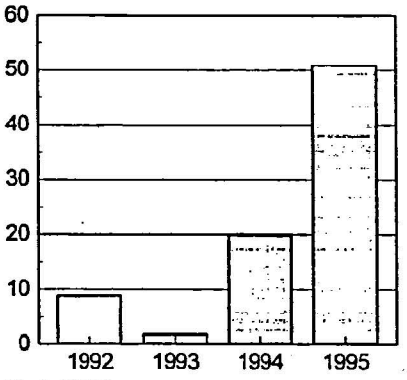
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Depakote Use for Dementia with Behavioral Disturbance

Dementia/Alzheimer's

Depakote Drug Use in 000s

Drug Uses in 000s

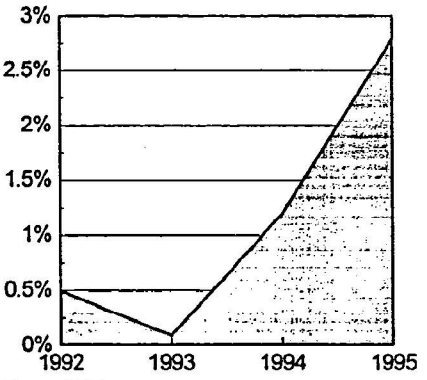


Source: NDTI.

Dementia/Alzheimer's

Depakote Share of Drug Use

% of Drug Use

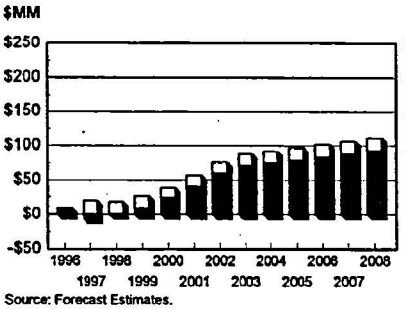


Source: NDTI

Dementia with Behavioral Disturbance

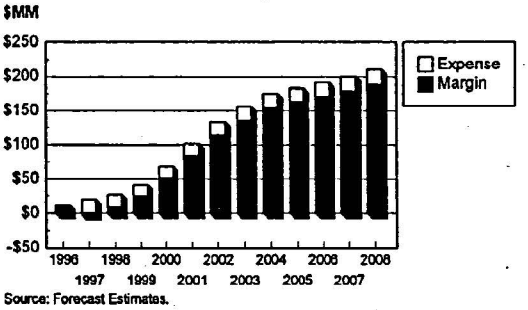
Market Forecast

Revenue - Base Case



Source: Forecast Estimates.

Revenue - Upside Case



Source: Forecast Estimates.

Assuming FDA Approval in July, 1999	Base Case	Upside Case
5th Year Sales in 2003	$88.8MM	$156MM
5th Year Contribution Margin	$71.5MM	135.7MM
NPV @ 15% (1996-2005, After-Tax)	$77.1MM	$163.0MM

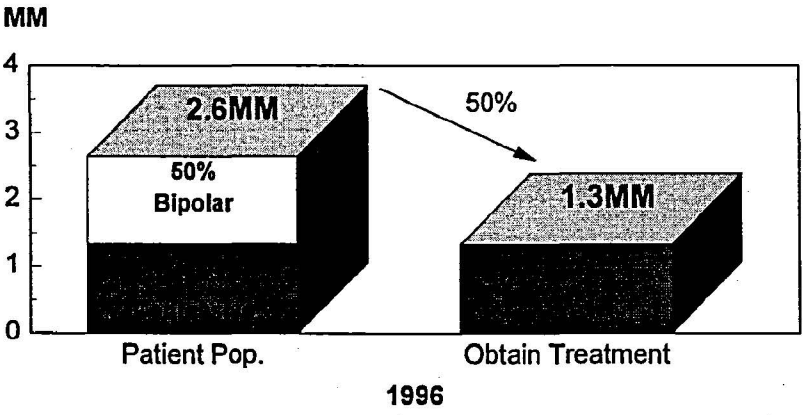
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Schizoaffective Disorder
Patient Population

Schizoaffective Patients

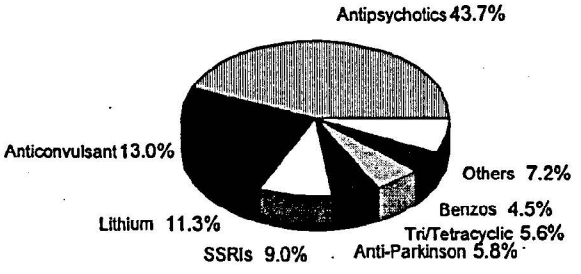
1% of the U.S. Population



Source: Population Profile of the U.S., relevant literature.

Competitive Situation
Schizoaffective Disorder

% Drug Use by Type
June 1995 thru May 1996
Total Market in Depakote Dollars: $195MM



Drug Uses = 1,979,000

Source: NDTI.

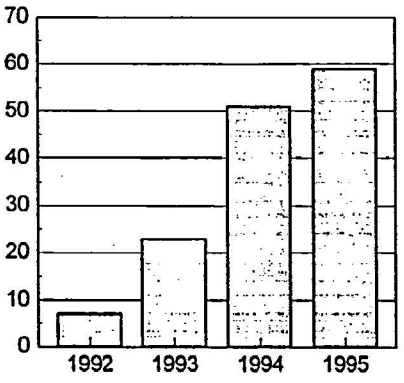
Current Depakote Market Share: 5.0%

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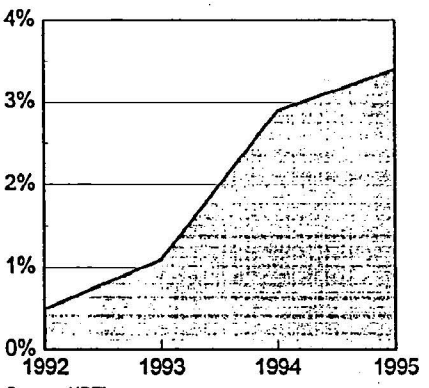
Depakote Use for Schizoaffective Disorder

Schizoaffective Disorder
Depakote Drug Use in 000s



Source: NDTI.

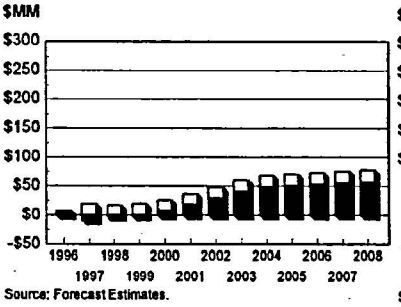
Schizoaffective Disorder
Depakote Share of Drug Use



Source: NDTI

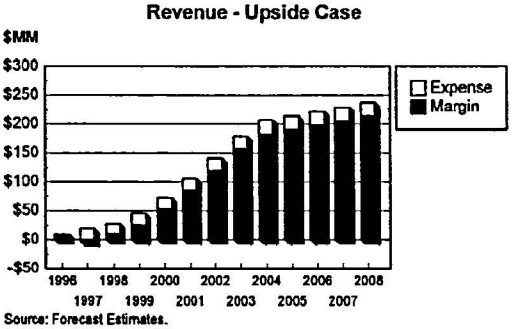
Schizoaffective Disorder
Market Forecast

Revenue - Base Case



Source: Forecast Estimates.

Revenue - Upside Case



Source: Forecast Estimates.

Assuming FDA Approval in July, 1999	Base Case	Upside Case
5th Year Sales in 2003	$60.2MM	$179.6MM
5th Year Contribution Margin	$40.9MM	$157.1MM
NPV @ 15% (1996-2005, After-Tax)	$34.1MM	$179.3MM

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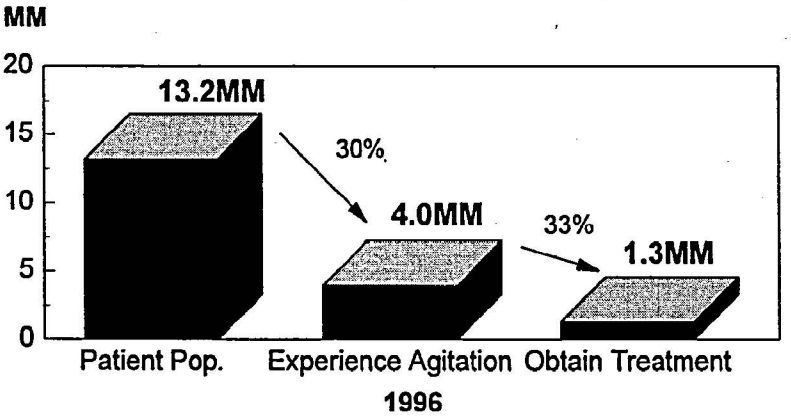
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Appendix II:
Other Market Opportunities
Market Size/Potential by Disease State & Patient Population Breakdown
Agitated Depression
Borderline Personality Disorder
Substance Abuse
Post-Traumatic Stress Disorder

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Agitated Depression
Patient Population

Depression Patients
5% of the U.S. Population (annually)

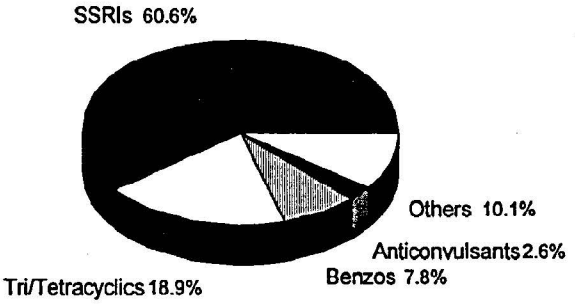


Source: Population Profile of the U.S., relevant literature.

Agitated Depression
Competitive Situation

% Drug Use by Type
July 1995 thru June 1996

Total Market in Real Dollars: $3.6B



Current Depakote Market Share: 0.6%

Drug Uses = 23,633,320 Source: NDTI

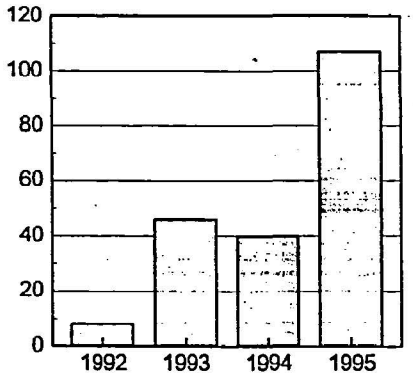
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Depakote Use for Depression

Depression

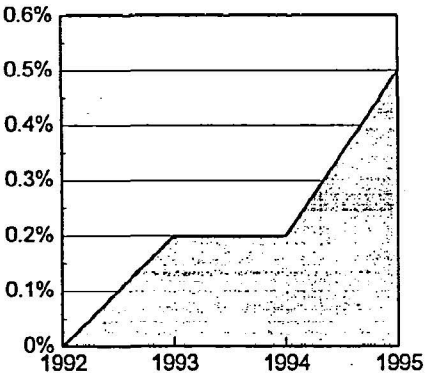
Depakote Drug Use in 000s



Source: NDTI.

Depression

Depakote Share of Drug Use

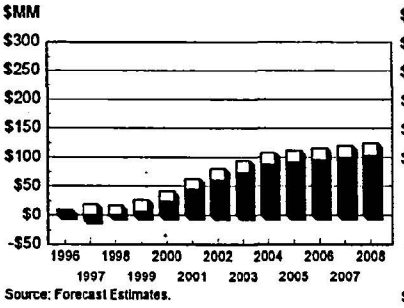


Source: NDTI

Depression

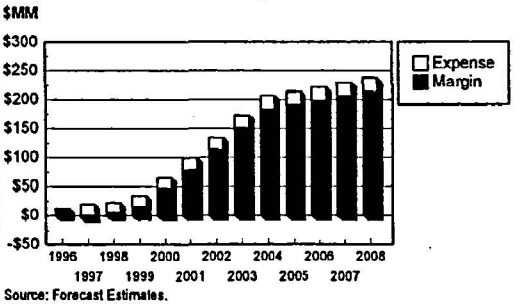
Market Forecast

Revenue - Base Case



Source: Forecast Estimates.

Revenue - Upside Case



Source: Forecast Estimates.

Assuming FDA Approval in July, 1999	Base Case	Upside Case
5th Year Sales in 2003	$94.1MM	$172.8MM
5th Year Contribution Margin	$74.0MM	$150.4MM
NPV @ 15% (1996-2005, After-Tax)	$81.8MM	$167.1MM

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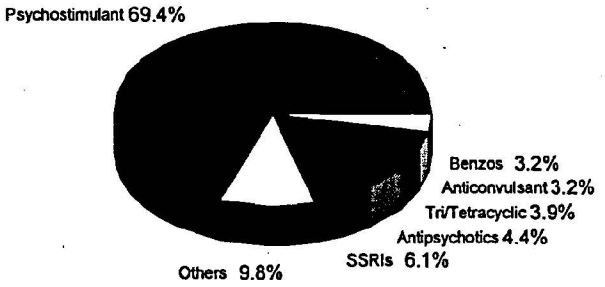
Borderline Personality Disorder

Competitive Situation

% Drug Use by Type

July 1995 thru June 1996

Total Market in Depakote Dollars: $580MM



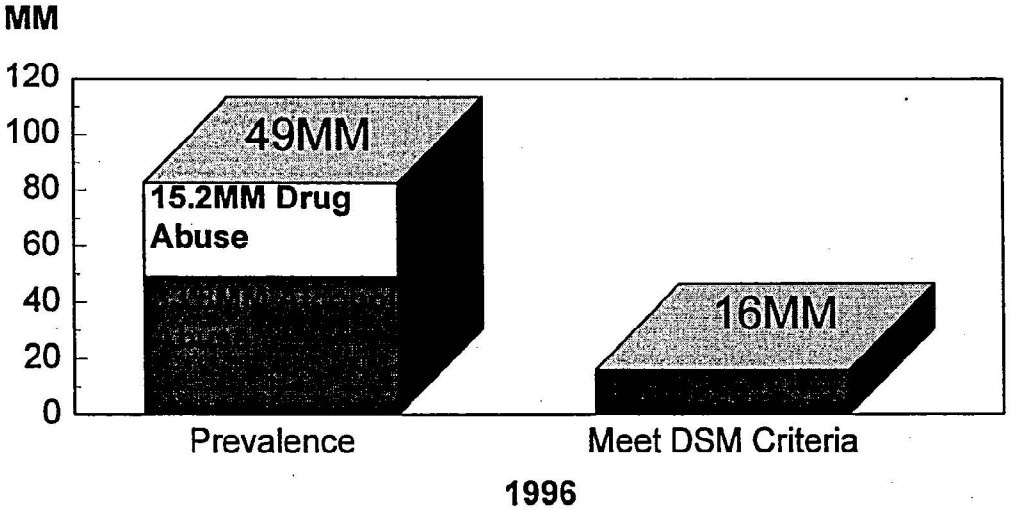
Drug Uses = 5,350,000

Source: NDTI.

Depakote Market Share: 0.5%

Substance Abuse

7% of the U.S. Population Meet DSM Criteria



Source: Population Profile of the U.S., relevant literature.

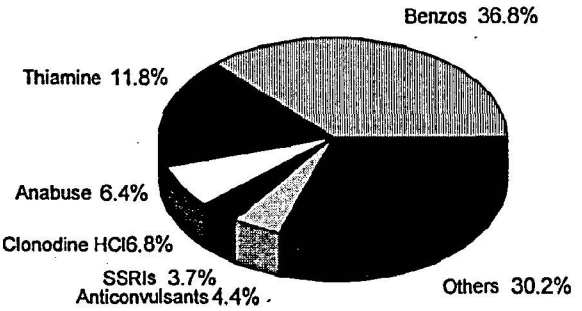
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Competitive Situation

Substance Abuse

% Drug Use by Type
June 1995 thru May 1996

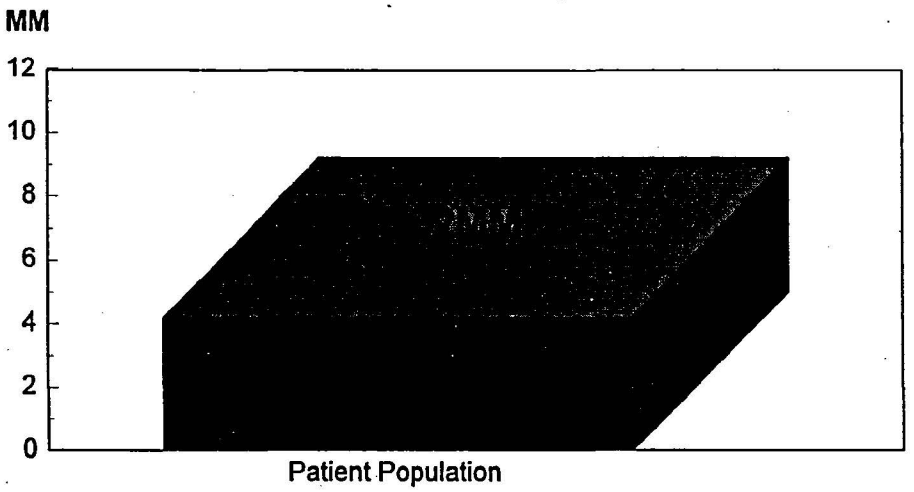


Source: NDTI.

Current Depakote Market Share: .5%
Market Size in Depakote Dollars: $221MM

Post Traumatic Stress Disorder

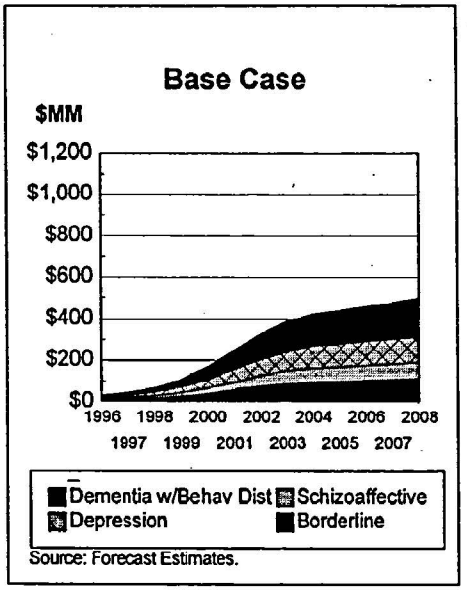
1.6% of Patient Population

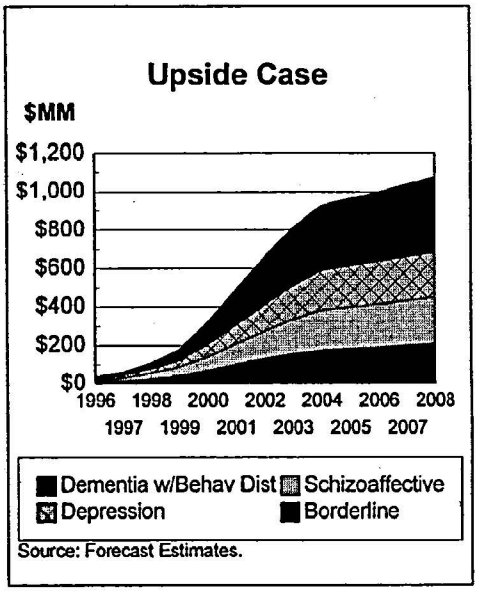


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Estimated Revenue from 4 New Indications





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2001 LTC Strategic and Tactical Plan

Strategic Summary
Market Segment Overviews
Tactical Plan Detail
Planning T&E

November 8, 2000

Depakote LTC
2001 Marketing Strategy

Situation Analysis

Background

- The geriatric market (65+ years of age) represented 13% of the U.S. Population in 1997 (34 million individuals). Approximately 16% of this group will present with a psychiatric diagnoses before death, and an additional 10% will be afflicted with Alzheimer's type dementia (3.5MM people).
- Of the Alzheimer's-specific group of patients approximately 30%, or 3% of the total elderly population, will exhibit significant psychopathological symptoms. Disruptive psychiatric behavior (ie: verbal/physical agitation and aggression) occurs in between 70-90% of dementia patients, and is the primary reason for nursing home admissions.
- Below are the 1-year prevalence rates for primary DSM-IV diagnostic category illnesses in the 65+population (MM):

    - Major Depression: 0.9
    - Bipolar Disorder: 0.2
    - Anxiety Disorder: 2.2
    - Schizophrenia: 0.2
    - Cognitive Impairment
        - Mild 19.1
        - Severe 13.5

- Based on identified growth within the LTC channel, Abbott launched a devoted Long Term Care sales force in January of 1998. Market research indicated that the primary driver for prescription growth of Depakote was as a treatment for symptoms of agitation associated with Alzheimer's dementia. A sales force of 28 representatives and 1 account manager began detailing efforts focused towards consultant pharmacists, nursing directors, and medical directors in nursing homes.

    - The base nursing home business is 1.7 MM beds, and is growing at roughly 2-3% per year. Market dynamics (Medicaid reimbursement issues, staffing shortages, quality of care issues, expansion of assisted living facilities with higher acuity capabilities) are forcing a shift in the number of available beds and admissions; as a result, the nursing home business appears to be facing a slowdown in growth.
    - Seven pharmacy providers dominate the prescription drug management business and account for over 60% of the total nursing home beds. These providers are covered at the national level by Account Manager activity and by sales force members at the local level.

- The market for "anti-agitation" therapy has typically been comprised of antipsychotic and antidepressant or anxiolytic medications. Physicians typically considered neuroleptics (Haldol) as the first-line treatment for acutely aggressive patients, and continued treatment as maintenance in many cases. Benzodiazepine hypnotics were also highly prescribed as PRN medication.

- With the introduction of the atypical antipsychotic risperidone (Risperdal, REDACTED) in 1994, a major move away from neuroleptic medications was solidified. The OBRA act of 1987 and later the HCFA regulations have helped move atypical antipsychotics to the forefront of treatment for this cluster of symptoms in dementia. Market perception has been that atypical antipsychotics provide "safe haven" from regulatory restrictions. This in fact is not the case, and HCFA continues to refine codes to monitor atypical usage. Currently, divalproex is not grouped in the antipsychotic definition and therefore is not open to the same regulatory restrictions.

- Currently, Risperdal maintains the market share lead for treatments used in behavioral disturbances in dementia. Olanzapine (REDACTED, REDACTED), launched in 1996 has moved to the 2nd most prescribed position. Zyprexa

  - Both products have devoted LTC sales forces (100 and 125 representatives respectively), and will sell between **($300-375MM: CONFIRM)** in 2000.
  - Quetiapine (Seroquel, REDACTED) launched as the third atypical antipsychotic entrant in 1997, and is currently expanding its' presence in LTC through increased clinical research and marketing activity. It is currently completing the deployment of a devoted LTC sales force and account management team. **($ SALES)**
  - A fourth entrant, ziprasidone (REDACTED) may enter the market as early as 2Q01. This will be a particularly strong entry as REDACTED co-promotes REDACTED (donepezil) with REDACTED. REDACTED and promotes Zoloft, the number one prescribed SSRI in LTC. REDACTED will enter the market with a strong understanding of the LTC market and the related provider issues.
  - Two cholinesterase inhibitors are currently marketed in the US Market. REDACTED (Aricept) and REDACTED (Exelon) are both developing and promoting combined cognition and behavior management messages. A third compound was recently approved and is preparing to enter the US market (**BRAND**, selegeline; REDACTED).

- Mood stabilizer/anticonvulsant competition has been moderate and has consisted primarily of pockets of activity by Neurontin (REDACTED). Market advisors estimate increased clinical activity and promotional efforts for Neurontin to coincide with the product's takeover by REDACTED **(2000 $ SALES LTC)** Relatively little data exists documenting efficacy of other mood stabilizers; product safety profiles preclude uptake of lithium or carbamazepine. REDACTED appears poised to initiate data collection for oxcarbazepine.

Key Issues

- **Factors enhancing Depakote growth for 2001 include:**
  - Sales force expansion from 28 to 55 devoted LTC representatives (completed 2Q00) and an two additional Account Managers (3 total LTC) to work with key influencers at the local level and pharmacy providers at the national level.
    - Territory disruption absorbed in 2000
    - Initial LTC physician-level data rolled out 4Q00
    - LTC Consultant Meetings executed 3/4Q00
  - Commercial Analysis initiative
    - Message recall (4Q00)
    - Rx Influencer definition (1Q01)
    - Market Expansion definition (Assisted Living, Retail; 1/2Q01)
  - Publication of two pivotal datasets for Depakote in nursing home patients (4Q00/1Q01)
    - M97-738: Depakote in Elderly Mania
    - VALIDATE: Depakote in signs/symptoms of Elderly Mania
  - LTC Provider contracting for Depakote (growth incentives) initiated 3Q00
  - Launch of Depakote ER and subsequent ER growth incentives with LTCPP
  - Account Manager implementation of disease state management programs to key providers (REDACTED and REDACTED initially).
    - Define market (agitation) vs. Competitive focus (psychosis)
    - Focus provider staff on safety advantage and lack of regulatory control vs. antipsychotics (OBRA and HCFA)
    - Leverage pivotal data publications
  - Increased promo spend vs. 2000
    - Comprehensive Educational initiative roll-out (2Q01)
    - Consultant Programs (1Q01)
    - NAM Program funding
  - Ongoing clinical activity involving Depakote (M99-082 and ADCS study).
    - Development of "neuroprotective" data and commercial message

- **Factors limiting growth include:**
  - Short term perceived lack of clinical data (controlled).
  - Diversity of influences on LTC Rx's.
  - Competitive pressure:
    - Sales force expansions; added nursing/pharmacy coverage
    - Relative promotional spend and lost SOV **(BACKUP/ LTC)**
    - New entrants (Exelon, ziprasidone, selegeline)
    - Aggressive competitive contracting/bundling at provider level

- Entrenched treatment pattern (antipsychotics) at primary care level and current lack of PCP channel coverage.
- Depakote labeling considerations:
  - Perception of monitoring requirements at PCP level
  - Hepatotoxicity, pancreatitis, geriatric dosing warnings
- Valproic Acid initiatives at provider level
- Lack of clinical data for Depakote ER; size of 500mg formulation.

Segmentation

- The Long Term Care Channel is segmented in terms of prescribers and non-prescribers
  - Prescribers: Geriatric Psychiatrists, Consultant Psychiatrists, Medical Directors, Consulting Geriatricians (GP/FP), Nurse Practitioners
  - Non-Pre scribers: Pharmacy Providers, Consultant Pharmacists, Nurses

- **Use Segmentation**
  - Estimated available uses for Geriatric population;
    - Behavior Disorders associated with Dementia: 70-80%
    - Seizure Disorders/other: 20-30%
  - Behavioral Disturbances
    - Of 4.1MM dementia patients, minimally 2.9MM (70%) will experience BDD
      - Primary disturbances
        - Depression: 10-80%
        - Anxiety: 20-60%
        - Psychosis: 5-49%
        - Agitation/Aggression: 10-90%
      - Depakote is 1st-line therapy in agitation/aggression; adjunctive therapy (for suboptimal control) in agitated depressed, anxious, or psychotic patient
  - Seizure Disorders (all)
    - Approximately 24% of population 65 years+ have a seizure disorder
    - Total SNF population estimated to be taking anticonvulsant at given time: 10-25%
      - Depakote is 1st-line therapy for geriatric seizure patients who are candidates for maintenance AED therapy

- **Channel Segmentation: Messages**
  - Prescribers:
    - Psychiatry: 1st line maintenance treatment and effective adjunctive control of agitation and aggression associated with Alzheimer's disease.
      - Safe (well tolerated), proven effective alone and as adjunct TX, easy to initiate and titrate with flexible dosing and new ER formulation.
    - General Medicine: 1st line maintenance treatment and effective adjunctive control of symptoms of agitation and aggression associated with normal progression of Alzheimer's disease.

- Safe (vs. antipsychotics, not regulated by OBRA/HCFA), proven effective and considered 1st line by Expert Consensus panel, easy to initiate and monitor with flexible dosing, allows antipsycotic dose reduction. ER formulation offers improved tolerability and once daily dosing.
- Secondary Message: Depakote is a first-line treatment for seizure disorders in the elderly, with specific benefits (broad spectrum, use in co-morbidity, use as mono or combo-therapy, lack of drug interactions, and lack of negative cognitive adverse effects) compared to phenytoin and carbamazepine in this population.

- Non-prescribers: Consultant Pharmacists
  - Proven 1st line maintenance for symptoms of agitation and aggression in dementia.
    - Depakote is clinically proven, safe treatment for maintenance treatment in the nursing home; use is not regulated by OBRA/HCFA. This allows antipsychotic reduction/removal at the individual nursing home level.
    - Depakote is a cost-effective alternative to atypical antipsychotics.
    - Flexible formulations are ideal for geriatric patients (ER allows improved tolerability and QD dosing, fewer med pass errors, and reduced staff time) while sprinkle provides smooth blood levels ideal for initiation and maintenance at lower doses.
    - Secondary Message: Depakote is a first-line treatment for seizure disorders in the elderly; lack of cognitive effects and drug/drug interactions provide benefit over current first-use therapies phenytoin and carbamazepine.
- Non-prescribers: Nursing
  - Proven 1st line maintenance for symptoms of agitation and aggression in dementia.
    - Clinical data supports Depakote as a safe and effective treatment in this population. It is not an antipsychotic, and therefore is not associated with adverse events such as EPS/TD, anticholinergic effects, or hypotension. It is also not regulated by OBRA/HCFA, and allows for either antipsychotic dose reductions or elimination. Depakote ER and sprinkle offer convenient formulations for initiating and titrating; ER can be dosed once daily which helps significantly save staff time and cut down on Medication Pass errors.
    - Depakote is also an effective therapy for seizure disorders, with substantial benefits vs. Carbamazepine and phenytoin in terms of broad spectrum of activity, use in co-morbidity, relative lack of drug interactions, and lack of cognitive adverse events particularly associated with phenytoin.
- Non-prescribers: LTC Pharmacy Providers with NAM coverage
  - Proven 1st line maintenance treatment for agitation and aggression in dementia
    - Substantial clinical data to support clinical use
      - As effective in agitation and aggression as antipsychotics with more benign adverse event profile
      - Cost savings vs. Atypical antipsychotics (combination use allows lower AP doses)
    - ER available; data is being generated at nursing home level
      - ER formulation will help cut med pass errors and reduce staff time in dispensing tablets
    - Not monitored by OBRA/HCFA

- Committed effort by Abbott to partner with providers
  - Depakote contract and ER incentive
  - DSM Programs include ER data

- **Channel Segmentation in 2001**

  - Current focus is prescribers. Targets include geriatric/consulting psychiatry and Medical Director/Geriatrician in nursing home channel. Representatives detail Rx influencers at nursing home at retail settings.
  - Secondary emphasis is on nursing home staff (nurses/consultant pharmacists).
  - NAM coverage of key LTC Provider personnel at national/regional level; sales force management and rep coverage of pharmacy staff at local level.

  - **2001 Plan**
    - Maintain focus on prescribers 1st trimester; initiate analysis of Rx influencers on national level 4Q00/1Q01 to identify ideal customer mix and message.
      - Regional call focus to be determined by business conditions (sales management).
    - Evaluate BDD message in neurology
    - Evaluate epilepsy message in nursing home and LTC market.
    - Target non-prescribers through educational programming and direct personal promotion at key accounts. NAM coverage to continue at national level; secondary influence through national DSM programs.
    - Evaluate market expansion (ALF, regional providers, SNF chains) opportunities 1/2Q01.
    - Evaluate potential for new neuroscience products and non-neuroscience products in the LTC/geriatric markets.

Channel Segmentation: plan

- Currently focus on physicians and staff who work within framework of nursing home facilities. Large nursing homes have historically been the outlets which house advanced Alzheimer's dementia patients. As stated earlier, presentation of psychiatric symptoms is a primary driver of patients into nursing facilities. Trends today point towards earlier treatment of dementia and its' associated behavioral disturbances. Additionally, increased operational costs have begun to limit the growth of true nursing homes.

- In order to optimize penetration, we will perform analysis and identify expansion strategy into LTC Channel growth segments:
  - Assisted Living and Home Health Care: these are the two fastest growing segments of the LTC/geriatric market. High operating costs and the prospective payment system now limit the ability of large, staffed nursing homes to function profitably.
  - We will evaluate both of these markets and implement a two-part plan to impact pharmacy providers and prescribers in these channels. Due to key LTCPP involvement in

ALF market, initial strategy will address this segment. Home Health Care and Regional Providers/Nursing Chains will be evaluated during Tri.2/01.

- Commercial Analysis plan to be completed 11/00. (See attachment "Commercial Analysis" for channel segment plans, data collection methodology, and timelines.

Product Positioning

- Launch position (1/98): 1st line treatment for manic-like agitated symptoms ("Psychobehavioral Metaphor").
  - Message: Logical, Rational, Safe, Easy to Use

- Re-position/M97-738 results (8/99): 1st line treatment for agitation in elderly dementia patients
  - Message: Safe, Effective, Easy to Use

- Current position (10/00): 1st line maintenance treatments for symptoms of agitation and aggression in elderly dementia patients.

  - This position more accurately reflects the treatment process followed by geriatric physicians and psychiatrists. Agitation manifests as numerous specific symptoms, most of which tend to respond to treatment with a mood stabilizer (Consensus Guidelines). This clarified statement positions Depakote as a first choice for maintenance treatment of agitation and aggression, regardless of specific symptomology, and allows for flexibility as an initial or adjunctive treatment. It also aligns more directly with clinical use of mood stabilizers vs. Antipsychotics (which are initiated for acute Tx and then erroneously left on as maintenance treatment).

    - Safety vs. atypical antipsychotics is the key differentiation for Depakote (lack of EPS, cholinergic AEs, hypotension). This is reinforced with the noticeable exclusion to date from regulatory action in OBRA or HCFA.

    - Antipsychotics are currently believed to be more effective based on historical use and a large database of clinical trials. Antipsychotics position themselves as first line for the "psychotic" symptoms of dementia. Through interpretation of cognitive deficit associated with Alzheimer's itself as "psychotic" symptoms, competitive companies have gained acceptance as first-line therapy.

    - Depakote has been proven effective in clinical trials (open and double-blind). *Expert Consensus Guidelines* published in 1998 also position Depakote as first or second-line (adjunct) maintenance treatment for agitation and aggression. Two pivotal publications are planned for 4Q00 and 2Q01 supporting claim.

    - M97-738 has helped us more clearly understand the dosing parameters and patient monitoring issues related to Depakote use in the nursing home. Doses in the

500-1000mg range will typically be considered maintenance doses. In clinical studies, initiation over 2-4 weeks was well tolerated by subjects.

- M99-082 will define optimal dosing for the nursing home population and will establish primary criteria for efficacy in "agitation" vs. "Mania."
- NIA Protocol will support the dosing, efficacy and safety message utilizing the sprinkle formulation, which currently accounts for 15-20% of LTC use.

Neuroscience Market Segment Analysis

Priority Segment: Agitation (Dementia)

Criteria	Comments / Analysis
Rationale for Focus	-Depakote proven effective in multiple pilot studies of agitated dementia population (clinical utility high); Two double-blind, clinical studies accepted for publication (Q400 and Q101). -Market has high clinical unmet need. There is moderate to heavy competitive activity in this market, however Depakote is positioned uniquely as a non-antipsychotic compound. Cholinesterase inhibitors are marketed for cognitive and behavioral symptoms associated with Alzheimer's disease. -Alzheimer's dementia continues to grow as population ages, placing emphasis on need for early and continued treatment of symptoms of agitation. The primary reason for skilled care facility admissions is uncontrollable behavioral disturbances (~70%).
Positioning	-Depakote is a first-line maintenance treatment for symptoms of agitation and aggression associated with Alzheimer's dementia. -It holds a unique position as the only well-documented mood stabilizer proven effective in this population; this position is supported primarily by the safety profile Depakote offers compared to current first-line therapy (antipsychotics). It also offers ease of use in this population (dosing flexibility, few drug interactions, lack of monitoring, and a broad array of formulations).
Core Messages	-Depakote is safe medication in the geriatric population. It uniquely offers no risk of EPS/movement disorders, anticholinergic effects, and relatively few drug interaction considerations. It is well tolerated in the geriatric population when dosed appropriately. -Depakote has been proven effective in significantly reducing the symptoms of agitation and aggression in patients with Alzheimer's dementia. It can be used as monotherapy or in combination with commonly prescribed psychotropic medications in the symptomatic treatment of agitated and aggressive symptoms. -Depakote therapy is easy to initiate and maintain. Formulation flexibility allows initiation at low doses (125mg tablet or sprinkle), titration to effective levels, and maintenance treatment with once daily Depakote ER.
Clinical Data Inventory	Completed ABT Studies -M97-738: Depakote in the Treatment of Mania Associated with Alzheimer's Dementia. Study initiated in 1997 with goal of supporting Depakote Mania label. Study was suspended in March of 1999 due to abnormally high incidence of somnolence and anorexia. Primary data analysis did not support efficacy in mania; secondary analysis did support a statistically significant response for Depakote treated patients in verbal and overall agitation scores. Adverse events were deemed to be the result of an overly aggressive initiation and titration schedule. Study results were presented as poster at APA 2000. Manuscript has been accepted for publication Q101 in Current Therapeutic Research. In-Progress ABT Studies -M99-082: Depakote in the Treatment of Agitation Associated with Alzheimer's Dementia. Initiated

	January 2000; double-blind, placebo controlled, randomized study of Depakote in agitation. Primary efficacy variable is reduction in agitation scores (Cohen-Mansfield Agitation Index). Goal is publication of data in tier 1 journal, with potential use as one of two labeling studies (pending FDA decision on agitation definition; Abbott-led consensus panel planned 2Q01). External Publications -Multiple pilot studies support efficacy and safety message in Alzheimer's dementia market. See clinical data inventory "Depakote in Dementia." -VALIDATE study (U. of Rochester) accepted for publication in 12/00 issue of JAAGP.
Key Strategies	-Position Depakote as first-line maintenance treatment for agitation and aggression either alone or as adjunctive therapy in uncontrolled patients; position ER appropriately. Secondary epilepsy detail. -Continue to direct sales force efforts to key LTC prescribers trimester 1 01. Support education of LTC non-prescribers (RN/Consultant Pharmacist) at territory level based on influence of local business. -Initiate LTC Commercial Analysis plan 4Q00/1Q01 to answer key questions related to target channels, customer segments, and messaging. Implement findings beginning trimester 2 01. -Support Nam and field pull-through initiatives with national pharmacy providers (DSM and other). -Increase CME programming to support product positioning. Drive dissemination of major data (M97-738 and VALIDATE) through sales force and educational efforts. -Support ongoing clinical research (NIA/Alzheimer's Agitation) and basic science (Neuroprotection) efforts. Develop and disseminate educational message for neuroprotective therapy.

Neuroscience Market Segment Analysis

Priority Segment: Geriatric Seizure Disorders

Criteria	Comments / Analysis
Rationale for Focus	-Depakote is a broad-spectrum anticonvulsant effective in controlling partial and generalized seizures. Approximately 25% of the population 65+ will experience a seizure disorder. It is estimated that between 20-40% of patients in long term care facilities receive anticonvulsant treatment. -Depakote is currently gaining acceptance as maintenance pharmacotherapy for behavioral disturbances in this population. It has a broad array of formulations including an I.V. for the emergency room setting, a sprinkle formulation, and an ER form, which provides improved tolerability and once daily dosing. In the geriatric market, the "nuisance" adverse events often mentioned in the child or adult populations do not inhibit use (particularly, teratogenicity, weight gain, and hair loss). Despite a significant adverse event profile, Dilantin continues to be heavily prescribed in the LTC market. -The LTC sales force has capacity to deliver a secondary detail to appropriate customers in long term care (Medical Directors, GP/FPs, Nurse Practitioner/RNs, Consultant Pharmacists).
Positioning	-Depakote is a proven, broad-spectrum AED ideal for first-line use in the elderly.
Core Messages	-Depakote is a clinically proven, safe treatment for all seizure types in the geriatric population. It offers few drug interactions and a lack of cognitive adverse events compared to other first-line AEDs. -Depakote is effective in both partial and generalized seizures. Additionally, it can be used for patients with co-morbid seizures and behavioral disturbances. -Depakote is easy to use in the geriatric population. It offers multiple formulations including an I.V. for use in emergency settings, a sprinkle capsule and ER tablet which offer smooth, steady blood levels, an improved adverse event profile and once daily dosing.
Clinical Data Inventory	Completed ABT Studies -Pivotal studies in the label for partial seizures (Beydoun and Willmore) support first-line use alone or as adjunctive therapy. Other supportive data available for Depacon. In-Progress ABT Studies -Depacon rapid infusion study will support PCP educational efforts. External Publications -Multiple review papers support valproate as a first-line treatment in geriatric seizure patients.
Key Strategies	-Continue to detail Depakote for geriatric seizure disorders during 1st trimester using pivotal data. Initiate commercial analysis (ATU) and MDS database projects to clearly define phenytoin/other AED use in LTC and to create specific, targeted message for customer segments. -Incorporate seizure treatment into CME plan for 2001 educational programming. -Coordinate Depacon educational efforts to impact Rx initiators.

LTC TACTICS	JAN-DEC 01											
Category	Promo Category	Promo Code	Program/Event	Objective	Channel Targeted	Dates/places (if applicable)	Total cost (if applic)	Expected reach	Total Cost in 2001	Cost/Exposure	Person Responsible/Vendor	Comments
Sales Force Support	Samples/Free Goods	6	Vouchers	Drive initial/switched MDs	LTC MDs (Retail) and Geriatric Psychs; NPs?	Q1	$20,000	500	$20,000	$40	Psych Team	Vouchers TBD per Mike/Rick
	Reminder Items	7	LTC Branding: Pens/Pads/Clipboards	MD Premiums/leave behinds	All LTC Segment Targets	Q1-4	$75,000	10000	$75,000	$8	Creative Services	Trimester 1-3 premiums
	Reprints	8	738 Reprint for dissemination	Distribute data under dissemination policies to target customers	All LTC Segment Targets	Q1-4	$20,000	10000	$20,000	$2	MPD/Creative Services	M97-738 Q1: based on publication date
		8	VAL/DATE Reprint for dissemination	Distribute data under dissemination policies to target customers	All LTC Segment Targets	Q1-4	$20,000	10000	$20,000	$2	MPD/Creative Services	VALIDATE Q7 based on publication date; roll out for Jan. Nat'l mtg
		8	M99-002 Data (Psychosis)	Data distribution by LTC	All LTC Segment Targets	Q4	$20,000	10000	$20,000	$2	MPD/Creative Services	Timeline TBD
	Other Publications	9	Educational/non-product literature	Rep Ed and motivation	Sales Force	Q1-4	$20,000	70	$20,000	$250	Training/Creative Services	Account Management; Motivation Training
	Sales Aids	10	LTC Flashcards	Patient-type support of LTC message	All LTC Segment Targets	Q1 and Q3	$10,000	10000	$10,000	$1	Creative Services	Re-work for clinical data pubs (738 and 002)
			LTC Hospital Panel	Patient-type flashcard data on display panels for in-services	Consult Phcy, RN/DON	Q2	$10,000	NA	$10,000	NA	Creative Services	Based on M/R approval
	Warchest	14	Sales Force Warchest Funding	Funding to support territory and district-level promo initiatives	LTC Targeted MDs/Consult, Phcy, RN/DON	S1 and S2 Allocations	$710,000	4500	$710,000	$157	Marketing/DMs	Based on 5000/Rep/Semester; $0 Reserve of 50K
			NAM Project Warchest Funding	Support NAM pull-through activities for key LTC Pharmacy Providers	LTC Pharmacy Providers, Key SNF Chains, VA GREC, (NAM tbd)	Q1-4 01	$300,000	TBD	$300,000	TBD	NAMs/Marketing	Final amount TBD based on funds available from non-executed CME
	Meetings	15	Sales Force	National/Other Sales Meeting Charges	Sales Force	S1 and S2	$80,000	NA	$80000	NA	Marketing	Marketing coverage of meeting costs; estimate per G.Ryan
	Launch Meetings	16	Sales Force	Marketing support	Sales Force	NA	$0	NA	$0	NA	Marketing	
	Incentives	17	Motivational/Premiums	Rep motivation	Sales Force/Management	National and Tri mtgs	$30,000	70	$30,000	NA	Creative Services	TBD w/Neuro Mktng/SOs
	Other	21	Misc. printing/shipping	Rep support	Sales Force	Trimester meetings	$30,000	NA	$30,000	NA	Marketing/Creative	Misc. charges
	Sales Training		ISTC Preceptorships	LTC training	Sales Force	TBD, based on ISTC schedule	$5,000	TBD	$5,000	TBD	Sales Training Manager	Split nursing home preceptorship w/ Training
			ASTC Preceptorship w/Alan Siegal	Advanced LTC training for expansion reps	Sales Force	April and May/June	$22,500	30	$22,500	$750	Marketing/Lamy Warfield	Committed to 2 classes; size and final dates TBD
			Training Materials	Expand LTC/Dementia background/over initiative	Sales Force	Q2	$15,000	NA	$11,000	NA	Sales Training	ISTC Materials/Rep Ed (topllines/ background etc.)
	Field Advisory Board		Post Jan meetings feedback conf calls	Obtain field feedback on new promo materials and sales training- usefulness, effectiveness, what else needed, etc	NA	Feb/March	$0	NA	$0	NA	Marketing, sales training, agency	
Peer/Opinion Leader	Related Speaker Costs	31	Misc. Speaker Costs	Cover ad hoc requests for OL speaker fees etc.	LTC Advisory Board and Opinion Leaders	Q1-4	$20,000	NA	$20,000	NA	Marketing/NAM/Managers	Covers ad hoc requests
	Conventions	32	AAGP	Increase awareness, educate	Geriatric Psych Assoc.	Feb; San Francisco	$15,000	1500	$25,000	$15	Marketing/Convention Services	Exhibit/Rep costs
			AMDA	Increase awareness, educate on Depakote	American Medical Directors Assoc.	March; Atlanta	$21,800	2000	$21,800	$11		
			AGS	Increase awareness, educate on Depakote	American Geriatrics; Geriatrician and LTC MDs, Consult. Phcy, RN	May; Chicago	$34,000	1500	$34,000	$23		
			US Geriatric/LTC	Increase awareness, educate on Depakote	LTC MDs (primary), Consult Phcy and RN (secondary)	June; San Diego	$27,000	1800	$27,000	$15		
			AMDA Summer Conf.	Increase awareness, educate on Depakote	AMDA members	June; TBD	$2,000	200	$2,000	$10	Sales Manager in host city	
			NADONNA	Increase awareness, educate on Depakote	Directors of LTC Nursing	August; TBD	$4,000	350	$9,000	$26		
			US Gerontological NP	Increase awareness, educate on Depakote	Geriatric Nurse Pract.	Sept; TBD	$1,000	300	$1,000	$3	Sales Manager in host city	
			ASCP Summer Conf.	Increase awareness, educate on Depakote	Consultant LTC Pharmacists	May; TBD	$10,000	400	$10,000	$25		
			ASCP Fall	Increase awareness, educate on Depakote	Consultant LTC Pharmacists	Nov; TBD	$20,000	600	$20,000	$33		
			APNA	Increase awareness, educate on Depakote	Gen Psych/Psych RNs	October; TBD	$7,500	400	$7,500	$19		
			AAPA symposia	Increase awareness; educate on Depakote	Psychiatry/Geriatric Psych	May; TBD	$10,000	4000	$10,000	$3	Marketing	Split cost w/Psych; send LTC reps?
	Symposia	34	AAGP	Develop ALZ/Neuroprotection Message	Geriatric Psychiatrists	Feb; San Francisco	$135,000	400	$131,000	$300	Marketing/ABcomm	F/U w/AAGP and CME Followup programs targeting LTC
			AMDA	Develop BDD/Agitation Message	Medical Directors	March; Atlanta	$85,000	400	$85,000	$225	Marketing/ABcomm	Followup content w/LTC target CME and publications
			APA	Develop Mood/Neuroprotection message w/Psychs	Psychiatrists/Geriatric Psychs	May; New Orleans	$110	1000	$110,000	$110	Split w/Psych team 50/50; Mktng/ Abcomm	Followup content w/target CME and publications
			AGS	Role of Anticonvulsants in Geriatrics	Geriatricians/GP/FP, Consult Phcy and RN (secondary)	May; Chicago	$110,000	500	$110,000	$190	Mktng/ABcomm	Followup w/Lavery/Neuro for content and residuals
			US Geriatric/LTC Congress	Mood Stabilizers in BDD	Geriatricians/LTC MDs, Consult Phcy, RN	June; San Diego	$95,000	800	$95,000	$120	Marketing/CME Inc.	Build CME component as f/u
			ASCP	BDD/Consultant Message	Consultant Psycho	Nov; Chicago	$50,000	300	$50,000	$118	Marketing/TBD	In conjunction w/ASCP CME program?
			AMDA Summer Conf	BDD/Medical Director msg	Medical Directors	TBD	$20,000	200	$20,000	$100	Mktng/TBD	Irene Angelos' content?

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Attachment 7 to Agreed Statement of Facts
Abbott

LTC TACTICS JAN-DEC 01

Category	Promo Category	Promo Code	Program/Event	Objective	Channel Targeted	Dates/places (if applicable)	Total cost (if applic)	Expected reach	Total Cost in 2001	Cost/Exposure	Person Responsible/Vendor	Comments
Sales Force Support	Samples/Free Goods	6	Vouchers	Drive Initial trial/retail MDs	LTC MDs (Retail) and Geriatric Psychs; NPs?	Q1	$20,000	500	$20,000	$40	Psych Team	Vouchers TBD per Mike/Rick
	Faculty Advisory Boards	35	District Consultants: Q1	LTC Peer Influence	LTC MDs/Prescribers; some high potent	Jan-Mar 2001	$420,000	350	$420,000	$1,200	Marketing/TBD	Q1 only; Q2 Masters starts
			Psych Advisory	LTC involvement w/Natl psych	LTC National Advisors	Jan; Beaver Creek	$15,000	2	$15,000	$7,500	Marketing/HALO	Only 2 LTC Advisors
			Sale Force National Meeting	LTC MD Presentation/Training	LTC Sales Force	Jan; New Orleans	$5,000	75	$5,000	NA	Marketing/RTS	Confirm Natl agenda; speaker
			LTC National Advisory	LTC faculty development	Geriatric Opinion Leaders	2Q01; location TBD	$40,000	15	$40,000	$2,500	Marketing/TBD	LTC Faculty development
	Fellowships	38	LTC CME Min Fellowships	LTC Message Development	LTC MDs/NPs/Gen Psychs	2/3Q01	$180,000	150	$180,000	$1,200	Marketing/ABcomm	TBD based on Masters?
	Seeding Trials (NML)	37	NML LTC Projects	Support message/clinical	LTC MDs/Phcy Providers	Q1-4'2001	$150,000	NA	$150,000	NA	Sickler/NMLs	Schedule projects w/meetings
Peer Opinion	Grants	39	Abcomm Grant Process	LTC Support of CME/Non-CME programming	Physicians/LTC Targets	Q1-Q42001	$420,000	NA	$420,000	NA	Linda Saari/ABcomm	$Amount TBD based on Masters Allocation per district
			CME Grant/Neuroscience Masters Program	Support LTC Portion of 2001 Comprehensive CME program	LTC: Gs/Psych, Medical Dir, RN/Phcy	Trimester 2-3, 01	$400,000	1000	$400,000	$400	Marketing/Vendor TBD; see proposals re: specifics	Bid process ongoing; SPMs manage channel content; SEE incremental funds to make up 2nd part of LTC portion
			UCLA Foundation	Support Alzheimer's Clinical Program	UCLA Alz/Psych Dept	May 2001; LA	$10,000	TBD	$10,000	NA	Roger Aumann/Gary Small MD	Support for UCLA Alz Charity
			Yale Geriatric Psych Program	Support Craig Nelson	Geriatric Psychs / LTC MDs	2Q01	$5,000	TBD	$5,000	NA	Marketing/Contact Larry Warfield	Supported 99/00; call Craig re: 01 plans
			USC Outreach Program	Support Lon Schneider	Geriatric Psychs	2Q01	$5,000	TBD	$5,000	NA	Marketing/contact Roger Aumann and Cedric C	Supported 00; call Lon re: 01
			Craig Nelson; Am Society of Neuropsychopharmacology	Grant for publication by Nelson, Sweam, TBD targeting IA	Psych/Gen Psychs	1Q01	$40,000	TBD	$40,000	TBD	Marketing/Craig Nelson	Committed support for 01 pub in 00; call re: content
			ANPA National Meeting	New Psych/LTC Messages for Neuropsychiatry airports	Neurops advertising	Jan; D1	$5,000	TBD	$5,000	TBD	Marketing/Tom McAllister	Call Tom to make payment; issues 10K/ spat w/psych
			National Conf. Gerontological Nurse Practitioners	Support CME/Natl Mtg	LTC NPs	Sept 2001; TBD	$5,000	500	$5,000	$10	Mktg; DM at Natl Mtg site	Contact Jodie Arnzen-Lasca
Direct Marketing	Direct Mail etc.	10	Member list acquisition	Cover yearly list requests	LTC Target Organizations	Q1-4/01	$10,000	NA	$10,000	NA	Commercial Analysis	List acquisition fees depend on org; contact Comm.Analysis
Market Research	Misc. Studies	73										
			LTC ATU (message development)	Identify key messages by LTC segment type	Physicians, Pharmacy Provider, RN	Initiate Q1 01	$40,000	NA	$40000	NA	Marketing/Jeff Borman	Need to frame questions and objectives
			Rx "Influencer" Targeting Analysis	Create channel/target segmentation	All LTC (MD/RN/Phcy)	Initiate Q101	$100,000	NA	$100,000		Marketing/Jeff Borman	Goal: call plan and targeting (value/LTC Target type)
			Omnicare MDS Database	Define LTC key Dx and Tx patterns; Deplete base	LTC Pharmacy Providers and Rx Influencers	Initiate Q400; queries will continue 1Q01	$25,000	NA	$25,000		Dave Molnar/Jeff Borman	LTC Business overview based on p. database (actuals)
			LTC Channel Segmentation	Segment potential/plan (ALF, Home Health, Retail)	LTC	Initiate Trimester 201	$30,000	NA	$30,000	NA	Marketing/Jeff Borman	Initial ALF/Home Health analysis and recs

LTC TACTICS JAN-DEC 01

Category	Promo Category	Promo Code	Program/Event	Objective	Channel Targeted	Dates/pieces (if applicable)	Total cost (if applic)	Expected reach	Total Cost in 2001	Cost/Exposure	Person Responsible/Vendor	Comments
Below Fcns Support	Samples/Free Goods	#	Vouchers	Drive initial/retrial HCPs	LTC HCPs (Retail) and Geriatric Psych: NPs	Q1	$20,000	600	$20,000	$40	Payer Team	Vouchers TBD per Mike/Rick
						Target main study publication in JanCQ; continue with additional analyses and papers						
Public Relations	Public Relations		PR Support: Tip, VALDATE data; Neuroprotection	Target key geriatric data	LTC Professionals; consumer	Q1Q1	approx $ 50000	TBD	$50,000	TBD	Marketing/PR in house	Time released re: pub data (see Neuroprotection present times)

Non Tactical Costs Agency fees ALL

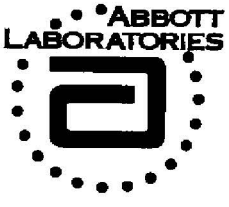
Budget Outline 11/00: $4,200,000

LTC 2001 Planning T&E

January Trimester 1	May Trimester 2	August Trimester 3
In Development **Commercial Analysis** LTC Market ATU Rx "Influencer"Analysis (Optimal Detailing Anaylsis) LTC/SR Overlap analysis REDACTED MDS Database Analysis LTC Consultant Surveys Neurology • Geriatric Epilepsy Analysis (Market Potential/Message) • BDD Neurology Potential **Sales Reporting** Retail Sales Impact of LTC Sales Force LTCPP Contract Impact Tracking ER Sales Tracking **Tactics** CME Video/Monograph: BDD: Role of Mood Stabilizers Comprehensive CME Package ("Masters") Training • Advanced LTC Preceptorships: REDACTED MD LTC Pilot Studies (NML) "Progress Notes": Psychopharm publication	**In Development** **Comercial Analysis** Rx "Influencer" Analysis (Optimal Detailing Analysis) Market Expansion: ALF Message • ALF Account Management: Purchasing/Provider (NAMs) • Rx Influencer Overlap (SNF/ALF) Regional Account Management (Nursing Home Chains/Providers) LTC Sales Force Expansion ROI **Tactics** NAM Provider pull-through programs SNF/ALF Promo Materials (premiums) Comprehensive CME Package: BDD/Epilepsy content LTC Pilot Studies (NML) Impulsive Aggression (002) Data	**In Development** **Commercial Analysis** Program ROI Analysis Market Expansion • Home Healthcare Account Management • Rx Influencer Overlap (SNF/ALF: HHC) **Tactics** Comprehensive CME Package components LTC Pilot Studies Trimester 1 02 Promo
Implementation **Commercial Analysis** Q400 LTC Message Recall Q400 LTC Consultant Surveys LTC Sales Force Optimization Analysis Sales Force 2001 Reports (revised) **Incentive Plan** Revised LTC Incentive Plan: DDD, Retail, Impact Goals **Tactics** LTC Consultant Programs BDD Supporting Articles (738/VALIDATE) ER Geriatric Data AAGP: CME Symposia "Neuroprotection" AMDA: CME Symposia "BDD: Role of Mood Stabilizers" CME Monograph: "Treating Agitation/Aggression" LTC "branded" premiums **Training** ISTC Preceptorships ISTC LTC Training Program (revised)	**Implementation** **Commercial Analysis** LTC Market ATU Rx "Influencer" Analysis (part 1: District/geographical targeting) REDACTED MDS Database Analysis LTC Consultant Surveys Neurology • Geriatric Epilepsy Targeting/Message • BDD in Neurology **Tactics** Comprehensive CME Package ("Masters") • Regional CME Meetings • CME Video/Monograph BDD Supporting Articles (738/VALIDATE) APA CME Symposia: "Neuroprotection" AGS CME Symposia: "Anticonvulsants in LTC" US Geriatric/LTC Congress CME Symposia: "New Perspectives in Managing BDD" LTC Advisory Meeting LTC "branded" premiums LTC Pilot Data (NML) "Progress Notes": Am. Society of Psychopharm national publication Training: Advanced Preceptorships (April and May w/REDACTED, MD)	**Implementation** **Commercial Analysis** Rx Influencer Analysis (part 2) Market Expansion • SNF/ALF: NAM/Rep Targeting • Regional Account Management **Tactics** Comprehensive CME Package ("Masters") • CME Monograph • Teleconferences CME Symposia: NADONNA CME Symposia: ASCP LTC Pilot Data Impulsive Aggression (002) Data

Dementia
Backgrounder

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Introduction

In broad terms, ***dementia*** refers to cognitive and/or psychological deterioration associated with organic brain dysfunction. Dementia is more prevalent in the elderly, and the prevalence of dementia is increasing in the United States and the world as the population of individuals born after World War II (often referred to as the "baby-boomers") ages. This increase has far-reaching repercussions on health care and its delivery worldwide.

This backgrounder will define the types of dementia and will describe their impact on both the individuals who suffer from it and their caregivers. While the etiology of dementia remains to be clearly defined, prevailing theories of its pathophysiology will be related.

Recognition of dementia is not always straightforward; the disease is often insidious and differential diagnosis is complex. Current evaluative methods and diagnostic criteria will be described in accordance with current clinical standards of practice. Nonpharmacologic and pharmacologic treatment will be explained, along with the role of the caregiver in therapy.

Dementia Defined

Dementia refers to a broad clinical syndrome that involves deterioration of intellectual abilities due to impairment of the CNS.

Dementia refers to a broad clinical syndrome that involves deterioration of intellectual and cognitive abilities.[1] Pathogenesis is due to impairment of, or damage to, the central nervous system (the brain), but the exact dysfunction is not always easily defined.

Cognitive abilities are those that encompass the "knowledge" of events that continually occur during consciousness. When cognitive abilities are impaired there is diminished perception, recognition, idea or thought conception, judging, sensing, reasoning, and imagining. Memory of events, both recent and long-term, is impaired, and the ability to think abstractly and make appropriate judgments declines. Mental deterioration often is progressive, eventually leading to alterations in personality and diminished capacity to perform the most basic activities of daily living (ADL). Independent living may become unsafe for the patient, his or her environment, and caregivers. Depending on the individual patient's support system, institutionalization may be inevitable.

Primary dementias are those for which no other identifiable disease or condition can be found as the cause of the syndrome.

Secondary dementias are those for which a pathological process has been found as the cause, eg, infections, trauma, toxic/metabolic disorders, circulatory disorders, brain tumors, or neurological diseases or conditions.

Etiology[1]

Dementia is characterized as an organic brain syndrome. *Organic brain syndrome* is a general term used to describe conditions of impaired mental function that are associated with diseases of the central nervous system. This contrasts with the majority of psychiatric syndromes which are called *functional* and have no physical basis. Dementias are classified into 2 types; secondary dementias occur as part of some other pathological process, and primary dementias are those dementias that the major abnormality is the dementia.[1]

Table 1.
Classification of Dementias

Primary Dementias
Alzheimer's disease
Pre-senile dementia (before age 65)
Senile dementia (after age 65)
Pick's disease

Secondary Dementias
Infections
Chronic granulomatous meningitis (tuberculous, fungal)
Advanced syphilis
Creutzfeldt-Jakob disease (transmissible virus dementia)
Acquired immunodeficiency syndrome (AIDS)
Trauma, eg, subdural hematoma
Toxic and metabolic disorders
Pernicious anemia
Folic acid deficiency
Hypothyroidism
Bromide poisoning
"Alcohol" (withdrawal, Vitamin B1 deficiency)
Circulatory disorders
Multi-infarct dementia
Cerebral ischemia leading to brain anoxia
Brain tumors
Other neurological diseases
Huntington's chorea
Parkinson's disease
Parkinson-dementia complex
Progressive supranuclear palsy
Multiple sclerosis
Cerebellar degeneration
Normal pressure hydrocephalus

Seltzer B. Organic mental disorders. In: Nicholi AM, ed. *The New Harvard Guide to Psychiatry*. Cambridge, Mass: Belknap Press;1988;358-383.

Prevalence

Alzheimer's disease represents 50% to 75% of dementia cases. Approximately 4 million Americans suffer from AD.

While prevalence data for dementia vary depending on the definitions and criteria used, generally accepted data according to age are shown in Table 2.[2] Alzheimer's disease is the most common type of dementia; vascular dementia is probably the next most common, but its prevalence is unknown.[2]

Vascular dementia is probably the next most common, but its prevalence is unknown.

Table 2.
Prevalence of Dementia

Age Group	Percent
Over 65 years	5% to 8%
Over 75 years	15% to 20%
Over 85 years	25%

American Psychiatric Association. Practice Guideline for the treatment of patients with Alzheimer's disease and other dementias of late life. *Am J Psychiatry* 1997;154(suppl 5):1-39.

Alzheimer's Disease

Alzheimer's disease (AD) is the most common of the dementias, accounting for 50% to 75% of all dementias.[2] Approximately 4 million people in the United States currently suffer from Alzheimer's disease.[3] AD can occur early, in the 40s and 50s, but typically presents after the age of 60.[2] AD also may be referred to as pre-senile or senile dementia, depending on whether it occurs before or after the age of 65.[1]

Typical initial presentation of AD includes memory loss of recent events, and confusion and disorientation, eventually leading to deterioration in general health that greatly increases morbidity and mortality. Average survival is 8 to 10 years after diagnosis.

The course of AD is progressive.[2] Disease onset and course typically are gradual. Typical initial presentation includes memory loss of recent events, and confusion and disorientation, eventually leading to deterioration in general health that greatly increases morbidity and mortality. Average survival is 8 to 10 years after diagnosis.[4] Decline is progressive with occasional periods of stability that can last as long as a year or more.[2]

Multi-infarct (Vascular) Dementia

MID:
Multi-infarct dementia
Vascular dementia

Multi-infarct dementia (MID), also called vascular dementia, stems from one or more episodes of cerebral ischemia, which cause brain damage that leads to dementia. Risk factors for MID include advanced age plus those for general stroke and other cardiovascular disease (ie, cigarette smoking, high blood pressure). MID typically begins in the same ways as Alzheimer's disease, but MID can have an abrupt onset and a more fluctuating course.[4] MID accounts for approximately 10% to 20% of dementia cases.[4] AD and strokes often coexist.[2]

Risk Factors

The major risk factors for dementia include advanced age, family history, and presence of the apolipoprotein E gene.

The major risk factors for dementia include advanced age, family history, and presence of the apolipoprotein E gene.[5]

Advanced Age

From the age of 65 to 85, the prevalence of AD doubles approximately every 5 years.[5]

Family History

Individuals with first-degree relatives who have suffered from AD have a four times greater risk than others in the general population at any age.[5]

Apolipoprotein E Gene

The presence of the apolipoprotein E (APOE) gene has been found to correlate with both the prevalence and age of onset of AD, but not its clinical outcome.[5] The APOE gene is not found in all patients with dementia and all patients with dementia do not have APOE; therefore, it is important to recognize that the presence of APOE is a risk factor and not a diagnostic test.[5]

Other Risk Factors

Other risk factors for dementia that have been suggested, but not proven, include: history of head trauma; episodic depression or personality disorder; and mutations on chromosomes 21 or 14.[5] Differences of opinion exist about socioeconomic variables as risk factors for dementia. It has been suggested in one study that gender (females), limited education, and unskilled occupations were at greater risk for vascular dementia, and to a lesser degree AD, but this is not conclusive.[5]

Diagnosis

There are no definitive clinical or laboratory tests to diagnose dementia, but with a careful clinical workup skilled clinicians can make an accurate diagnosis in 90% of cases.

There are no definitive clinical or laboratory tests that can be used to diagnose dementia, but with a careful clinical workup skilled clinicians can make an accurate diagnosis in 90% of cases.[3] A diagnosis of dementia is made by combining patient history, family and patient interviews, cognitive screening, and a neuropsychologic examination (Table 3). The clinical challenge is to correctly distinguish cognitive changes due to normal aging from those due to dementia or another disorder, such as depression (Table 4).[6,7,8]

Table 3.
Diagnostic Evaluation for Dementia

Assessment	Information Sought
History	
• Family history	History of Alzheimer's disease, Parkinson's disease
• Caregiver interview/evaluation of patient's previous and current cognitive abilities	**Aphasia** • Has difficulty finding correct word • Substitutes incorrect words • Breaks off in midsentence; loses train of thought • Stutters/repeats words over and over **Apraxia** • Difficulty in dressing or bathing alone • Difficulty in using a brush or comb • Difficulty in self-feeding **Agnosia** • Loses ability to recognize people, places, things **Executive dysfunction** • Difficulty in understanding activities around him/her • Difficulty in using familiar tools, such as appliances, eating utensils **Changes in behavior or personality** • Passivity, apathy • Aggression, agitation, disinhibition

Table 3 continues on the next page

Table 3. (continued)
Diagnostic Evaluation for Dementia

Assessment	Information Sought
History (continued)	
• Review of medications, substance abuse	Use of antidepressants, sedatives/hypnotics, anticonvulsants, anti-parkinsonian drugs, antihypertensive agents, antihistamines, narcotics, past and present alcohol use
• Physical	Onset of symptoms, progression of symptoms, duration of symptoms, other acute or chronic medical disease, known neurological and psychological disorders, substance abuse, exposure to environmental toxins
Laboratory panel • CBC, urinalysis, electrolytes, calcium, urea, creatinine, hepatic enzymes, thyroid hormones, B_{12}, serology for syphilis, HIV, metabolic profile	Detection of anemia, diabetes, renal disease, liver disease, thyroid disease, vitamin deficiency, syphilis, infection, AIDS, metabolic disorder, blood disorder, endocrine disease, etc.
• Genetic testing (apolipoprotein E [APOE]) (Not a diagnostic test)	Genetic predisposition
Neurological imaging and other tests • Computed tomography (CT) • Magnetic resonance imaging (MRI) • Lumbar puncture • Electroencephalogram (EEG) • Single-photon emission computed tomography (SPECT) • Positron emission tomography (PET)	Rule out brain tumors, brain abscess, stroke, hematomas, arteriovenous malformations, hydrocephalus
Neuropsychological testing • Attention and concentration • Orientation to time, person, place, situation, and general insight • Intellect • Learning and memory • Language • Visuospatial function • Executive functioning: abstract ideation, creativity, multitasking, and behavioral flexibility • Bilateral sensorimotor function • Mood and personality	Degree and types of impairment, if any

Steffens DC, Morgenlander JC. Initial evaluation of suspected dementia. *Postgrad Med* 1999;106(5):73-83.
Daly MP. Diagnosis and management of Alzheimer's disease. *J Am Board Fam Pract* 1999;12(5):375-385.

Table 4.

Approximate Degree of Cognitive Impairment Associated with Aging, Alzheimer's Disease, and Depression

Cognitive Feature	Normal Aging	Early Alzheimer's Disease	Depression
Attention			
Selective	+	++	+++
Nonselective	++	+++	+++
Learning and Memory			
Learning	+	++	+++
Retrieval	++	++	+++
Immediate memory	N	N	+++
Recall	+	++++	+++
Recognition	N	++	N
Working memory	+	+++	+++
Intellect			
Nonverbal IQ	++	+++	+
Verbal IQ	N	N	N
Language			
Naming	N	+	N
Fluency	N	+	++
Comprehension	N	N	N
Calculation	N	++	N
Visuospatial ability			
Perception	+	+	N
Spatial judgment	N	++	N
Praxis	N	++	N

N = normal
+ = mild impairment
++ = moderate impairment
+++ = severe impairment
++++ = very severe impairment

Welsh-Bohner KA, Morgenlander JC. Determining the cause of memory loss in the elderly. *Postgrad Med* 1999;106(5):99-119.

Diagnosis

After history and physical examination, certain findings should raise suspicion that dementia is not caused by Alzheimer's disease (Table 5).

Table 5.
Findings that Exclude Diagnosis of Alzheimer's Disease

Findings Obtained by History-Taking	Possible Explanation
Sudden onset	Systemic disease, drug adverse effects, cerebrovascular disease, infection, tumor
No memory deficit	Psychiatric disorder, cerebrovascular disease, early frontal lobe dementia
Lack of progressive decline	Stroke, amnesic syndrome
Depression	Pseudodementia secondary to dementia
Personality change with minor memory deficits	Frontal lobe dementia
Seizures	Stroke, cerebral lesions (seizures are uncommon in the early stages of Alzheimer's)
Findings Obtained by Physical Examination	**Possible Explanation**
Hemiparesis (inability to move on one side of the body)	Cerebrovascular disease, lesion
Sensory impairment	Cerebrovascular disease or peripheral vascular disease
Memory loss without other deficits	Cerebrovascular disease, Wernicke's encephalopathy
Abnormal motor movements	Huntington's disease, Creutzfeldt-Jakob disease, Parkinson's disease
Early gait disturbance	Parkinsonian disease or normal pressure hydrocephalus (especially if incontinence also present)
Cerebral abnormalities	Spinocerebellar degeneration (usually genetic)

Burke JR, Morgenlander JC. Update on Alzheimer's disease. *Postgrad Med* 1999;106(5):86-96.

Memory impairment and other symptoms of dementia also can be symptomatic of psychiatric diseases.

Furthermore, since memory impairment and other symptoms of dementia can also be symptomatic of other psychiatric diseases, such as delirium, amnesic disorders, mental retardation, schizophrenia, and major depressive disorder, the diagnosis of dementia must meet specific DSM-IV criteria (Table 6).

Table 6.
DSM-IV Diagnostic Criteria for Alzheimer's and Vascular Dementia

Alzheimer's Dementia

To be given a diagnosis of ***Alzheimer's Dementia***, the patient must have:

A. Multiple cognitive deficits, as follows:
   1. Memory impairment
      – Impaired ability to learn new information or to recall previously learned information
   2. One (or more) of the following cognitive disturbances:
      a. Aphasia (language disturbance)
      b. Apraxia (impaired ability to perform motor activities despite intact motor function)
      c. Agnosia (failure to recognize or identify objects despite intact sensory function)
      d. Disturbance in executive functioning (ie, planning, organizing, sequencing, abstracting)

B. The cognitive deficits must each cause severe impairment in social or occupational functioning and represent a major decline from a previous level of functioning.

C. Onset of the disease must have been gradual, with progressively worsening cognitive decline.

D. The cognitive deficits in criteria A1 and A2 must not be due to any of the following:
   1. Other central nervous system conditions that cause progressive deficits in memory and cognition (for example, cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor).
   2. Systemic conditions known to cause dementia (for example, hypothyroidism, vitamin B_{12} and folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV [human immunodeficiency virus] infection).

E. The deficits do not occur exclusively during the course of a delirium.

The disturbance is not better accounted for by another axis I disorder (eg, major depressive disorder, schizophrenia).

Vascular Dementia

To be given a diagnosis of ***Vascular Dementia***, the patient must have fulfilled Criteria A & B and E above ***and*** there must be evidence of:

- Focal neurological signs and symptoms (eg, exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity), or
- Laboratory evidence indicative of cerebrovascular disease that is judged to be etiologically related to the disturbance (eg, multiple infarctions involving cortex and underlying white matter).

AD or vascular dementia may be subtyped according to prominent associated symptoms:

- With Delirium
- With Delusions
- With Depressed Mood
- Uncomplicated
- With Behavioral Disturbance

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: (DSM-IV)*, Washington DC; American Psychiatric Press, 1994:(4)142-146

Interdisciplinary and Multidisciplinary Team

Because of the insidious nature of dementia, the primary care physician (PCP) is often the first clinician to perform the differential diagnosis for dementia. When patients or family members describe problems of cognitive impairment, the PCP must consider dementia as a possibility and begin clinical assessment, usually with initial interviews with the patient and his or her family, and using some type of diagnostic screening tool and/or cognitive rating scale (Table 7). As evaluations reveal positive findings for dementia, and/or cognitive deterioration accelerates, the PCP will eventually refer the patient to a neurologist or psychiatrist for a thorough neuropsychologic evaluation (Figure 1) and involve other professionals in the treatment of the patient (Table 8).

Evaluation is meant not only to determine if the dementia is primary or secondary, but also to determine the level of cognitive impairment.

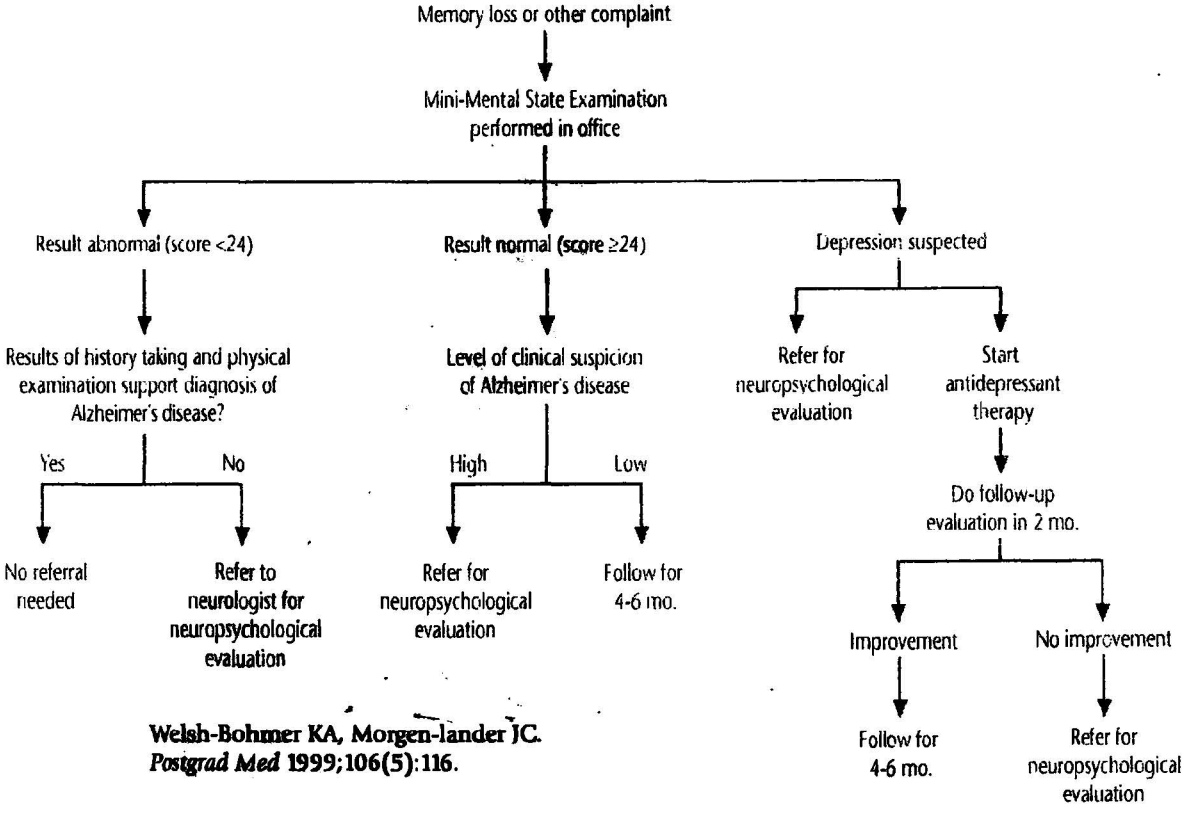
Table 7.
Diagnostic Tools for Dementia [5,6]

- DSM-IV criteria
- NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association) criteria
- World Health Organization Diagnostic Criteria for Vascular Dementia (International Classification of Diseases, 10th edition)
- Mini Mental State Examination (MMSE)
- Geriatric Depression Scale

Table 8.
Interdisciplinary and Multidisciplinary Team

Primary care physician
Geriatrician
Neurologist
Neuropsychologist or psychiatrist
Nurse
Social worker
Physical or occupational therapist

A thorough evaluation as delineated in Table 3 is important, not only to determine if the dementia is primary or secondary to another treatment or disease that may be correctable, but also to determine the level of cognitive impairment.



Welsh-Bohmer KA, Morgen-lander JC.
***Postgrad Med* 1999;106(5):116.**

Figure 1.
Decision Tree for Dementia Evaluation and Referral

Staging of Dementia

Questionable
Mild
Moderate
Severe
Profound
Terminal

Staging of Dementia[2]

Dementia is typically categorized in stages according to the level of functional impairment, ie, the ability to perform certain functions compared to the patient's previous level of functioning.

The following categories may be used to describe the level of functional impairment, and the same categories may be used to describe the degree of severity of any dementia.

Questionable

- No definite functional impairment
- Dementia is not diagnosed
  - May or may not progress to dementia
- Re-evaluation at appropriate intervals

Mild

- Definite but mild impairment, eg, difficulties with balancing checkbook, following complicated recipes, or medication regimens

Moderate

- Impairment causes difficulties with functional tasks, eg, simple meal preparation, household cleanup, raking leaves and other yard work, may require assistance with self-care (reminding to use bathroom, shaving, fastening clothing).

Severe

- Impairment necessitates help with many aspects of self-care and activities of daily living (ADL), eg, eating, grooming, bathing, and using the toilet.

Profound

- Patients may become oblivious to their surroundings and are almost totally dependent on caregivers.

Terminal

- Impairment necessitates continual care. Patients are generally bed bound, may be susceptible to accidents and infectious diseases, which often prove fatal.

Presentation of Specific Dementias[2]

While the various dementias have major commonalities, there are some differences in the patterns of presentation.

Specific Dementia Presentations

Alzheimer's dementia
Vascular dementia
Dementia due to
Parkinson's disease
Dementia due to
Lewy Body disease
Dementia due to
frontal lobe dementia
(Pick's disease)
Other progressive dementias
Dementia due to other causes

Alzheimer's Dementia

- Gradual onset and progression
- Usually begins with impairment of recent memory. Impairment in the following areas follows over several years:
  - Aphasia (impaired language/speaking)
    - In normal conversation, does the patient: have difficulty finding the right word to use; substitute an incorrect word, eg, calling a table a chair; break off in midsentence and lose his or her train of thought; stutter or repeat the same word over and over?[8]
  - Apraxia (impaired movement despite intact motor function)
    - Does the patient have any difficulty with dressing or bathing, or using a brush or comb, or using feeding utensils?[8]
  - Agnosia (impaired recognition/identification of objects despite intact sensory function)
    - Does the patient have difficulty recognizing familiar people or places, objects or personal items?[8]
- Impaired "executive" functioning also present in early phases, eg, inability to plan, organize, sequence, think abstractly
- Personality changes or increased irritability may occur in early stages
- Psychotic behavior is common in middle and late stages
- Incontinence, and gait and motor impairment typically lead to patient becoming totally bedridden

- Seizures and myoclonus may occur in advanced stages
- May be subtyped by predominant features: with delirium, with delusions, with depressed mood, or uncomplicated[16]

Vascular Dementia

- Caused by one or more episodes of cerebral ischemia or stroke
- Abrupt onset may occur at any age, but less common after age 75
- *Stepwise course as opposed to gradual progressive decline of AD*
- Cognitive deficits depend on what area of the brain was damaged due to ischemia
- Imaging studies may find multiple vascular lesions in the cerebral cortex and subcortical structures
- As with AD, may be subtyped as With Delirium, With Delusions, With Depressed Mood, Uncomplicated, and With Behavioral Disturbance[16]

Dementia Due to Parkinson's Disease

- Parkinson's disease
  - Progressive neurological disease typified by tremor, rigidity, bradykinesia (slow movement), postural instability
  - Onset middle to late in life
- 20% to 60% of Parkinson's disease cases will be accompanied by dementia
- Dementia usually occurs late in the course of Parkinson's disease

Dementia Due to Lewy Body Disease

- Clinically similar to Alzheimer's disease
  - Visual hallucinations and parkinsonian features occur earlier and are more prominent than in AD
- More rapid evolution than AD
- Biopsy of cerebral cortex demonstrates Lewy inclusion bodies
- May account for 7% to 26% of dementia cases
- Patients are very sensitive to the ***extrapyramidal*** (pronounced extra-pyr-RAM-ih-dahl) ***effects*** of antipsychotic medications.

Dementia Due to Frontal Lobe Dementias (eg, Pick's Disease)

- Difficult to diagnose and differentiate from atypical AD
- Brain imaging shows atrophy of frontal and/or temporal lobes
- Diagnosis is confirmed at autopsy by finding characteristic Pick inclusion bodies in the brain
- Onset usually between age 50 and 60, but can occur in older population
- Progressive course that is more rapid than AD
- Early stages
  - Personality changes
  - Executive function impairment
  - Deterioration of social skills
  - Emotional blunting
  - Lack of behavioral inhibition
  - Language abnormalities
- Follow later in the course:
  - Memory deficits, apraxia, and other symptoms of dementia
  - Primitive reflexes (eg, snout, suck, grasp)
  - Either apathy or extreme agitation

Other Progressive Dementias

- Huntington's disease
  - Hereditary neurological disease that causes motor, behavioral, and cognitive deterioration
- Creutzfeldt-Jakob disease
  - Rapidly progressive disease of the brain caused by a slow virus or prior infection

Dementia Due to Other Causes

- Structural lesions
  - Brain tumor or subdural hematoma, normal pressure hydrocephalus (NPH)
- Head trauma
- Endocrine disorders
  - Hypothyroidism, hypercalcemia, hypoglycemia
- Nutritional deficiencies
  - Thiamin, niacin, vitamin B_{12}
- Infectious diseases
  - HIV, neurosyphilis, *Cryptococcal meningitis*
- Effects of medication
  - Benzodiazepines, beta-blockers, diphenhydramine (anti-allergy medication)
- Toxic effects due to long-term substance abuse, especially alcohol
- Derangements of renal and hepatic function
- Neurological conditions
  - Multiple sclerosis

Options to Facilitate Care

Once the diagnosis of dementia is made, treatment must begin as soon as possible. Treatment decisions are made in accordance with the stage of the dementia, symptoms present, and any other comorbid medical or psychiatric diseases and conditions. The goals of treatment[7] are interrelated and are to:

1) enhance the current functioning level;

2) maintain quality of life as long as possible; and

3) preserve independence as long as possible.

The medical, psychological, and social needs of the patient and caregivers must be part of the short-term and long-term treatment plan. A multidisciplinary team is necessary to delay and/or prevent the onset of comorbid medical conditions in the patient, to help caregivers and family members cope with the disease and its repercussions, and to help in short-term and long-term treatment planning.

Care Environment

The success of treatment, the presenting symptoms, and the stage of the illness determine whether the patient can be managed in a home setting or whether institutionalization is necessary. In addition, the presence of a caregiver and his or her ability to manage the patient must be considered.

Home Management

Home management requires a caregiver. In very early stages, part-time care and surveillance may be sufficient if steps are taken to simplify the home environment and make it safer. Several regional or national support organizations are now available to assist caregivers in their care of patients with dementia: Alzheimer's Association; Alzheimer's

Disease Education and Referral Center; Administration on Aging; and Children of Aging Parents.[7]

Safety-proofing the Home

In the early stages, patients may remain in the home, if:

- certain precautions are taken to ensure that the patient cannot accidentally harm him or herself or others;
- a spouse who does not have dementia is in the home; or
- a caregiver makes scheduled visits to check on the patient. A move to a small, one-story home will simplify the environment and eliminate stair hazards. The entire contents of the home must be examined, and potentially harmful utensils, tools, cleaning supplies, and furniture must be eliminated or locked away from the patient's access.

Adult Day Care[2]

Adult day care is similar to child day care in that patients may be dropped off at a facility for a certain period of time. Adult day-care facilities provide social stimulation and meals to patients with dementia in a safe, therapeutic environment.

Long-term Care Facilities[2]

Eventually, as dementia progresses, patients will require treatment in a long-term care facility either periodically or permanently, usually due to the progression of the illness, behavioral problems, or because the caregivers are unable to continue to care for the patient. Combativeness and physical violence tend to occur more often in the later stages of disease, often in response to frustration, misinterpretation, delusions, or hallucinations. If this behavior cannot be brought under control at

home, nursing home or hospital placement is necessary.

Table 9 lists the factors that have been shown to predict hospitalization.[5]

Table 9.
Factors that Predict Institutionalization in Patients with Dementia

Cognitive/behavioral problems, especially aggressive behavior, delusions, incontinence
Not married
Caregiver is son or daughter (especially if employed)
Large number of caregivers
High level of stress in caregiver
Poor health in caregiver
Increased use of health care or home help services
Increased functional impairments (by ADL scales)
Lower cognitive status at baseline
Death of spouse
Hospitalization
Prior institutionalization

Fleming KC, Adams AC, Petersen RC. Dementia: diagnosis and evaluation. *Mayo Clin Proc* 1995;70:1093-1107.

Group Living

Several types of long-term care facilities exist under a variety of names: group living (GL); residential care; group homes; and collective living. Group living was developed in Sweden in the 1980s[15] as a housing alternative in the management of dementia. GL units house six to nine patients, who are supervised by round-the-clock staff. GL units may be part of a nursing home or may be specially built facilities.

Symptoms

Estimates are that behavioral problems will occur in up to 90% of patients with dementia.[10] Psychiatric symptoms exhibited with dementia, especially in Alzheimer's disease, include: depression; suicidal ideation and behavior; hallucinations; delusions; anxiety; psychosis; agitation/aggression; disinhibition; sleep disturbances; and apathy/vegetation.

Agitation is broadly described as inappropriate verbal or motor activity that is not explained by apparent needs or confusion.[11] As shown in Table 10, as many as 50% of patients with dementia are likely to exhibit agitated behaviors during the course of their disease, and 25% to 33% may demonstrate aggressive behaviors.[10]

Table 10.
Behavioral Problems in Dementia Based on Worldwide Review of Literature

Behavior	Patients Affected % (Median)
Disturbed affect/mood	0-86 (19)
Disturbed ideation	10-73 (34)
Altered perception	
Hallucinations	10-90 (44)
Misperceptions	0-50 (18)
Agitation	
Global	21-49 (28)
Wandering	1-49 (23)
Aggression	
Verbal	11-51 (24)
Physical	0-46 (14)
Resistive/uncooperative	27-65 (14)
Anxiety	0-50 (32)
Withdrawn/passive behavior	21-88 (61)
Vegetative behaviors	
Sleep	0-47 (27)
Diet/appetite	12-77 (34)

Tairot PN. Treatment of agitation in dementia. *J Clin Psychiatry* 1999;60(suppl 0):11-20.

Neuropsychiatric Presentation of Agitation in Dementia[12]

The presence of agitation in a patient with dementia is serious and can be life-threatening. Since some types of agitation can be caused by medical conditions, attention to and treatment of any comorbid medical problems must be given, along with treatment of the agitation. (Treatment of agitation will be discussed later in the treatment section of this backgrounder.) Agitation associated with dementia can include one or more of several behavioral states.

Delirium

Delirium is a change in the patient's baseline mental status caused by a general medical condition. There is an impairment in the level of consciousness and cognition, which can fluctuate rapidly over minutes or hours. Delirium indicates the presence of a medical emergency requiring urgent identification and treatment..

Psychosis

A psychosis is said to occur when the inability of the patient to recognize reality causes severe confusion and the patient is unable to relate to and communicate with others in a normal way. Patients often believe they have had items stolen from them (because they have forgotten where they placed them), or that their spouse is having an affair (because the spouse was away on a trip). Hallucinations, altered perceptions of reality, may occur, and may be visual or auditory.

Depression

Depression in dementia patients may be mistaken because the symptoms resemble the symptoms of a general medical illness (e.g., weight loss, sleep disturbance, fatigue) or dementia (e.g., flat affect, loss of interest, poverty of speech).

Anxiety

Patients with generalized anxiety exhibit symptoms of anxiety through facial expressions, nervousness, fear, or physical complaints, such as palpitations or stomach disorders. Patients often express obsessive concern about heart or stomach pain, the safety of their belongings, or the whereabouts of their loved ones.

Insomnia

Insomnia is a common source of distress in the elderly who often sleep less and have reduced sleep efficiency as part of the aging process. Insomnia may be due to an identifiable cause, such as arthritic pain, and should be treated appropriately.

Sundowning

The clustering of agitation, confusion, and disorientation beginning in the late afternoon and becoming more severe at night is referred to as sundowning. Patients may wander, climb over bed rails, or behave in other ways that are unsafe.

Aggression or Anger Not Due to Other Causes

Anger that does not include physical aggression is considered mild. Anger that is accompanied by physical aggression, such as pushing, slapping, scratching, and extremely loud and extended yelling, is considered severe.

Treatment

There is no cure for dementia. Treatment goals are to maintain the independence and quality of life of the patient and the caregivers, as safely as possible, for as long as possible.

There is no cure for dementia. As stated previously, treatment goals are aimed at maintaining the independence and quality of life of the patient and the caregivers, as safely as possible, for as long as possible.

Nonpharmacologic Treatment

Nonpharmacologic treatment strategies can be used to enhance the patient's orientation and help him or her to avoid confusing situations, but they can only provide limited assistance in the daily care of the patient. This is why a multidisciplinary approach is necessary for the treatment and support of both the patient and caregiver. Nonpharmacologic treatments are listed in Table 11.

Table 11.
Nonpharmacologic Strategies for Management of Dementia [7,10,12]

Target	Activity
Family and caregivers	• Education program about dementia, short- and long-term management, course, and prognosis
	• Support groups
Physical and psychosocial environment	• Make patient's daily regimen routine and predictable
	• Minimize noise and disruptions in immediate environment
	• Control accessibility to certain rooms that are deemed unsafe, as well as doors to outside
	• Use a nightlight in the bedroom during sleep
	• Provide stimuli that increase patient awareness of time and place, eg, clocks, calendars, family pictures
	• Provide good daytime and evening lighting
Behavior management	• Reduce isolation
	• Identify activities or people who increase patient's agitation and minimize exposure
	• Provide continual verbal assurances
	• Provide a safe place for patient to pace
	• Encourage pleasant, calming activities, such as recreation, pets, arts

Pharmacologic Treatment[2]

Because most patients with dementia are of an advanced age, there are certain pharmacokinetic and pharmacodynamic factors that may affect medications that are prescribed. Some of these factors will make patients more susceptible to adverse events and/or drug interactions.

Special Considerations in the Elderly

The elderly population typically has decreased renal clearance and slowed hepatic metabolism. Therefore, lower starting doses, smaller increases in dose, and longer intervals between dosage increments should be used. This population can have multiple medical problems requiring multiple medication and attention should be paid to potential drug interactions and side effects. In some demented patients, medications can lead to worsening of cognitive impairment. Sedative effects of many medications can leave patients more prone to falls, and patients with AD or Parkinson's are especially susceptible to extrapyramidal side effects. For Depakote information, please see the WARNINGS section of the package insert.

Treatment for Cognitive and Functional Loss Due to Dementia

Goals

As stated earlier, there is no cure for dementia, but within the past ten years, several medications have become available that can be used to prevent further reduction in and/or restore cognitive and functional abilities to patients diagnosed with dementia.

Many medications are used in the treatment of dementia; however, it is important to note that some of the medications listed here do not have labeled indications for this use.

Cholinesterase inhibitors (tacrine, donepezil, and others)

Acetylcholine is a neurotransmitter that transmits impulses between the forebrain and the parts of the brain responsible for memory and information

processing.[3] The rationale for use of cholinesterase inhibitors in the treatment of dementia and specifically Alzheimer's disease is based on several known facts about acetylcholine and AD.

AD is accompanied by a loss of cholinergic neurons. The level of enzymes responsible for the synthesis of acetylcholine is reduced by 58% to 90% in selected areas of the brain. By inhibiting the enzyme ***acetylcholinesterase (AChE)***, which hydrolyzes acetylcholine at the neuron, the concentration of acetylcholine at the nerve endings is increased; in some patients this can lead to improved cholinergic functioning and improved cognitive processing. The two cholinesterase inhibitors currently approved for AD in the United States are tacrine and donepezil.

Other drugs currently being investigated for their affect on cognitive functioning in the dementia patient include metrifonate, rivastigmine, and physostigmine.[7]

Side Effects of Cholinesterase Inhibitors

Cholinergic Excess

The most commonly experienced side effects with cholinesterase inhibitors are those associated with "cholinergic excess" (increased levels of acetylcholine).

- Mild to moderate nausea and vomiting occur in 10% to 20% of patients.
- Bradycardia (slow heart rate) may also occur, which can be dangerous for patients with cardiac conduction problems.
- Stomach acid may increase, which is a particular problem for those who already have a history of ulcer or who are taking NSAIDs.

Hepatotoxicity

Tacrine is associated with a direct medication-induced hepatocellular injury. Approximately 30% of patients develop significant (three times the upper limit of normal) but reversible and

asymptomatic liver enzyme elevations. Marked elevations (10 times the upper limit of normal) occur in 5% to 10% of patients requiring discontinuation of the medication. However, perhaps 80% of patients who initially develop elevations can be successfully rechallenged with more gradual increases in dose. Alanine aminotransferase (ALT) should be monitored prior to treatment initiation and after each dose increase. Donepezil has not been associated with this adverse event, but experience with the agent is limited.

Vitamin E

One theory of aging is that free radicals cause oxidative damage, which causes neuronal death characteristic of many diseases, including AD. Vitamin E, also known as α-tocopherol, initially was tried for treatment of AD because of its antioxidant properties, and because in animal models it was shown to slow damage and death of neurons. One study evaluated Vitamin E, selegiline alone, both or placebo and found single therapy with Vitamin E or selegiline alone decreased the rate of functional decline equivalent to approximately 7 months. It should be noted that there was no improvement in function compared to baseline and all groups showed similar rates of cognitive decline during the 2 year study period. Vitamin E (200-3000 IU/day) has been shown to be safe and well-tolerated in many studies. At high doses it has been found to worsen blood coagulation defects in patients with vitamin K deficiency.

Selegiline

In the United States, selegiline (also known as l-deprenyl) is used for Parkinson's disease, and in Europe it is approved for dementia. While its mode of action is not fully known, it has been suggested that selegiline may act as an antioxidant or neuroprotective agent and slow the progression of AD, although, because of its effects on catecholamine metabolism, it could also act in a variety of other ways. The main side effect of selegiline is orthostatic hypotension (low blood pressure on standing, causing dizziness or fainting),

which may be more common in patients with Parkinson's disease than those with dementia. Selegiline has been reported to be activating which is helpful for some patients, but may lead to anxiety and/or irritability in others. Drug interactions have included changes in mental status, seizures, and even death have been observed with meperidine, SSRIs, and tricyclic antidepressants, although there have been reports of patients tolerating these combinations.

Ergoloid Mesylates

Ergoloid mesylates have been on the market for a number of years. A recent meta-analysis suggested that there might be improvements in neuropsychological and behavioral measures, but the overall benefits were not statistically significant. Ergoloid mesylates may cause mild nausea or gastrointestinal distress.

Other Agents Proposed for the Treatment of Dementia

Based on epidemiologic data or pilot studies, other agents have been proposed for the treatment of dementia; however, at this time their use is not recommended.

- Estrogen – Preliminary data show that estrogen replacement therapy can delay onset and/or decrease risk of cognitive loss. A clinical trial is in progress in postmenopausal women with AD.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) – Based on epidemiologic data, it has been suggested that these agents protect against the development of the disease. In addition, since one theory of the development of AD involves inflammation, NSAIDs may have a role in the treatment or prevention of dementia.
- Melatonin, Ginkgo biloba – Interest has been shown in both of these over-the-counter products. It should be advised that these agents are marketed with limited quality control and have not been subject to safety and efficacy evaluations.

- Desferrioxamine – a chelating agent theorized to have a place in AD treatment because of the hypothesis that heavy metals have a role in the pathogenesis of AD. However, efficacy data are sparse. Because of the toxicity of chelating agents, they are not recommended for treatment of dementia.

Managing Common Behavioral Problems in Dementia[13]

Disruptive behavior related to dementia is the chief factor leading to institutionalization. Common behavioral symptoms include: aggression and psychotic features, depression, and sleep disturbances.

Treatment for Psychosis and Depression[13]

Psychosis and agitation are common in demented patients and often coexist.[2] Usually a pharmacologic agent is the treatment of choice, but which drug is best for an individual case requires careful consideration.

It should be noted that the psychotic symptoms associated with dementia are not considered schizophrenia even though the terminology used to describe behaviors may be shared between definitions. Furthermore, there currently is no treatment approved for the agitation, aggression, psychosis, and depression due to dementia. The antipsychotic drugs used to treat psychotic behaviors in dementia are typically those found effective in treating psychotic behaviors due to schizophrenia, but antipsychotic drugs are approved only for schizophrenia.

Drug selection is based on the relationship between the side effect profile and the characteristics of a given patient.[2]

Antipsychotics

Antipsychotics (neuroleptics): Haloperidol and thioridazine are often referred to as "high-potency" neuroleptics.[13]

Atypical antipsychotics: Clozapine, risperidone, olanzapine, and quetiapine are referred to as "atypical" antipsychotics and are associated with a lower frequency of extrapyramidal side effects than the typical antipsychotics.[13]

Antipsychotic agents are associated with serious complications that must be considered in the risk/benefit analysis for treatment of any psychosis, especially in the elderly with dementia.

Extrapyramidal symptoms (EPS) of antipsychotic medications include:[9]

- Dystonia (dis-TOE-nee-ah)[9]
  - Facial grimacing
  - Torticollis (tort-tih-KOLL-is) – spasm of neck muscle that turns head sideways and to one side
  - Oculogyric (ock-ku-low-JYE-ric) crisis – rotation of eyeballs
  - Opisthotonos (oh-pis-THOUGH-oh-nohs) – backward arching of head
- Parkinsonism[9]
  - Akinesia (ay-ki-NEE-shah) – involuntary movement
  - Masked facies
  - Rigidity
  - "Pin-rolling" hand tremor
- Akathisia (ay-kah-THIZ-ee-ah) –Continual nervousness and restlessness
- Tardive dyskinesia (TAR-div disk-in-NEE-shah)[9], with and without EPS, may also be seen as an adverse effect of antipsychotic medications.

- Involuntary movements of tongue, face, mouth, jaw, extremity muscles, eg, repeated lip-smacking, chewing, protruding of the tongue, jerky or writhing movements

The risk of tardive dyskinesia increases with increasing dose and duration of treatment, and is greater in women, the elderly, and those with dementia.[2] The risk of tardive dyskinesia with antipsychotics is as high as 30% in the elderly.[2]

Neuroleptic malignant syndrome (NMS) is also a risk of antipsychotic medication, and is potentially fatal.[2,9] NMS, which may occur at any time during antipsychotic therapy, includes the following: increased temperature; muscle rigidity; altered mental status; altered pulse and blood pressure; sweating; and irregular heartbeat.

Benzodiazepines[2]

Studies of benzodiazepines in the treatment of behavioral symptoms are limited by poorly specified diagnosis, a mixture of target symptoms, limited outcome measures, and in most cases, high doses of long-acting agents. Benzodiazepines have been shown to perform better than placebo, but not as well as antipsychotics in reducing behavioral problems. The most common side effects of benzodiazepines are dose-related and include sedation, ataxia, amnesia, confusion and delirium, and paradoxical anxiety. These side effects must be watched for, as they can lead to worsening of cognition and behavior problems and/or may be responsible for falls.

Anticonvulsants[13]

Divalproex sodium and carbamazepine have been shown to be effective in treating behavioral disturbances in preliminary clinical trials, but their efficacy has yet to be proven in placebo-controlled, double-blind clinical trials. They do not have the same potential for tardive dyskinesia and NMS as antipsychotics.

Some important side effects of divalproex sodium include: hepatic failure, pancreatitis, somnolence, nausea, and dizziness. Some important side effects

of carbamazepine include: aplastic anemia, agranulocytosis, dizziness, drowsiness, and nausea.

In psychiatry, divalproex sodium has a labeled indication for the treatment of mania associated with bipolar disorder.

Treatment for Depression

Depression occurs in up to 20% of patients with dementia.[13] Patients may experience depression as a result of their progressive neuronal loss, or, less frequently, as a reaction to the disease process.

Antidepressants

- **SSRIs (selective serotonin reuptake inhibitors):** Fluoxetine, paroxetine, and sertraline are first-line therapy for depression in patients with dementia. Psychotherapy is not at all useful in this population with impaired insight, and these agents generally are well-tolerated in patients with concomitant dementia and depression.
- **Tricyclic antidepressants:** Desipramine and nortriptyline have lower anticholinergic activity than amitriptyline, which is associated with an increased risk of worsening cognitive impairment.
- Phenethylamine antidepressant: venlafaxine is useful when marked apathy is present because it stimulates both the serotonergic and adrenergic neurotransmitter systems.[13]

Treatment for Sleep Disturbance

Hypnotics or benzodiazepines: Trazodone and zolpidem are useful in the short-term treatment of sleep disorders that lead to wandering and behavior disorders during normal sleep hours. Families often can cope with the agitation, delusions, and other behavior disorders when they occur during the daytime, but when sleep disorders cause them to continue into the night, institutionalization is often considered.[13]

Approach to Treatment of Agitation and Psychopathology of Dementia

Behavioral psychopathology due to dementia is a key factor in the overall management of dementia for three reasons:[10]

1) The distress caused by behavioral symptoms is significant and affects the well-being of both the patient and the caregiver.

2) Behavioral psychopathology, especially when physical hyperactivity and aggression are involved, can be dangerous for the patient and for the caregiver as well.

3) The practice of treating behavioral symptoms with antipsychotic medication can lead to serious adverse events that further affect the well-being of the patient and caregiver.

Prevalence and Impact of Caregiving[14]

Data from the 1996 National Survey on Family Caregiving was analyzed in order to provide a detailed description of the differences between dementia and nondementia caregivers.

This report showed when compared to other caregivers, dementia caregivers:

- spent more than 40 hours/week on caregiving;
- provided assistance for more activities of daily living;
- experienced employment complications, necessitating taking a less demanding job, taking early retirement, turning down a promotion, or having to give up work completely and losing job benefits;
- reported forfeiting pleasurable activities, having less time for other family, holding grudges against other family members for not doing their fair share, and experiencing a greater degree of family conflict;
- experienced greater emotional and physical strain; and
- experienced higher levels of financial hardship, but both types of caregivers spent the same amount of money per month on caregiving.

Glossary

acetylcholine – a neurotransmitter that transmits impulses between the forebrain and the parts of the brain responsible for memory and information processing

acetylcholinesterase (AChE) – a naturally occurring enzyme that hydrolyzes acetylcholine at the neuron

activities of daily living (ADL) – routine activities required for self-care, such as bathing, grooming, dressing, walking, preparing meals, and household cleanup

agitation – inappropriate vocal or motor activity that is not explained by perceived needs or confusion. Types of agitation include psychosis, delirium, depression, anxiety, anger, and insomnia. Agitation may take the form of aimless wandering, pacing, cursing, screaming, biting, hitting, and scratching.

agnosia – impaired recognition/identification of objects despite intact sensory function

alanine aminotransferase (ALT) – a liver enzyme that indicates liver dysfunction; can be used to monitor potential hepatotoxicity

apathy/vegetation – lack of interest in surroundings, grooming, and social interaction, progressing to staring into space without being aware of people, places, or things in the environment

aphasia – impaired language/speaking

apraxia – impaired movement, despite intact motor function

bradycardia – slow heart rate

Glossary (continued)

cholinesterase inhibitors – drugs that inhibit the enzyme *acetylcholinesterase (AChE)*, which hydrolyzes acetylcholine at the neuron; increases the concentration of acetylcholine at the nerve endings

cognition – the "knowledge" of events that continually occur during consciousness. When cognitive abilities are impaired there is diminished perception, recognition, idea or thought conception, judging, sensing, reasoning, and imagining.

Creutzfeldt-Jakob disease – rapidly progressive disease of the brain caused by a transmissible virus or other type of infection

delusions – incorrect beliefs or judgments that are held with conviction, despite reality to the contrary. Delusions of grandeur: belief of possessing immense wealth, intellect, power; delusions of persecution: belief that people/society are "out to get you"

dementia – a broad clinical syndrome that involves global deterioration of intellectual and cognitive abilities. Pathogenesis is due to impairment of, or damage to, the central nervous system (the brain), but the exact dysfunction is not always easily defined.

disinhibition – a state in which previously held social inhibitions are lost, eg, acts of aggression, not wearing clothes

dystonia – a category of extrapyramidal symptoms that includes facial grimacing, torticollis, oculogyric crisis, and opisthotonos

executive functioning – inability to plan, organize, sequence, think abstractly

extrapyramidal (extra-pyr-RAM-ih-dahl) *effects* – side effects of antipsychotic medications, which include dystonia, parkinsonism, akathisia, and tardive dyskinesia

hallucinations – seeing, hearing, smelling, tasting, or feeling things that are not there; the false perception of sight, sound, smell, taste, or touch, with no basis in reality, eg, seeing people or things that are not present, feeling bugs crawling on skin

Huntington's disease – hereditary neurological disease that causes motor, behavioral, and cognitive deterioration

multi-infarct dementia (MID) – also called vascular dementia; stems from multiple episodes of cerebral ischemia, sometimes referred to as "mini-strokes" or TIAs, which cause the brain damage that leads to dementia

oculogyric (ock-ku-low-JYE-ric) *crisis* – rotation of eyeballs

opisthotonos (oh-pis-THOUGHT-oh-nohs) – backward arching of head

parkinsonism – a combination of neurological signs and symptoms that include akinesia, masked facies, rigidity, and "pin-rolling" hand movements

Pick's disease – a type of frontal lobe dementia that is difficult to diagnose and differentiate from atypical AD. Brain imaging shows atrophy of frontal and/or temporal lobes. Autopsy findings identify Pick inclusion bodies in the brain. Most common between age 50 and 60, but can occur in older population.

primary dementias – those for which no other identifiable disease or condition can be found as the cause of the syndrome

psychosis – distortion/confusion of mental state, emotional response, and overall ability to recognize reality, causing an inability to relate to and communicate with others normally

secondary dementias – those for which a pathological process has been found as the cause, eg, infections, trauma, toxic/metabolic disorders, circulatory disorders, brain tumors, neurological diseases or conditions

suicidal ideation – thinking about death, the act of suicide, and ways to commit suicide

sundowning – agitation, confusion, and disorientation beginning in the late afternoon and becoming more severe at night

syphilis – a sexually transmitted disease that causes dementia in late stages

tardive dyskinesia (TAR-div disk-in-NEE-shah) – involuntary movements of tongue, face, mouth, jaw, extremity muscles, eg, repeated lip-smacking, chewing, protruding of the tongue, and jerky or writhing movements

torticollis (tort-tih-KOHL-is) – spasm of neck muscle that turns the head sideways and to one side

vascular dementia – also called multi-infarct dementia (MID); stems from multiple episodes of cerebral ischemia, sometimes referred to as "mini-strokes," which cause the brain damage that leads to dementia

Case Studies

Betty Green

Betty has been brought to Dr. Hager's office by her daughter-in-law, Sue. Dr. Hager is a primary care physician in the small town of Robinson, Indiana. Betty is 76 years old, is widowed, and lives alone in the same neighborhood she has lived in for 40 years. On her last visit to see Betty, Sue noticed several large bruises on Betty's arm and leg. When asked about them, Betty said the "bites," as she called them, were from the cat. Betty's cat died five years earlier and she currently has no pets.

Upon physical examination, Betty is alert and responsive to questions. Betty has lost 8 pounds since Dr. Hager last saw her over a year earlier. He notices additional old bruises on her ribs, but there are no other remarkable signs or symptoms of disease. As Dr. Hager examines Betty, she gives the following answers to his questions:

Dr. Hager: You've lost weight, Betty. How is your appetite?

Betty: Well, Bill (Bill was Betty's husband) just doesn't cook like he used to, and I never was much of a cook.

Dr. Hager: Have you fallen lately, Betty?

Betty: Oh, no. I have good shoes.

Dr. Hager: How are your grandkids? What are their names again? (Sue and Betty's son, Bill, Jr., have a five-year-old boy and a one-year-old girl.)

Betty: Oh, we're all great.

Dr. Hager: What are your grandkids' names?

Betty: Well, uh, fine, fine, fine.

Case Studies (continued)

Dr. Hager asks Betty to sit in the waiting room and asks to see Sue. Betty sits and watches a television game show while Sue goes in to see Dr. Hager. Dr. Hager interviews Sue and learns the following:

Betty's neighbor said that Betty keeps getting lost when she drives them to the new mall outside of town. On their last trip, Betty spilled gasoline all over herself when she tried to fill the gas tank. Betty has stopped asking Sue and Bill about her grandchildren and doesn't seem to recognize them at all when Betty comes to visit. Sometimes she recognizes Sue and sometimes she doesn't. Betty can no longer operate the can opener, and is unable to organize herself enough to cook the holiday meals, which had always been her favorite family events. She can't even prepare any of her favorite dishes. She eats mostly cold cuts and cereal, saying she isn't very hungry. Sue finds the casseroles and soups she brings to Betty untouched in the refrigerator, molding, apparently forgotten. Betty is continually forgetting which day to take the trash out. When asked if there is any history of Alzheimer's or any other type of abnormal behavior in the elderly of the family, Sue relates that Betty's mother had gone "crazy" when she was older and was hospitalized at the age of 82 when she almost burned down her house.

All Betty's lab work comes back normal with the exception of a low hemoglobin, suggesting a low degree of anemia. Dr. Hager suspects early dementia, possibly due to Alzheimer's disease.

Dr. Hager refers Betty to a psychiatrist who does a full diagnostic workup and confirms Dr. Hager's preliminary diagnosis of dementia due to Alzheimer's disease. Betty is given a cholinesterase inhibitor and referred with the family to an Alzheimer's disease support group. Her next-door neighbor is hired to look in on Betty at least four times a day, and Betty is sent to a senior day care center three times a week. Her son and daughter-in-law visit her weekly, and have taken over her grocery and other types of shopping.

Case Discussion

Questions

1) What clues suggested a diagnosis of dementia? Underline the clues.

2) Which of the following symptoms of dementia did Betty exhibit? Give an example of each symptom from Betty's history.

   A. apraxia

   B. aphasia

   C. agnosia

   D. memory impairment, especially recent memory

   E. impaired executive functioning

3) Name the available cholinesterase inhibitors that are prescribed for AD.

4) What stage of dementia do you think Betty is in? Why?

5) As Betty enters the later stages of AD, what symptoms/behavior might cause her to be hospitalized?

Answers

1) Betty has been brought to Dr. Hager's office by her daughter-in-law, Sue. Dr. Hager is a primary care physician in the small town of Robinson, Indiana. Betty is 76 years old, is widowed, and lives alone in the same neighborhood she has lived in for 40 years. On her last visit to see Betty, Sue noticed several large bruises on Betty's arm and leg. When asked about them, Betty said the "bites," as she called them, were from the cat. Betty's cat died five years earlier and she currently has no pets.

Upon physical examination, Betty is alert and responsive to questions. Betty has lost 8 pounds since Dr. Hager last saw her over a year earlier. He notices additional old bruises on her ribs, but there are no other remarkable signs or symptoms of disease. As Dr. Hager examines Betty, she gives the following answers to his questions:

Case Studies (continued)

Dr. Hager: You've lost weight, Betty. How is your appetite?

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Betty: Oh, we're all great.

Dr. Hager: What are your grandkids' names?

Betty: Well, uh, fine, fine, fine.

Dr. Hager asks Betty to sit in the waiting room and asks to see Sue. Betty sits and watches a television game show while Sue goes in to see Dr. Hager. Dr. Hager interviews Sue and learns the following:

Betty's neighbor said that Betty keeps getting lost when she drives them to the new mall outside of town. On their last trip, Betty spilled gasoline all over herself when she tried to fill the gas tank. Betty has stopped asking Sue and Bill about her grandchildren and doesn't seem to recognize them at all when Betty comes to visit. Sometimes she recognizes Sue and sometimes she doesn't. Betty can no longer operate the can opener, and is unable to organize herself enough to cook the holiday meals, which had always been her favorite family events. She can't even prepare any of her favorite dishes. She eats mostly cold cuts and cereal, saying she isn't very hungry. Sue finds the casseroles and soups she brings to Betty untouched in the refrigerator.

molding, apparently forgotten. Betty is continually forgetting which day to take the trash out. When asked if there is any history of Alzheimer's or any other type of abnormal behavior in the elderly of the family, Sue relates that Betty's mother had gone "crazy" when she was older and was hospitalized at the age of 82 when she almost burned down her house.

All Betty's lab work comes back normal with the exception of a low hemoglobin, suggesting a low degree of anemia.

2) A. Apraxia

spilled gasoline

can no longer operate the can opener

B. Aphasia

Betty called bruises "bites"

Oh, no. I have good shoes.

C. Agnosia – Agnosia is impaired recognition/ identification of an object despite intact sensory function. The history did not include any examples of agnosia.

D. Memory impairment, especially recent memory

Bill doesn't cook like he used to and I never was much of a cook.

Betty's cat had died five years earlier and she currently has no pets

Food untouched in the refrigerator

Well, uh, fine, fine, fine.

Getting lost driving to the mall.

Betty had stopped asking about her grandchildren.

Case Studies (continued)

Doesn't seem to recognize them at all

Sometimes she doesn't recognize Sue.

E. Impaired executive functioning

Unable to organize herself enough to cook the holiday meals

Couldn't prepare any of her favorite dishes

Unable to schedule/predict which day to take the trash out

3) Tacrine, donepezil

4) Mild-to-moderate. Impairment is mild, but Betty is still able to perform most activities of daily living and is able to live alone, with supervision.

5) Behavioral/psychiatric problems

Incontinence

Joe Dougherty

Joe and Mary Dougherty are 68 and 72, respectively. Joe has had hypertension since he was in his 50s. At the age of 64, Joe had several TIAs (transient ischemic attacks) during a six-month period, followed by a major stroke that left him with right-sided weakness. He walks with a walker.

In the past two months, Joe has become increasingly forgetful and confused and has experienced aphasia, agnosia, and worsened gait. Mary has awakened several times to find him in another part of the house. When Mary has awakened him to bring him back to bed, he has become angry and belligerent, telling her to go away and let him be. He is no longer able to shower or shave himself.

In the evening, he has started pacing up and down the hall with his walker, and often talks angrily to people who are not there. He has tried to slap Mary on a couple of occasions when she was helping him get ready for bed.

Mary has brought Joe to the neurologist and explained his latest symptoms. A complete physical exam has revealed no apparent physiological cause of the symptoms.

Case Discussion

Questions

1) Based on the history so far, what might the diagnosis be?

2) Underline the major factors that suggest this diagnosis.

3) What stage of this condition is Joe in? State your reasons.

4) Which of Joe's symptoms could be considered "sundowning"?

5) Which of the following medications might the neurologist prescribe for Joe? Explain your rationale for choosing or not choosing each type of drug.

A. hypnotic

B. anticonvulsant

C. cholinesterase inhibitor

D. SSRI

Answers

1) **Multi-infarct dementia, vascular dementia**

2) **Joe and Mary Dougherty are 68 and 72, respectively. Joe has had hypertension since he was in his 50s. At the age of 64, Joe had several TIAs (transient ischemic attacks) during a six-month period, followed by a major stroke that left him with right-sided weakness. He walks with a walker.**

Case Studies (continued)

In the past two months, Joe has become increasingly forgetful and confused and has experienced aphasia, agnosia, and worsened gait. Mary has awakened several times to find him in another part of the house. When Mary has awakened him to bring him back to bed, he has become angry and belligerent, telling her to go away and let him be. He is no longer able to shower or shave himself.

In the evening, he has started pacing up and down the hall with his walker, and often talks angrily to people who are not there. He has tried to slap Mary on a couple of occasions when she was helping him get ready for bed.

Mary has brought Joe to the neurologist and explained his latest symptoms. A complete physical exam has revealed no apparent physiological cause of the symptoms.

3) Severe-to-profound

Joe is having difficulty using the bathroom, and is experiencing sundowning and agitation/ aggression.

4) In the evening, he has started pacing up and down the hall with his walker and often talks angrily to people who are not there. He has tried to slap Mary on a couple of occasions when she was helping him get ready for bed.

Mary has awakened several times to find him in another part of the house. When Mary has awakened him to bring him back to bed, he has become angry and belligerent, telling her to go away and let him be.

5) A. Hypnotic

Short-term use of a hypnotic or benzodiazepine might be indicated to help Joe (and Mary) get a good night's sleep.

B. Anticonvulsant

An anticonvulsant might be indicated for treatment of agitation/aggression.

C. Cholinesterase inhibitor

A cholinesterase inhibitor would probably not be used in this case since it has already advanced to the severe/profound stages.

D. SSRI

Joe does not show any major symptoms of depression for which an SSRI might be indicated.

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Dementia Backgrounder – Quiz

1. Which of the following statements is not true?

   A. Dementia refers to cognitive and/or psychological deterioration associated with organic brain dysfunction.

   B. Dementia is more prevalent in the elderly, and the prevalence of dementia is increasing in the United States and the world as the "baby-boomers" age.

   C. There is no cure for dementia.

   D. Dementia is referred to as a "functional" brain disease because it has no organic pathogenesis.

2. Mark each statement True or False.

   A. Primary dementias are those for which no other identifiable disease or condition can be found to be responsible for the syndrome. True

   B. Secondary dementias are those for which a pathological process has been found as the cause. True

3. What neurotransmitter is the target of cholinesterase inhibitors?

   A. glycine

   B. acetylcholine

   C. alanine aminotransferase (ALT)

   D. phenothiazine

4. What is known about the pathologic process that occurs in Alzheimer's disease?

A. AD is accompanied by a loss of cholinergic neurons, and acetylcholine is reduced by as much as 90% in patients with AD.

B. The concentration of acetylcholine at the neuron accumulates to toxic levels, eventually causing such symptoms as hyperactivity and aggression.

C. Cholinesterase is absent from the nerve endings in the brain.

D. Cognitive functioning is accelerated by AChE.

5. One of the cholinesterase inhibitors, tacrine, used to treat AD is associated with asymptomatic, reversible _____ in as many as 30% of patients.

A. aggression

B. depression

C. hepatotoxicity

D. bradycardia

6. Which of the following drugs, believed to slow the progression of AD because of neuroprotective effects and antioxidant properties, is used for Parkinson's disease in the United States, and is approved for dementia in Europe?

A. selegiline

B. donepezil

C. trazodone

D. haldol

E. vitamin E

Dementia Backgrounder – Quiz (continued)

7. Antipsychotics:

   A. are also referred to as neuroleptics.

   B. include haloperidol and thioridazine.

   C. are considered "high-potency."

   D. include clozapine, risperidone, olanzapine, and quetiapine.

   E. All of the above

   F. A, B, C

8. "Atypical" antipsychotics:

   A. are also referred to as neuroleptics.

   B. include haloperidol and thioridazine.

   C. are considered "high-potency."

   D. include clozapine, risperidone, olanzapine, and quetiapine.

   E. All of the above

   F. A, B, C

9. True or False?

   Typical antipsychotics are associated with a lower frequency of extrapyramidal side effects than the atypical antipsychotics.

   False

10. In the treatment of dementia, benzodiazepines are effective in the treatment of certain types of agitation and behavioral problems, but they generally are not as effective as antipsychotics. Which of the following is true about the side effects of benzodiazepines?

A. They are dose-related.

B. They include sedation, ataxia, amnesia, confusion and delirium, and paradoxical anxiety.

C. They can lead to worsening of cognition and behavior problems, and/or may be responsible for falling accidents.

D. All of the above

E. B & C

11. What is true about the use of the anticonvulsants, divalproex sodium and carbamazepine, in treating behavioral disturbances in dementia patients?

A. They have been shown effective in preliminary clinical trials.

B. They have been shown effective in many placebo-controlled, double-blind clinical trials.

C. They do not have the same potential for tardive dyskinesia and NMS as antipsychotics.

D. None of the above

E. A & C

F. B & C

Dementia Backgrounder – Quiz (continued)

12. Which of the following statements is true about depression in dementia?

A. Depression occurs in up to 20% of patients with dementia.

B. Patients probably experience depression as a result of their progressive neuron loss.

C. Intensive psychotherapy is useful as an adjunct with a course of antidepressant drug therapy.

D. All of the above

E. A & B

F. A & C

13. Which is **not** true about the treatment of depression associated with dementia?

A. SSRIs may be used, and include desipramine and nortriptyline.

B. SSRIs may be used, and include fluoxetine, paroxetine, and sertraline.

C. SSRIs are first-line therapy for depression in patients with dementia.

D. SSRIs generally are well-tolerated in patients with concomitant dementia and depression.

E. Tricyclic antidepressants have no anticholinergic activity and are not effective in dementia patients.

F. Amitriptyline is associated with an increased risk of worsening cognitive impairment.

G. A & E

H. B & F

14. True or False?

Hypnotics, or benzodiazepines (trazodone and zolpidem), are useful in the short-term treatment of sleep disorders that lead to wandering and behavior disorders during normal sleep hours.

15. True or False?

Dementia caregivers and caregivers for other chronic illnesses have a comparable burden in terms of hours per week giving care, employment complications, stress, mental and physical health problems, compromised leisure and family time, and general family conflict.

16. In elderly patients, why should drug therapy be started with lower doses and dosage titration progress more slowly than in a younger population?

A. Because the elderly often have decreased renal clearance of drugs and decreased hepatic metabolism.

B. This population often has multiple medical conditions requiring attention for drug interactions and side effects.

C. Elderly patients are less likely to experience the beneficial extrapyramidal effects of drugs.

D. In elderly patients, some medications make them more susceptible to anticholinergic side effects, and may lead to worsening of cognitive deficits, confusion, and possibly delirium.

E. A, B, C

F. A, B, D

G. B, C, D

Dementia Backgrounder – Quiz (continued)

17. Mark each of the following statements **True** or **False**.

A. Delirium is a type of agitation syndrome in which the consciousness and cognition of the patient change, with fluctuations over minutes to hours. True

B. The cause of delirium may be a medical condition, which requires immediate diagnosis and treatment. True

18. **True** or **False?**

Depression in dementia patients may be mistaken because of its resemblance to medical illness (eg, weight loss, sleep disturbances, fatigue) or dementia (eg, flat affect, loss of interest, poverty of speech).

19. Which of the following is not considered a type of anxiety experienced by patients with agitation?

A. Nervousness, fear, or physical complaints, such as palpitations or stomach disorders

B. Obsessive concern over the safety of their belongings or the whereabouts of their loved ones

C. Observation of angels watering flowers on the windowsill

20. Which of the following is described as the clustering of agitation, confusion, and disorientation beginning in the late afternoon and becoming more severe and at night?

A. hallucinations

B. sundowning

C. psychosis

D. hyperactivity

E. insomnia-induced aggression

21. Anger that is accompanied by physical aggression, such as pushing, slapping, scratching, and extremely loud and extended yelling, is considered:

A. severe

B. mild

C. sundowning

D. paranoid

22. Which of the following is not considered the most common reason for institutionalization in dementia?

A. delusions

B. insomnia

C. agitation

D. sleepwalking

E. apathy

Dementia Backgrounder – Quiz (continued)

23. Which of the following is **not** an extrapyramidal effect of antipsychotic medications?

A. dystonia

B. parkinsonism

C. tardive dyskinesia

D. agitation

For questions 24–28, match the word or phrase with its correct description listed below.

A. facial grimacing, torticollis, oculogyric crisis, opisthotonos

B. akinesia, masked facies, rigidity, "pin-rolling" hand movements

C. dystonia, parkinsonism, akathisia, tardive dyskinesia

D. involuntary movements of tongue, face, mouth, jaw, extremity muscles, eg, repeated lip-smacking, chewing, protruding of the tongue, jerky or writhing movements

E. increased temperature, muscle rigidity, altered mental status, altered pulse and blood pressure, sweating, irregular heart rate

24. Dystonia A
25. Extrapyramidal effects C
26. Parkinsonism B
27. Tardive dyskinesia D
28. Neuroleptic malignant syndrome E

29. Which of the following types of dementia is most likely to have a gradual onset?

A. Alzheimer's disease

B. Vascular dementia

C. Pick's disease

30. **Which of the following types of dementia is most likely to have a sudden onset?**

A. Alzheimer's disease

B. Vascular dementia

C. Pick's disease

D. Parkinson's dementia

Quiz Answers

1. D
2. True, True
3. B
4. A
5. C
6. A
7. F
8. D
9. F
10. D
11. E
12. E
13. G
14. True
15. False
16. F
17. True, True
18. True
19. C
20. B
21. A
22. E
23. D

24. A

25. C

26. B

27. D

28. E

29. A

30. B



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Maximizing the Long-Term Care Market Opportunity

Abbott Laboratories, Inc.

Abbott Laboratories

Orientation

REDACTED

Long-Term Care Market Development

Maximizing Geriatric Healthcare Opportunities

REDACTED **offers a comprehensive training program to representatives of Abbott Laboratories who will serve the long term care (LTC) industry. This training program is designed to provide an overview of the LTC industry and familiarize each attendee with its associated components and terms. Additionally, the attendee will gain insight into how to favorably position Abbott Laboratories' core products, including Depakote ER, in the LTC environment.**

OBJECTIVE:

The complete training program takes place over a two-day period. The days are spent in classroom, long term care pharmacy, nursing facility and assisted living facility settings. Upon completion of the REDACTED LTC Training Program each participant will be able to:

1. Describe the roles of the various healthcare professionals who practice in long term care
2. Explain the meaning of common terms and abbreviations used in long term care
3. List the services provided by health care professionals practicing in long term care
4. Describe the role of a pharmaceutical manufacturer representative in the long term care environment
5. Describe the impact of state and federal regulations for the long term care industry in general and for long term care pharmacy in particular

PROGRAM SCHEDULE:

Day	General Description	Location	Time
Day 1	Program Orientation & Industry Review	Abbott Training	8:00a – 5:00p
Day 2	LTC Pharmacy & NF/ALF Site Visits	TBA	8:00a - 12:00n
Day 2	Reimbursement, Market Share, Partnering	Abbott Training	1:00p – 5:00p

REDACTED

Program Components:

Day 1 (8am - 5pm) CLASSROOM

Long Term Care (LTC) Overview

1. The Aging of America
   a. Facts and figures
   b. Trends
   c. Projections
   d. Where aging Americans live (types of LTC facilities)

2. Long Term Care (LTC) Rules and Regulations
   a. Federal statutes & State laws
   b. Regulations specifically impacting LTC pharmaceutical care
   c. Quality Indicators and pharmaceutical opportunities

3. Key Decision Makers in Long Term Care
   a. Institutional LTC Pharmacy (operations and consulting)
   b. Nursing Facility Staff
   c. Medical Directors
   d. Communication skills workshop

Day 2 (8am - 12n) SITE VISITS

The Provider/Consultant Pharmacist

1. Specific Duties and Tasks
   a. Specialized medication packaging
   b. Medication Ordering and Dispensing
   c. IV and other "special" medications
   d. Staff
      Technicians, Medical Record clerks, Billing and Accounting staff, Customer Support staff, Medical Supply staff, Enteral Therapy, etc...

2. Special Services Provided - Dispensing Pharmacy
   a. Medical records (charting forms)
   b. Infusion therapy training
   c. Medical supplies
   d. Medicare Part B billing (enteral, wound care, urological)
   e. Specialized Billing (medicaid, medicare, insurance, capitated contracts, etc..)
   f. Emergency medication
   g. Drug information services (24hr/day)

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Day 2 (con't) SITE VISITS

3. Specific Duties and Tasks - Consultant Pharmacist
   a. Patient assessment
   b. Drug regimen review
   c. Med pass and treatment observations
   d. Med storage/cart reviews
   e. Review of procurement, receipt, storage, distribution & administration of medications in the long-term care facility
   f. Drug destruction and/or returns
   g. Inservice presentations
   h. Meeting attendance and presentations

4. Interaction with Pharmaceutical Manufacturer Representatives
   a. Setting up meeting with key decision makers
   b. Contracting
   c. Formulary issues
   d. Market share issues
   e. Lunch/dinner presentations

5. Special Services Provided
   a. Research (Phase IV and Outcomes)

Long-Term Care Facilities

1. Nursing Facility
   a. Interview with key staff
      i. Administrator
      ii. Director of Nursing
      iii. Staff Nurses
      iv. CNAs
   b. Medication administration observation
   c. Review of consultant pharmacist's activities
   d. Discussions with patients

2. Assisted Living Facility
   a. Interview with key staff
      i. Director
      ii. CAN
   b. Medication Observation (compare with nursing facility)
   c. Review of consultant pharmacist's activities
   d. Discussion with patients

3. Medical Director
   a. Role in the nursing facility
   b. Specific duties and responsibilities
   c. Interaction with key facility staff
   d. Interaction with the LTC pharmacists and consultants

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DAY 2 (1p - 5p) REVIEW & DISCUSSION

1. Review of Participant's Experiences

2. Reimbursement (Medicaid & Medicare) Challenges for the LTC Industry
   a. Prospective Payment System (PPS)
   b. Cost-Based Payment System
   c. Pharmacy reimbursement
   d. Contracting

3. Therapeutic Interchange
   a. How to select preferred products
   b. How to design therapeutic interchange programs
   c. Collaborative practice agreements
   d. Benchmarking and monitoring

4. Discussion of Applicability of LTC Experience to Sales
   a. Who are the decision makers
   b. How to conduct sales meetings
   c. What decision makers want to hear
   d. How to present your products

5. Summary & Conclusion

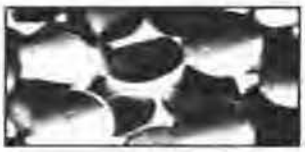
Maximizing the Long-Term Care Market Opportunity

Background

Abbott Laboratories

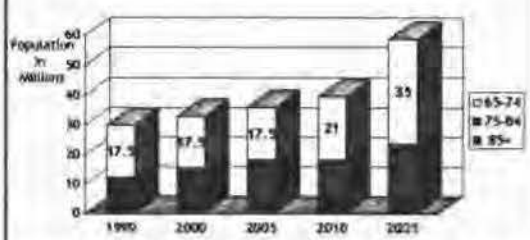
Purpose

As the fastest growing segment of health care, the long term care (LTC) market accounts for nearly $5.7 billion in total pharmaceutical purchases.



Source: DHS 2001

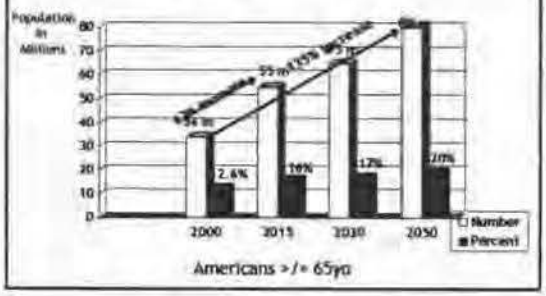
Graying of America



Quality of life

Frail Elderly

Graying of America



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2002

Americans Over 50 Years Old

- 58% of all health care spending
- 61% of all OTC spending
- 74% of all prescription drug expenditures

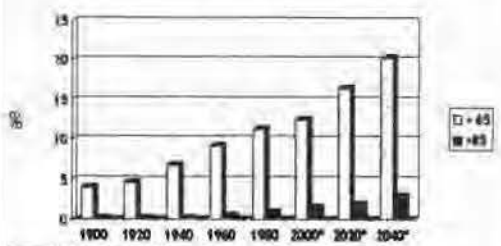
Source: Kan Dychtwald, Age Power: How the 21st Century Will be Ruled by The New Old. (J.P.Tarcher Inc., Los Angeles 1999).

Elderly = 65yr & Older

- 34 million Americans who are currently 65 & over make up 12.6% of population but utilize
  - 44% of all hospital days
  - 40% of all visits to internists
  - 33% of the nation's personal health care expenditures
  - 40% of all medications
    - 2.8 billion prescriptions

Source: IMS 1999
Meszaros EC. The onslaught of the elderly: MCOs prepare for America's fastest growing demographic with special drug problems. Managed Healthcare. 1995;S13-S16.

% of US Population



Source: US Census Bureau 2000
* = estimated

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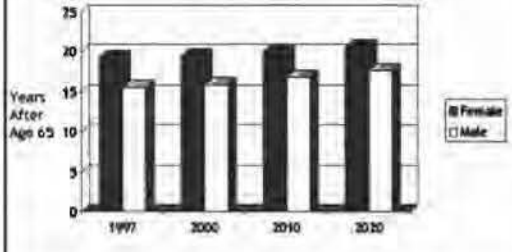
2002

2

Elderly = 85yr & older

- 3 million Americans
  - 1.2% population
  - 3x the hospital resources
  - 2x the prescription drugs
- Fastest growing segment of elderly
- Will double by 2025 (5.2 million)
- 25% live in NHs

Age 65 Life Expectancy



Why All the Fuss?

"Medications are probably the single most important health care technology in preventing illness, disability, and death in the geriatric population."

Source: Avorn J. Medication Use and the Elderly: Current Status and Opportunities. Health Affairs 1995, Spring

REDACTED

2002

3

Objectives

Upon the completion of this program, the attendee will be able to:

- Define LTC
- Recognize LTC customers
- Identify key regulations
- List the key decision-makers who make up the LTC pharmacy & facility teams
- Describe a typical LTC pharmacy operation
- Identify the challenges facing the LTC industry
- Understand how Abbott Pharmaceuticals can partner with LTC pharmacies and facilities

REDACTED

What is LTC ?

What Is Long Term Care?

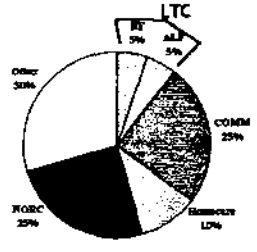


Types Of LTC Customers

- Nursing facilities
  - ICF, SNF, ICF-MR, NF, NH
- Assisted living facilities
  - ALF, PCH, RCC, board & care, CCRC
- Sub-acute facilities
- Hospices
- Group homes
- Correctional facilities
- Small hospitals
- Out-patient surgery centers
- NORC's
- Employer groups
- ?
- ?

Where Are the Elderly?

34.3 million individuals 65 & older



Long-Term Care Goal

To help people with disabilities to be as independent as possible. Focus is more on caring than on curing.



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2002

1

Long-Term Care Patients

People who have functional limitations or chronic health conditions and who need **ongoing health care or assistance with normal activities of daily living (ADL).**



Activities of Daily Living (ADL)

- Eating
- Transferring (to and from bed, chair, etc...)
  - Ambulating
- Toileting
- Dressing
  - Grooming
- Bathing



Traditional Long-Term Care

- Takes place in Nursing Facilities (NF)
  - Subacute services,
    - IV therapy, ventilator pts, (hospital-like care)
  - Rehabilitative services,
    - Therapies that restore to prior functioning levels
  - Medical services,
  - Skilled nursing services,
  - Supportive social services

Adapted from The Managed Care Resource

CPR - Administers Medicine
P.P Adverse Events in
Butt side
Don't Realize Effects.
Teach how to
avoid Side Effects.
$15 HR
CNA
6-8 HR

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2002

2

90% occupancy is needed to be prof. table

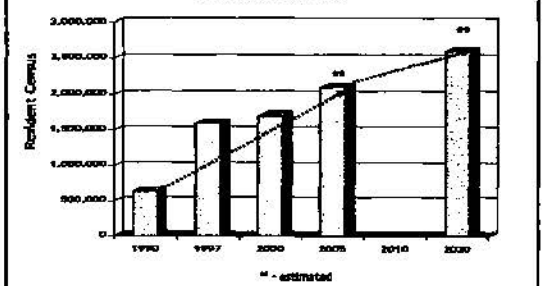
Nursing Facility (NF)

- State licensed
- Skilled nursing available 24hr/day
- Residents need frequent medical or nursing support
- Average size: 106 beds
- Average occupancy: 81%

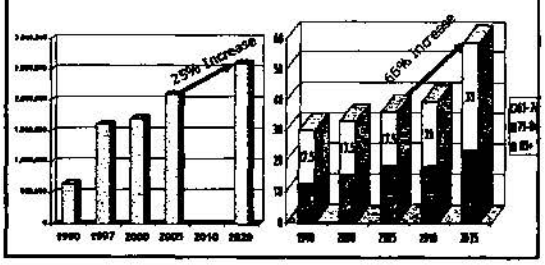
- Restorative or maintenance assistance with:
  - Medications
  - Eating
  - Dressing
  - Ambulating
  - Toileting
  - Bathing
  - Grooming

Called "residents"

Growth in Nursing Facility Residents



NF Beds vs Elderly Growth



REDACTED

2002

3

Traditional Nursing Facility Goal

- Rehabilitation
- Community involvement
- Encouragement of resident "living"
- Focus on resident's total needs

Adapted from Nursing Home Association Membership Directory

Nursing Facility – (Medicare A)

- Highest level of care
- Requires an RN available 24hr/day
- PT, OT, ST, RT
- 100 days per event
  - 3-day hospital stay
  - Qualifying illness
  - 20 days-100%, 80 days-80%

Medicare Part A Costs

- 1999 - $9.6 billion
  - 5 % of total national Medicare expenditures
- PPS reimbursement
  - MDS
  - RUGs
  - Capitated

Source: HCFA Review, Summer 2001

Nursing Facility – Subacute (Medicare/Insurance)

- Merges intensity of hospital services with operation of a nursing home
- Reduces cost of care for seriously ill patients
- May be a wing of the hospital or a SNF
- 35,000 – 45,000 beds in USA dedicated to Subacute care
- Goal: To stabilize seriously ill patients (cardiac, pain, extensive wounds, or other labor intensive problems) so they can be moved to less care-intensive facilities

Nursing Facility (Medicaid/Private/Insurance)

- Lower level of care
- No requirement for 24hr RN monitoring
- Medical, nursing, and social services provided ... but little PT,OT, ST
- Room and board of persons not capable of independent living due to inability to perform ADL's
- Cost based
  - MDS – Case Mix

Medicaid / Private Costs

Medicaid	Private
▪ 1999 - $43 billion • 23% of total Medicaid expenditures	▪ 1999 – $ 38 billion

Total NF Costs 1999 - $90 billion
2000 - $92.2 billion

Source: HCFA Review, [illegible]

REDACTED

2002

5

Long Term Care Costs

- Average NF stay costs:
  - $46,000/yr
  - $120/day
- Daily rates include:
  - Room,
  - Board,
  - Nursing care,
  - Therapeutic activities,
  - Social services
- Other services are charged separately:
  - PT,OT,ST (therapy)
  - Supplies
  - **Pharmaceuticals**
  - Telephone
  - Cable TV

Pharmacy bills drugs directly to Medicaid, Private Pay, Insurance Company. The facility only pays for drugs on the 10% of patients who are on Medicare.

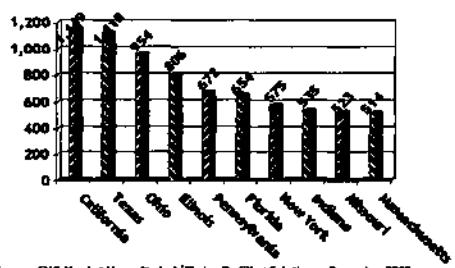
Source: American Council of Life Insurer's Report 2000

Top 10 NF Chains

Chain	Beds	Facilities
REDACTED	51,054	466
REDACTED	41,613	299
REDACTED	39,293	305
REDACTED	38,700	326
REDACTED	34,797	300
REDACTED	28,226	213
REDACTED	27,954	229
REDACTED	25,821	240
REDACTED	16,490	157
REDACTED	15,772	250

Source: Provider Magazine, July 2002 — 18.5% of Total US NF Beds

Top 10 States by # of Nursing Facilities



Source: SNG Nursing Home Market/Chains Profiling Solutions - December 2000

REDACTED

2002

6

Hospitals

- Approximately 20% of hospitals are in the LTC market
- Skilled beds for short-term care to sub-acute patients
  - Stroke
  - COPB
  - Orthopedic
- Average stay 100 days
- DRG debate
- Going away?

Called "patients"

ICF - MR

- Mentally retarded patients
- Slightly different regulations
- Usual age 5 - 25
- May also be cared for in:
  - Group residences
  - Semi-independent living facilities
  - State Institutions
- High emphasis on education and social programs
- Average stay 15 years

Called "clients"

Home Health Care

- Fastest growing sector of health care
- Nursing care provided in the patient's home
- Medicare and insurance is usual payor
  - Durable medical equipment (DME)
  - IV therapy
  - Ostomy/wound care
  - Nutritional supplements
  - Skilled nursing

Called "patients"

REDACTED

Home Health Care Costs

- Average Medicare home health visit costs $85/visit in 1996
- Costs 1999: $34.5 billion
- Home care costs
  - 44% paid by Medicare
  - 14% paid by Medicaid
  - 42% paid by private insurance

HCFA Review, Summer 2001



Correctional Facilities



- Growth in prison population is leading to more elderly prisoners
- Similar physical problems seen in other LTC settings
- Average stay 5 yrs

Called " ???"

Death with Dignity

Keeping Patient Calm -less agitated

Hospice

- Care for the terminally ill (home or institution)
- Medicare and private insurance pays
- Typical patient
  - Cancer
  - AIDs
  - Alzheimers (end stage)
  - COPD, emphysema
- Average stay 2 months (6 mo limit)
- Primary emphasis is PAIN MANAGEMENT

REDACTED

2002

Assisted Living Facility

- Social model
- Residents similar to unskilled NF residents
- Private pay
- Less regulation
- No requirement for RN or LPN care *
- Med administration &/or assistance by CNAs
- No medical care provided by facility *
- Average size: 40 beds
- Average occupancy: 85%

* May differ by state

Called "resident"

Top 10 ALF Chains

Chain	Beds	Facilities
REDACTED	20,182	430
REDACTED	14,637	151
REDACTED	14,241	186
REDACTED	11,967	132
REDACTED	8,981	90
REDACTED	7,115	184
REDACTED	6,774	58
REDACTED	6,200	60
REDACTED	5,940	34
REDACTED	5,434	49

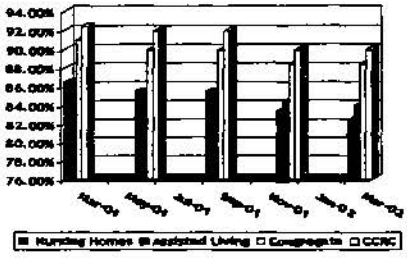
NH / ALF Chains

Chain	SNF Beds	ALF Beds
REDACTED	6,992	5,298
REDACTED	41,613	4,668
REDACTED	25,821	4,040
REDACTED	28,226	2,687
REDACTED	16,490	1,912
REDACTED	15,772	1,501

REDACTED

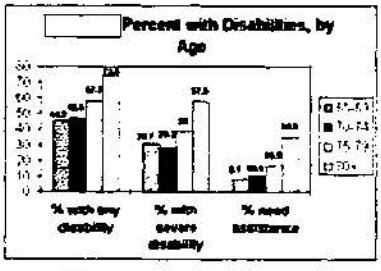
2002

Senior Housing Occupancy Rates



Accessed 7/02: National Investment Center for the Seniors Housing and Care Industries

Disabilities Can Lead to Institutionalization



Source: CMS Report, April 2002

Same Patient - Different LTC Facility

Nursing Facility		Assisted Living
75% female	→	75% female
Average age – 85	→	Average age – 85
Average # meds – 9	→	Average # meds - 9
Medical model	→	Social model
Medicaid/Medicare	→	Private pay
CON (bed control)	→	No or limited CON
Highly regulated	→	Little regulation
Average stay – 1.5yr	→	Average stay – 3yr

REDACTED

Who Lives in a Nursing Facility ?

- Americans with a nursing home address ...
  - 5.3% over age 65
    - 2% Americans age 65-74
    - 6% Americans age 75-84
    - 23% Americans age 85+

Who Uses NF Care?

- 89.3% over age 65
- 75% are women
- 10.7% ages 1 - 64

* Nursing Home Association Data

- Average NF resident - 4 ADLs
- Average home health patient - 2.5 ADLs
- Average ALF resident - 1 ADLs

Who Uses NF Care?

- 70 - 80% of USA facility population is disoriented or memory impaired
  - 34.5% Depression
  - 6.9% Psychiatric Dx



Source: CMS MDS Report Jan 2001

REDACTED

2002

11

ABC: The Key Symptom Domains of Alzheimer's Disease



Behavior Disturbances Exhibited in Dementia

- **DEPRESSION**
  - Depressed Mood
    - Irritable mood
  - Diminished interest or pleasure
  - Significant weight loss or anorexia
  - Insomnia or hypersomnia
  - Psychomotor agitation or retardation
  - Fatigue
  - Delusions of worthlessness or extreme guilt
  - Diminished ability to think, concentrate, or make decisions
  - Suicidal ideation
- **DEMENTIA**
  - Wandering
  - Poor self care/resisting care
  - Anxiety
  - Insomnia
  - Nervousness
  - Fidgeting
  - Uncooperativeness
  - Restlessness
  - Unsociability
  - Agitated behaviors
  - Impaired memory
  - Indifference to surroundings

Behavior Disturbances Exhibited in Dementia

- **PSYCHOSIS**
  - Delusions
  - Hallucinations
  - Disorganized speech
  - Grossly disorganized behavior
  - Catatonic behavior
  - Flat affect, alogia, avolition
- **DEMENTIA**
  - Wandering
  - Poor self care/resisting care
  - Anxiety
  - Insomnia
  - Nervousness
  - Fidgeting
  - Uncooperativeness
  - Restlessness
  - Unsociability
  - Agitated behaviors
  - Impaired memory
  - Indifference to surroundings

REDACTED

Factors Leading To NF Care

- Absence of family
- Exhaustion of financial resources
- Burden on existing family members
  - Traditional care givers (women) are increasingly in the work force
  - Family size is decreasing
  - Rising life expectancies find children caring for very old parents while they themselves are elderly and lacking stamina

Factors Leading To NF Care

- Women are more likely than men to enter a nursing facility.
  - Lifetime risk of being in a NF at age 65: 52% women - 30% men
- Lack of children
  - 37% of NF residents lack children
  - 19% of community dwelling elderly lack children
- Lack of spouse
  - 84% of NF residents lack spouse
  - 45% of community dwelling elderly lack spouse

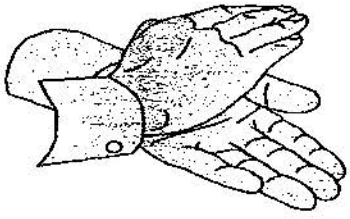
NF - ADL Total Dependency

Eating	34.2%
Transferring	68.4%
• Ambulating	26.6%
Toileting	75.2%
Dressing	81.2%
• Grooming	79.8%
Bathing	50.6%

Source: CMS MDS Reports, Jan 2001

REDACTED

CONGRATULATIONS !!



REDACTED

2002

14

The LTC Regulatory Environment



Objectives

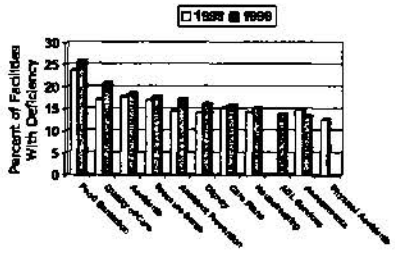
Upon completion of this section, the attendee will be able to:

- Recognize key legislative actions that have impacted the LTC industry
- Identify specific regulations that effect medication use in the LTC industry
- Differentiate how Abbott Laboratories' products can offer a benefit to the facility by improving compliance with regulations

Government Involvement In LTC - NF

- LTC (Nursing Facilities) is the most heavily regulated industry
  - CMS (Center for Medicaid and Medicare Services)
    - Formerly called: HCFA (Health Care Finance Administration)
  - State or Federal agencies have authority to:
    - impose monetary fines up to $10,000/day
    - suspend admissions to the facility
    - cut off Medicaid funds
    - place monitors in NF
    - hire temporary managers for the NF if the NF is having difficulty complying
- Over 300 pages of regulations (188 regs)

Top 10 Deficiencies



REDACTED

2002

1

Omnibus Budget Reconciliation Act (OBRA) 1987

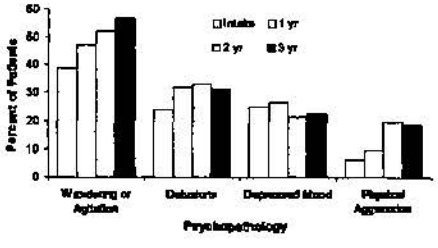
- Introduced "chemical restraint" regulations
- Required dose reductions & behavior monitoring on psychotropic medications
  - Antipsychotics
  - Anxiolytics
  - Sedative/Hypnotics
- Specified medication administration observation (med pass) procedures

Why Be Concerned With "Chemical Restraints"?

- 70-80%% of NF residents suffer from dementia
- Dementia mimics psychosis in many domains



Frequency of Patients With AD–Related Psychopathology During 3 Years of Follow-Up



Balanced Budget Amendment (BBA) 1997

- Cost control effort
- Introduced Prospective Payment System (PPS)
- Introduced Medicare "managed care" – Medicare + choice

Reimbursement NF = SNF + ICF

SKILLED CARE
(10% Medicare)
- Medicare
- Private Pay
- Insurance & Managed Care
- Capitation
- Maximum stay 100 days (Avg stay 60 days)
- DRUGS INCLUDED

UNSKILLED (ICF)
(47% MCD/43% Other)
- Medicaid
- Private Pay
- Insurance
- Capitation
- Maximum stay indefinite (Avg stay 1.5 years)
- DRUGS BILLED SEPARATELY

Medicare vs Medicaid

Medicare
- Administered federally
- Persons 65+ or disabled
- Rx meds not included w/few exceptions
- Part A - hospitalizations and SNF
- Part B - MD visits, DME

Medicaid
- Administered by states w/federal matching funds
- Medically "indigent"
- Rx meds included (voluntarily)
- Hospitalizations, NF, MD visits

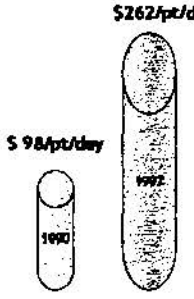
State & Federal expenditures for NF = $54 billion in 2001

REDACTED

2002

3

The Quest for Medicare PPS



Medicare PPS vs Cost Based

MDS

PPS Reimbursement

- Capitated Rate
- Requires 5 MDS evaluations (adm,14,30,60,90 days)
- Rate can change w/o MDS (RUGS)
- Encourages less spending
- Encourages less acute patients
- *Fluff has "gone with the wind"*

Cost Based Reimbursement

- Cost-Based Rate
- Cost + Overhead mark-up
- Encourages more spending
- Encourages more acute patients
- Room for fluff

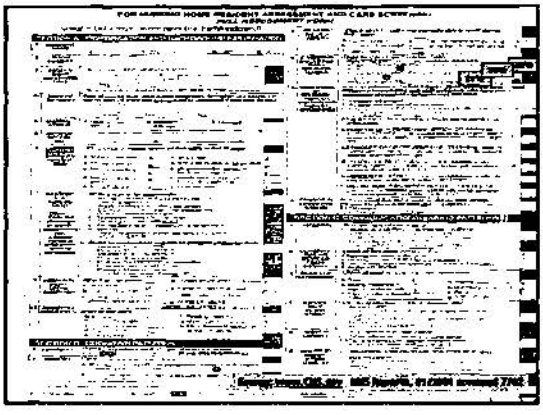
Minimum Data Set (MDS)

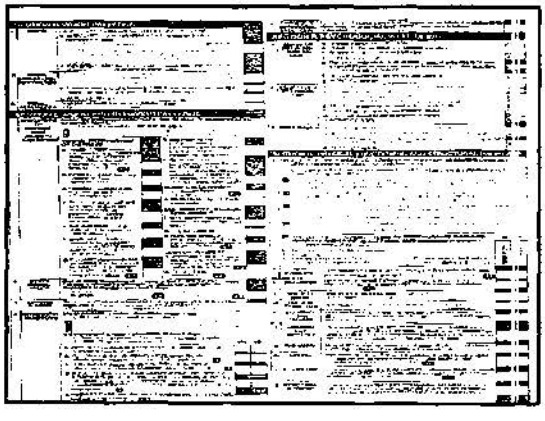
- Over 500 items assessed
- 22 Categories
- 10 pages
- All NF patients
  - On admission, quarterly, significant change
- Drives Medicare payment (PPS)
- Drives Quality Indicators
- Drives Medicaid payment-some states (Case Mix)

REDACTED

2002

4





HCFA Regulation Update 1999

- Added "Drugs Potentially Inappropriate in the Elderly" to "unnecessary drug" regulation
- Expanded medication administration requirements
- Required assessment and treatment of pain
- Focused attention on dialysis patients
- Quality Indicators

REDACTED

2002

5

Quality Indicators

- 24 Items
- Calculated from data elements that are included on the Minimum Data Set (MDS).
- Five of the 24 indicators are based upon Section O of the MDS. These five indicators are:
  - prevalence of symptoms of depression without antidepressant therapy
  - prevalence of residents who take 9 or more different medications
  - prevalence of antipsychotic use in the absence of psychotic or related conditions
  - prevalence of antianxiety/hypnotic use
  - prevalence of hypnotic use more than two times in last week

24 Quality Indicators

1. New fractures
2. Falls
3. Behavior symptoms affecting others
4. Symptoms of depression
5. Symptoms of depressed mood without treatment
6. Use of 9 or more medications
7. Cognitive Impairment
8. Bladder or bowel incontinence
9. Incontinence without a toileting plan
10. Indwelling catheters
11. Fecal Impaction
12. Urinary tract infections
13. Weight loss
14. Tube feeding
15. Dehydration
16. Bedfast
17. Decline in late loss ADLs
18. Decline in ROM
19. Anti-psychotic use, in absence of psychotic or related conditions
20. Anti-anxiety/hypnotic use
21. Hypnotic use more than 2x / week
22. Daily physical restraints
23. Little or no activity
24. Stage 1-4 pressure ulcers

29
20
10

Dep
Bowel

0 - 17.4
1, 5.8
22. 8
24. 9

French roast

Lorazepam and Divalproex in Nursing Facilities

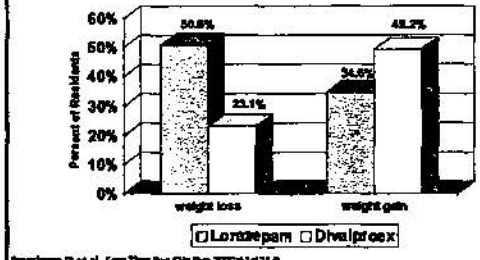
- 146 patient charts reviewed
- 81 patients (55.5%) received lorazepam; 65 patients (44.5%) received divalproex
- 37 patients (56.9%) treated with divalproex showed improvement
- 25 patients (30.9%) treated with lorazepam showed improvement

REDACTED

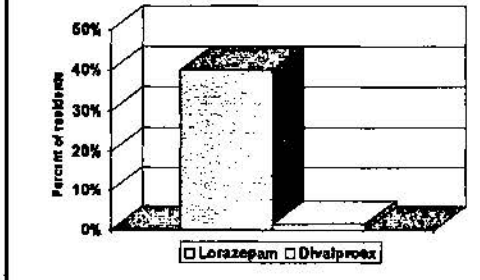
2002

6

Residents Experiencing Weight Gain or Loss



Residents Experiencing Falls



Sentinel Events- facility is flagged if only 1 resident triggers

- Fecal impaction
- Dehydration
- Acquired pressure ulcers

Anticholinergic Cause

REDACTED

2002

7

Additional considerations

- Hospice care
  - Plan of care must include directives for
    - Pain management (big JCAHO issue!)
    - Other uncomfortable symptom management
  - Drugs & supplies must be provided as needed for palliation & management of terminal illness & related conditions
    - Depression, Anxiety

Additional Considerations

- Dialysis services
  - Medication must be given at times for maximum effect

Additional New Investigative Protocols

- Unintended weight loss (diuretics, laxatives, cardiovascular meds)
- Dining & food services
  - Do not give meds at meals unless patient requests or necessary for optimal medication effect
  - Pain meds given prior to meals to allow eating in comfort
  - Do not use meal foods as med vehicles
- Nursing services, sufficient staffing

REDACTED

Nursing Staff Averages

	Natl	GA	MI	S.CA	WY
Avg # beds	80	100	97	77	64
Avg # RN FTE	9	6	12	8	9
Avg # LPN FT	12	19	15	76	14
Avg # C.N.A FTE	33	40	42	53	25
Avg # Total Nsg Staff FTE	54	65	69	137	48
Avg # Nsg FTE/ Resident	0.7	0.6	0.7	1.8	0.8

Source: HCFA OSCAR data 1999

F329 Unnecessary Drug

- Each resident's drug regimen must be free from unnecessary drugs. An unnecessary drug is any drug when used ...
  - Without **diagnosis or reason** to support drug use
  - Without **adequate monitoring**
  - In the presence of **side effects** or **adverse consequences** which indicate the dose should be reduced or discontinued
  - In the presence of **duplicate therapy or excessive dose**
  - For **excessive duration**

Medications Potentially Inappropriate in the Elderly

- Beers,M MD, *Explicit Criteria for Determining Potentially Inappropriate Medication Use by the Elderly*, Arch Intern Med/Vol 157. July 28, 1997
  - High Potential for Severe ADR ... F329, Unnecessary Drugs
  - High Potential for Less Severe ADR ... F428/429, Drug Regimen Review

REDACTED

Go to SLUD

The Problem

Cholinergic System Effects	Anticholinergic Effects
• Salivation	• Dry Mouth
• Lacrimation	• Dry Eyes
• Urination	• Urinary Retention
• Defecation	• Constipation
S L U D	

F329 - Potential for Severe ADR

- Pentazocine (Talwin)
- Long-Acting Benzodiazepines (Valium, Dalmane, et al)
- Amitriptyline (Elavil)
  - Except for neuropathic pain when benefit is greater than risk
- Doxepin (Sinequan)
- Meprobamate (Equanil)
- Disopyramide (Norpace)
- Digoxin > 0.125mg/day ** (Lanoxin)
- Methyldopa ** (Aldomet)
- Chlorpropamide (Diabenese)
- GI Antispasmodics (Levsin)
- Barbiturates (Phenobarb) *OK for seizures
- Meperidine ** (Demerol)
- Ticlopidine (except for ASA intolerant post CVA pts) (Ticlid)

** If started within last 31 days

F329 - Drug/Disease Combinations

- BPH
  - Anticholinergic antispasmodics
  - Anticholinergic antiparkinson meds
  - GI antispasmodic
  - Anticholinergic antidepressants
- Arrhythmias
  - Tricyclic Antidepressants

REDACTED

2002

F329 - Drug/Disease Combinations

- COPD
  - Long Acting Benzodiazepines
    - Short Acting Benzos are OK PRN for anxiety
  - Barbiturates
  - Hypnotics/Sedatives
- PUD, GERD, GASTRITIS
  - NSAIDs
- SEIZURES/ EPILEPSY
  - Metoclopramide
- BLOOD CLOTTING DISORDERS
  - Aspirin, NSAIDs, dipyridamole, ticlopidine

F429 - Potential for Less Severe ADRs

- Phenylbutazone
- Trimethobenzamide (Tigan)
- Indomethacin (Indocin)
- Dipyridamole (Persantine)
- Reserpine (Serpasil)
- Diphenhydramine (Benadryl)
- Ergot Alkaloids (Hydergine)
- Muscle Relaxants (Soma, Flexeril, Robaxin)
- Antihistamines (Vistaril, Atarax, Anthvert, etc...)

F429 - Drug/Disease Combinations

- Diabetes
  - Corticosteroids - if started within 30 days
- PUD, GERD, GASTRITIS
  - Aspirin > 325mg/day
  - Potassium supplements (unless benefit outweighs risk)
- SEIZURES/ EPILEPSY
  - Antipsychotic Drugs (unless used for </= 72hr for acute psychosis)
- BPH
  - Narcotics (unless use is periodic, 1x per 3months for < 7 days)
  - Incontinence meds (flavoxate, oxybutynin, bethanechol)
  - *interesting point: other Anticholinergic Drugs are listed as F329 !!!*

REDACTED

Relevance of ADR Regulations

- Average NF of 106 beds
  - 24 ADR events/yr
  - 8 "near misses"/yr
- 350,000 ADRs/yr for US NF's
- Nearly 50% of ADRs are preventable
- 80% of "near misses" associated with warfarin
- Cost of ADR's was $4 Billion in 1996.

Source: NIH Press release 8-9-2000

Causes of Preventable ADR

- Ordering Errors
  - Wrong dose
  - Harmful interactions
  - Wrong drug choice
- Monitoring Errors
  - Inadequate lab monitoring
  - Failure or delay in responding to s/s of drug toxicity

Most common ADR causes:

- Medications
  - Psychoactive meds:
    - **Anti-psychotic**
    - Anti-depressant
    - Sedative
  - Anti-coagulants
- Preventable ADR:
  - **Neuropsychiatric events**

REDACTED

2002

12

F330 Antipsychotic Drugs (APD)

- Residents who have not used antipsychotic drugs are not given these drugs unless antipsychotic drug therapy is necessary to treat a specific condition as diagnosed & documented in the clinical record

Allowable APD"conditions"

- Schizophrenia
- Schizo-affective disorder
- Delusional disorder
- Psychotic mood disorders
  - mania
  - depression w/psychotic features
- Acute psychotic episodes
- Brief reactive psychosis
- Schizophreniform disorder
- Atypical psychosis
- Tourette's disorder
- Huntington's disorder

Allowable APD "Conditions"

- Organic Mental Syndromes – OMS (delirium, dementia, amnestic/cognitive disorders) w/ associated psychotic &/or agitated behavior, which:
  - are quantitatively & objectively documented
  - persistent
  - not caused by preventable reasons, and ...
  - which are causing resident to:
    - present a danger to self or others
    - continuously scream, yell, or pace if these behaviors cause functional impairment
    - experience psychotic symptoms which cause resident distress or functional impairment

REDACTED

Depakote Read for Antipsy.
- reduce need
- can take at as whole

F331 APD Dose Reductions

- Must be gradual
- Must be attempted twice in one year
- Is "clinically contraindicated" IF:
  - resident has a specific condition (1-10), has a hx of recurrence of psychotic symptoms, is stable w/o significant side effects
  - resident has OMS, but had return of symptoms after 2 attempted dose reductions
  - MD has justified why continued use of drug and dose are clinically appropriate

F331 APD Dose Reductions

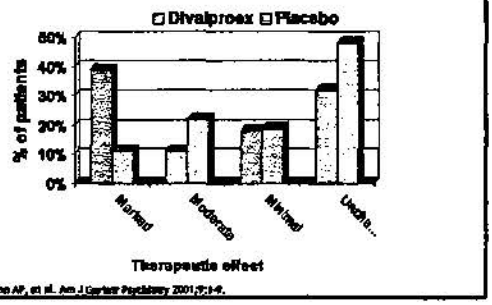
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  - MD has justified why continued use of drug and dose are clinically appropriate

Divalproex For Agitation In Dementia

- Fifty-six patients randomized (28 divalproex, 28 placebo)
- Mean dose at Week 6 = 826 mg/d; mean serum concentration = 45.4 µg/mL
- Improvement in BPRS agitation score; divalproex vs placebo (ANCOVA: $P=0.05$)
- Change in CGI showed trend for improvement (ANCOVA $P=0.06$)
- The average dose and serum levels were low compared with reports in younger subjects
- Larger follow-up study indicated

REDACTED

Clinical Global Impression: Therapeutic Effect

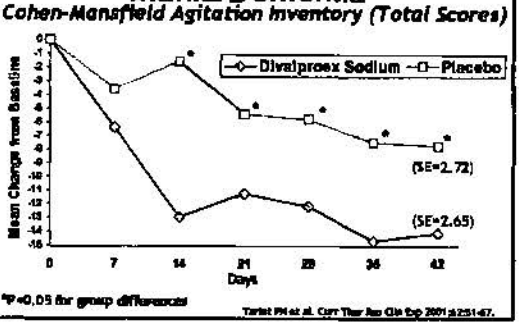


Divalproex in Elderly Mania/Dementia

- 173 randomized patients (87 received divalproex, 85 received placebo
- Divalproex group had a statistically significant decrease from baseline on CMAI score, compared to placebo (p=0.035)
- 47 patients in divalproex group withdrew prematurely due to somnolence (related to aggressive dosing and titration schedule)
- Somnolence generally rated as mild to moderate
- Further study of divalproex at a slower titration and daily doses below 15 mg/kg for agitation is warranted

Divalproex in Elderly Mania/Dementia

Cohen-Mansfield Agitation Inventory (Total Scores)



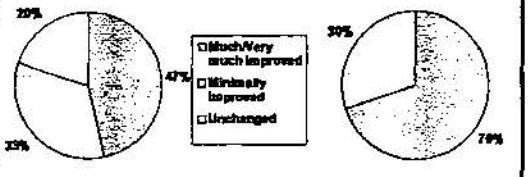
Stopped due to forced titration

REDACTED

2002

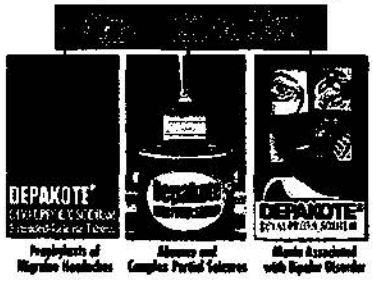
15

Divalproex Alone or In Combination with a Neuroleptic
Results



Narayan M. & Nelson JC. J Clin Psychiatry. 1997;58:351-4.

The Depakote Advantage



F329 Sedative/Hypnotic Drugs

- Overused (unless not paid for by Medicaid)
- High potential for side-effects
  - Sedation
  - Confusion
  - Amnesia
  - Anticholinergic
  - Falls
- Dose reduction required after 10 days of continuous use

REDACTED

F329 Anti-anxiety Drugs

- Overused
- High potential for side effects
- PRN vs Routine
- Dose reduction required after 4 months of continuous use
- Generalized anxiety vs Organic Mental Syndromes

1 Sedative Effect.

F329 Anti-anxiety Drugs

- Overused
- High potential for side effects
- PRN vs Routine
- Dose reduction required after 4 months of continuous use
- Generalized anxiety vs Organic Mental Syndromes

Depakote Pearl - reduce need for Anti-anxiety and Sedative/hypnotic drugs

Antidepressants

- Underused
  30 - 80% of NF residents may be depressed 34.5%
- Difficult to diagnosis depression
  - Co-existing diseases (dementia)
- AD drug selection is based on
  - Safety profile
    - Drug interactions
  - Cost

REDACTED

2002

17

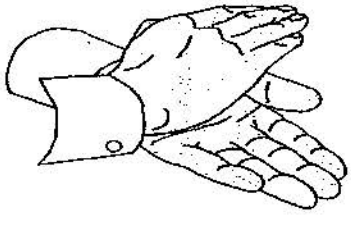
F333 Medication Administration

- Medication Error - the observed preparation or administration of drugs or biologicals which is not in accordance with:
  - MD orders
  - Manufacturer's specifications
  - Accepted professional standards

HCFA Med Error List

- Failure to "shake well"
- Failure to mix insulin by "rolling"
- Crushing meds that should not be crushed
- Giving meds without adequate fluids 4-8oz (bulk laxatives, potassium supplements, NSAIDS)
- Giving meds without food or antacids when manufacturer recommends (NSAIDS)
- Proper enteral feeding precautions
- Eye Drops - wait 3-5 min
- Swallowing sublingual meds
- MDIs - wait 1 minute

CONGRATULATIONS !!



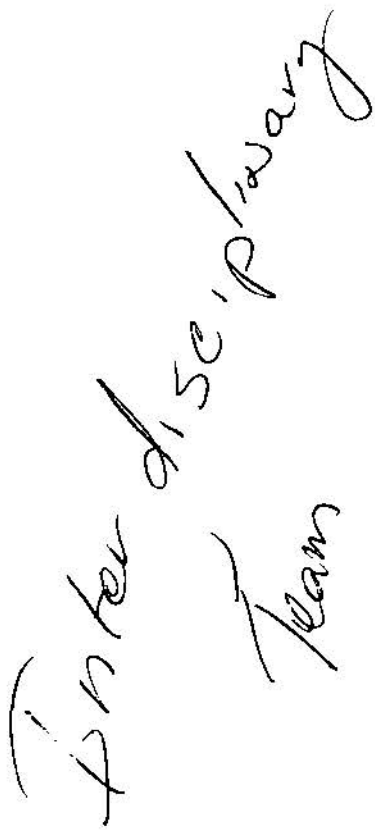
Depakote Pearl Can be given with food Sprinkles for pts who can't swallow and minimize GI side effects Can be Draw Back large amounts of water can

REDACTED

2002

18

Key Decision Makers


Enter disciplinary
Team


LTC Key Decision Makers
Administrator
Physician
Consultant Pharmacist
Dispensing Pharmacist
Technician
Nurse Practitioner
Charge Nurse
Certified Nurse Assistant
Dietician
Director of Nurses
Physician's Assistant

Objectives

Upon completion of this section, the attendee will be able to:

- Define LTC pharmacy
- List the health care practitioners who make up the LTC pharmacy team
- Identify services offered by the LTC pharmacy
- List the key decision-makers encountered in the LTC industry
- Recognize 3 different communication techniques to use when presenting information to the physician

Types Of LTC Customers

- Nursing facilities
  - ICF, SNF, ICF-MR, NF, NH
- Assisted living facilities
  - ALF, PCH, RCC, board & care, CCRC
- Sub-acute facilities
- Hospices
- Group homes
- Correctional facilities
- Small hospitals
- Out-patient surgery centers
- NORC's
- Employer groups
- ?
- ?

What's the Quickest Way to Reach All These LTC Customers??



- Long Term Care Pharmacists

REDACTED

2002

LTC Pharmacy

- Evolved over 30 ye
- Specialty practice
  - Products
  - Services
- High-tech systems
- Efficiency & accura expert
- Retail license
- Retail reimbursement



LTC Pharmacy

- Product
  - Dispensing pharmaceuticals
    - Specialized packaging
    - Delivery
  - Medical supplies/DME
  - Infusion therapy
  - Medical record production

LTC Pharmacy

- Services
  - Clinical consultative services
  - Education & training
  - Pharmacokinetics
  - Report generation/analysis

REDACTED

2002

2

LTC Pharmacy

- Consultant only 32%
- Consultant/Provider 61%
  - Retail 27%
  - Institutional Rx 33%
  - Nursing Home Rx 10%
  - Hospital Rx 5%
  - No Response 25%
- Provider only 3%

Provider vs Consultant Activities

- Provider:
  - Purchasing and distribution of drugs,
  - Billing,
  - Clinical review and therapy changes
- Consultant:
  - On-site clinical review of patient
  - Therapy recommendations,
  - Evaluation of facility compliance with regulations

What LTC Pharmacists Want ...

- Better understanding of disease states
- Knowledge of new pharmacological entities
- Improved communication skills
- Assistance with documentation of services

REDACTED

2002

3

LTC Pharmacy Team

- Consultant pharmacist
- Pharmacist manager
- Pharmacists
- Technicians
- IV Nurses
- Education Coordinators
- Inventory techs
- Med records techs
- Billing clerks
- Delivery personnel



DR VS
Te Program
everyone needs
to know

Ancillary Staff

- **Medical Records Technician**
  - Corrects MAR/POF
  - Alerts pharmacist when TS drug is "un-corrected"
- **Billing Clerk**
  - Interacts with family members
  - Transfers inquiries to pharmacist when family questions why a TS drug appears on bill
- **Driver**
  - Delivers and checks-in order with nurse
  - Communicates TS issues with recommendation to contact pharmacist for full explanation

explain why
the switch

LTC Pharmacy Technician

- Inventory Tech
  - Controls ordering
- Order Entry Tech
  - Discovers order for incorrect product.
  - Alerts pharmacist to call MD for substitution
- Dispensing Tech
  - Catches labels for incorrect product
  - Reminds pharmacist to call for switch
  - Places alert/monitoring labels on product

REDACTED

Punch card 90 %

Medication Distribution Systems

- Packaging
  - Unit dose
    - 24hr, 7day, 30day cycles
  - Bingo card
    - 30/31 day
  - Compliance packaging
    - Customizable cycle



Medication Distribution Systems

- Labeling
  - Only resident name, and medication name required
  - Most use modified retail prescription label format
  - Piggy back/peel off for re-ordering
  - Label placement for ease-of-use
  - Bar-coding

Medication Distribution Systems

- Unit Dose & Punch Card Packaging
  - Improves nursing staff efficiency & accuracy
- Multiple Dispensing/Month
  - Limit quantities of controlled substances
  - Limit quantities of large/bulky items
- Timely Delivery
  - 24 hour on-call
  - Emergency back-up 24hr/7day

REDACTED

2002

5

Equipment

- **Medication carts**
  - $2000 ea x 3/NF
- **Treatment carts**
  - $1000 ea x 1/NF
- **Fax machines**
  - 1 per station $250 ea
- **Computers ?**
  - Internet access
  - Direct on-line access
- **Software ?**
  - MDS, order/receipt



F426 Pharmacy Services

- The facility must provide routine & emergency drugs and biologicals to its residents or obtain them under an agreement ...
  - A drug, whether prescribed on a routine, emergency, or as needed basis, must be provided in a timely manner. If failure to provide a prescribed drug in a timely manner causes the resident discomfort or endangers his or her health and safety, then this requirement is not met.

Delivery

- Daily Mon-Fri
  - And Saturday 85%
  - And Sunday 5%
- Same day delivery
  - Multiple deliveries/day
- Courier vs employee drivers
  - Cost
  - Customer service
  - Consistency
  - Convenience



REDACTED

2002

6

Consult Pharm
Dega to be used to be in there

Emergency Boxes

- First dose box
  - After hours re-admissions
  - Antibiotics
- True emergencies
  - Cardiac
  - Respiratory
  - Behavior
- Limitations on contents in some states



Medical Records

- Medical records
  - POF - 30day physician order summary
  - MAR - 30day medication administration record
  - TX record – treatment record
  - ADL record – nursing assistant documentation
  - Phone orders
  - Q/A reports
- In-house vs pharmacy production



Medical Supplies

- Medical supplies
  - OTC drugs
  - Wound care
  - Nutritionals
  - Urologicals
  - DME



REDACTED

2002

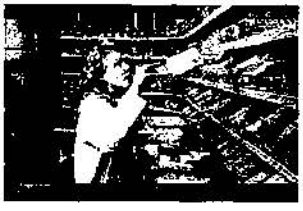
7

Infusion Therapy



- Infusion therapy
  - IV products & supplies
  - IV training for staff
  - 24hr IV nurse support
  - 24hr emergency service

LTC Pharmacists



LTC Pharmacist

Consultant Pharmacist

- Problem solvers
- Clinical Skills
- Administrative Skills
- Organizational Skills
- Communication Skills
- Persuasive
- Self Motivated
- Intuitive



REDACTED

2002

8

LTC Pharmacist

Consultant	Provider
Problem solvers ←	Problem solvers
Clinical Skills ←	Clinical Skills
Administrative Skills ←	Administrative Skills
Organizational Skills	
Communication Skills ←	Communication Skills
Persuasive ←	Persuasive
Self Motivated	
Intuitive	

LTC Pharmacists

- Consultant Pharmacist's Oath
  - *"I take responsibility for my patient's medication-related needs and am held accountable for this commitment."*
  - *"I ensure my patient's medications are the most appropriate, most effective available, safest possible, and are used correctly."*
  - *"I identify, prevent, and resolve medication-related problems that may interfere with goals of therapy."*

Consultant Pharmacist

- F 428 The drug regimen of each patient in a nursing home must be reviewed at least once a month by a licensed pharmacist.
- F 429 The pharmacist must report any irregularities to the attending physician and the director of nursing and ...
- F 430 ... these reports must be acted upon.

REDACTED

2002

9

Consultant Pharmacist

- Clinical component
  - Therapeutic drug review
  - Economic drug review
  - Improve patient care
  - Improve functional ability of patient
- Suggestions to physician, nurses, administration, support staff

Consulting is the business of selling solutions

Clinical Activities

- Drug regimen review (DRR)
- Resident assessment and care planning
- Drug utilization review (DUR)
- Drug use evaluation (DUE)
- Therapeutic drug monitoring
- Facility staff education and training
- Formulary development and management
- Nutritional support services
- Geriatric research

Compliance Activities

- Policy and procedure development
- Committee participation
- Medication administration observation
- Medication storage, accountability, destruction
- Participation in state survey process
- Quality assurance (QA)
- Infection control

REDACTED

2002

10

Therapeutic Drug Review

- "Any symptom in an elderly patient should be considered a drug side effect until proved otherwise"

Source: J Gurwitz, M Monane, S Monane, J Avorn, Brown University Long-term Care Quality Letter, 1995

Medication Therapy Management Services

- Diagnosis appropriate
- Duplicate therapy
- Dosage appropriate
- Length of therapy
- Outcome appropriate
- Adverse reactions
- *Improve functional ability*
- *Improve quality of life*



Assessment of Drug Related Needs

- Initial Clinical Review of Medication Order
  - Best drug for condition
    - Anticonvulsant vs Antipsychotic
  - Best drug in category
    - Depakote vs Carbamazepine, Gabapentin
  - Best route
    - Liquid, tab/cap, topical
  - Medicaid / Insurance formulary coverage
    - Tiered co-pays, PDLs

REDACTED

Economic Drug Review

- Product expense
  - Depakote vs Zyprexa, Risperdal, Seroquel, Geodon
- Preparation expense
  - Ability to crush tablet
  - Prepackaged punch cards
- Outcome expense
  - Treatment failure, treatment duration
- Adverse reaction expense
  - CYP450 vs NOT



Consultant Pharmacist Recommended Changes

Acceptance frequency by type of recommendation

- Discontinue drug 82%
- Change dosage/route 73%
- Switch agents 65%
- Add drug 38%

Source: SMG, TCP membership survey

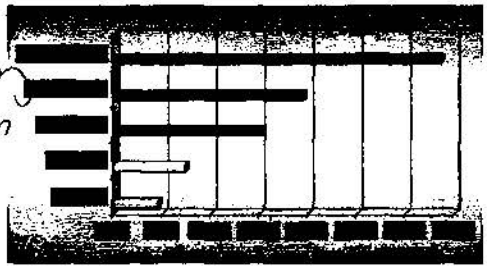
NF Resident Drug Use

9.30 medication orders/resident



Source: Tobias,D.,et al, The Consultant Pharmacist, 2000

NF Resident Drug Use by Category



Consultant Pharmacist Value

- Consultant Pharmacist-conducted drug regimen review
  - Improves therapeutic outcomes - 43%
  - Saves $3.6 billion annually (DRP).

Source: Boothman, J., et al: The Health Care Cost of Drug-Related Mortality and Morbidity in Nursing Facilities; Arch Intern Med/Vol 1997; 157:2089-2096

LTC Facility Personnel



REDACTED

2002

13

- wants to know what's going on

LTC Facility Personnel

- **Nursing Facility Administrator**
  - Licensed by board of examiners of nursing home administrators
    - Requires supervisory experience in nursing facilities
    - Requires CE
  - Responsible for the operation of facility
    - Financial, regulatory,
  - Planning of services
  - Compliance with state and federal regulations
  - Coordination of staff



Complaint of Profitable 30% hrs of CEUs
= Breakdowns

- RN Normally -

LTC Facility Personnel

- Director of Nurses (DON)
  - Registered Nurse (RN)
  - Supervisory position managing nursing staff
    - Certified nursing assistant (CNA)
    - Licensed practical nurses (LPN)
    - Registered nurses (RN)
  - Responsible for patient care
  - Responsible for financial performance of nursing department



Half time Administering meds.

7 1 5 9
8 8 1 4

LTC Facility Personnel

- Charge Nurse
  - RN or LPN
  - Responsible for care of up to 50 residents
    - Med administration
    - Documentation, progress notes, evaluations and assessments
    - Physician orders
    - Ordering and receiving meds and supplies
  - Supervises certified nursing assistants



REDACTED

2002

14

Pictures 3rd Grade Education
Deal with Behaviors

LTC Facility Personnel

- Certified Nursing Assistant (CNA)
  - High school diploma or GED
  - Certification by examination at facility or trade school
  - Performs direct resident care & assistance with ADLs
    - Bathing, grooming, eating, mobility, toileting
  - Requires 24hrs of CE yearly

The CNA is the most knowledgeable about the resident's behavioral and mental status



LTC Facility Personnel

- Nurse Practitioner & Physician's Assistant
  - Physician extender
  - Higher access
  - Frequent drug therapy changes
  - Authority varies by state
  - Operates under "physician protocol"



& Consultant Pharmacist TD

LTC Facility Personnel

- Medical Director
  - Usually attending MD for majority of residents (> 40%)
  - Oversees activities of other attending MD's
  - Provides educational and clinical support to patients & healthcare providers
  - > 45% are Medical Directors at 3 or more facilities



REDACTED

2002

15

Attending Physician

- **Responsible for:**
  - Patient's total program of care
    - Medical, nutritional, psychosocial
  - Medical assessment
  - Disease prevention / treatment
  - Charting progress notes each visit
  - Acting on the Consultant Pharmacist's recommendations
- **Works cooperatively with interdisciplinary team**
- **Must visit patient at least every 30 days**



Probably doesn't care about Regs.
90% - Are Done by Phone
Docs Don't See

Communication



Communication: LTC Pharmacist

Consultant

- Clinical information on all entities in class
  - Efficacy
  - Metabolism
  - Administration
  - ADR profile
- Differentiation of products
- Outcomes data
- Sample "comment" language

Dispensing

- Clinical information
- Reimbursement information
  - Medicaid formulary
    - Prior approval
    - MAC'd competitors
  - Managed care formulary
- Packaging options
- Good business practices

REDACTED

Communication: Physician

- Part of the team (although may not realize it)
- Responds to clinical & financial information
- Ask don't tell
  - Have you considered...?
  - What do you think about...?
  - Would you please....?
- Define conditions leading to request
- Ask for definite actions
- Support statements with references



Communication: Director of Nursing

- Improving resident care
- Time savings for nursing staff
- Improving accuracy of nursing staff
  - Documentation
  - Administration



Communication: Administrator

- Cost effective solutions
- Regulatory compliance
- Public relations
- Patient care
  - Some ADMs are RNs



REDACTED

2002

17

Communication: Charge Nurse

- Patient care
- Time savings



Case Study

- 87yo, Caucasian female
- Diagnosis: Alzheimer's Disease w/psychotic agitation, CHF, Depression, Osteoarthritis,
- Labs/Vital Signs – WNL
- MMSE – 10
- Drugs:
  - Aricept 10mg qd for Alzheimer's
  - Celexa 20mg po qd for Depression
  - Enalapril 10mg po BID for CHF
  - Vioxx 25mg po qd for Osteoarthritis
  - Risperdal 1mg po BID for psychotic agitation
  - Alprazolam 0.25mg po TID for anxiety
- Problem: Increasingly agitated with recent episode of hitting roommate. Nurse has asked to increase Risperdal dose.

Normal / Dementia

Sample Comment: Physician

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2002

18

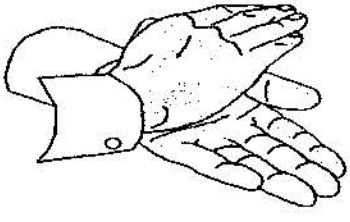
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Sample Comment: Administrator

Director of Nurses

Sample Comment: DON

CONGRATULATIONS !!



REDACTED

2002

19

Site Visits

REDACTED

LONG TERM CARE FACILITY VISIT

The LTC Facility Visit is designed to allow the attendee to experience the typical Nursing Facility (NF) and Assisted Living Facility (ALF) and participate in a routine consultant pharmacist visit.

OBJECTIVE

Upon completion of this section, the attendee will be able to:

- List the primary activities performed by the consultant pharmacist
- Prioritize the consultant pharmacist's role in both the NF and the ALF
- Recognize the importance of the consultant pharmacist in the care of the elderly and compliance with regulations in the NF and ALF
- Identify the health care professionals who make up the NF or ALF team
- List the primary activities performed by the NF and ALF team
- Identify the role of other professionals in the NF and ALF team

EXPERIENCES TO INCLUDE:

- Entrance interview with ADM and DON (approx 15 min)
- Tour of Facility (approx 30min)
- Introduction and Explanation of other Health Care Team Members
  - ADON
  - Charge Nurse
  - Med Nurse/Treatment Nurse
  - Certified Nursing Assistant
  - Medical Director / Attending Physician (if available)
  - Social Worker
  - Activity Director

RE [redacted]

- Meeting with ADM (approx 15min)
  - Role of ADM
  - What ADM expects from LTC Pharmacy and Consultant
  - Reimbursement Issues
  - Regulatory Issues
  - Challenges

- Meeting with DON (approx 15min)
  - Role of DON
  - What DON expects from LTC Pharmacy and Consultant
  - Staffing Issues
  - Patient Care Issues
  - Regulatory Issues
  - Challenges

- Medication Administration (approx 30min)

- Med Room and Med Cart Check (approx 15min)

- Chart Reviews (approx 15-30 min)
  - Inappropriate medication
    - Beer's Criteria
    - HCFA Regs
  - Therapeutic monitoring
  - Therapeutic interchange
  - Economic recommendation
  - Documentation review
  - Patient Assessment
  - Psychotropic Monitoring

- Preparation of Reports (approx 15min)

- Exit Interview with DON & ADM (approx 15 min)

REDACTED

REDACTED

LTC PHARMACY VISIT

The LTC Pharmacy Operations Visit is designed to allow the attendee to rotate through the various departments of the pharmacy and experience the type of activities performed.

OBJECTIVE

Upon completion of this section, the attendee will be able to:

- Identify the departments that make up a typical LTC pharmacy
- List the activities performed by each department
- Recognize the relationship of each department's activities to the LTC customer
- Identify the challenges LTC Pharmacy incurs in the operation of its business

ROTATIONS

The attendees will start in one of the 4 rotations. They will spend approximately 30 minutes in each rotation and should experience the listed activities. At the end of 30 minutes, the group will move to the next rotation.

Rotation 1 PRESCRIPTION PROCESSING

- Order taking (fax vs phone)
- Order entry
- Pharmacist Intervention
  - Preferred Product List
  - Medicaid Coverage
  - Allergy, Inappropriate Dose, Inappropriate Drug, etc.
  - Refill too early or too late
- Phone call to Nurse and/or Physician
- Automatic Stop Order Policy (ASOP)
- Challenges
  - Illegible Orders
  - Foreign Nurses
  - Orders coming late
  - Lack of communication

RE

Rotation 2 **PRESCRIPTION FILLING**

- Emptying and Setting up Totes
- Filling Baskets
- Filling Automed Cassettes
- Ordering and Receiving
- Checking and Refilling Emergency Boxes
- IV Admixture

Rotation 3 **MEDICAL RECORDS**

- Order Entry
- MAR/POF Production
- QA Report Production
- Interaction with Nursing Staff

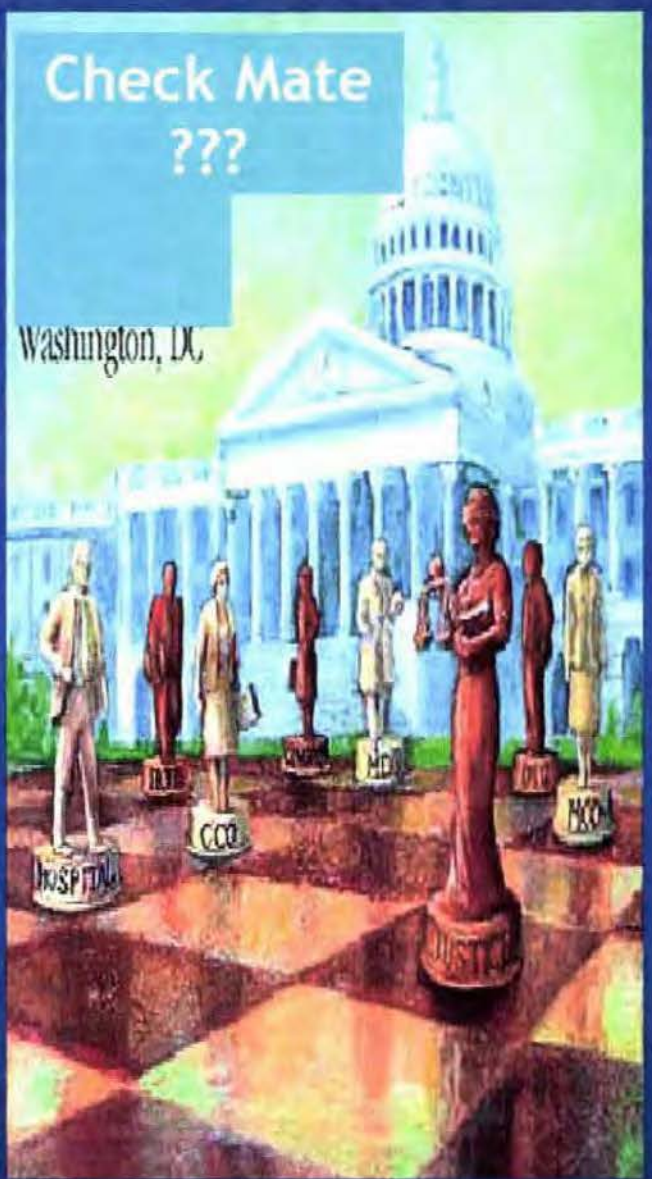
Rotation 4 **BILLING & MEDICAL SUPPLIES**

- Types of Billing (Understand how we bill)
  - Medicaid
  - Medicare
  - Private Pay
  - Insurance
- Challenges of Reimbursement and Billing
  - Manual manipulation
  - Medicaid denials and rebills
  - Length of Time for reimbursement
  - Low Rates with Insurance
- Medical Supply Department Processes
  - Order Taking
  - Order Delivery
  - Types of Products
  - Inventory Control
  - Challenges
  - Benefits

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LTC Challenges

LTC Challenges

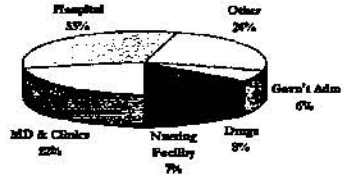


Objectives

At the completion of this section, the attendee will be able to:

- Identify reimbursement issues affecting LTC
- Discuss how consolidation of industry impacts LTC pharmacy
- Identify the primary competitors in LTC pharmacy

The Nation's Health Care Dollar



Who Owns Nursing Facility Beds?

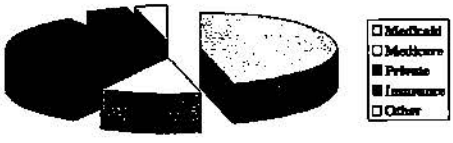


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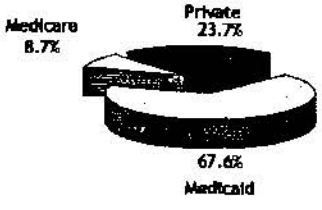
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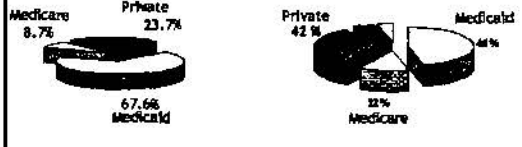
NF Reimbursement



NF Population Pay Type



NF Population Census vs Reimbursement



REDACTED

2002

2

National Medicaid Expenditures

- Medicaid cost 1999: $187 billion
- Federal government's share: $103 billion
- Federal & State Medicaid spending on nursing home care: $54 billion

1999

PPS vs Cost Based

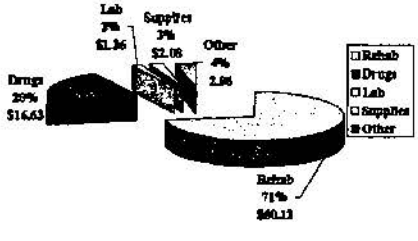
PPS Reimbursement

- Capitated Rate
- Requires 5 MDS evaluations (adm,14,30,60,90 days)
- Rate can change w/ea MDS (RUGS)
- Encourages less spending
- Encourages less acute patients
- *Fluff has "gone with the wind"*

Cost Based Reimbursement

- Cost-Based Rate
- Cost + Overhead mark-up
- Encourages more spending
- Encourages more acute patients
- Room for fluff

Average Cost of Ancillary Services per PPS Day = $83.16



REDACTED

2002

3

Two-Level Strategy to Manage Drug Costs

- FACILITY
  - Pricing strategies
  - Develop formulary
    - Preferred and non-preferred
    - Flexibility required
  - Physician practice patterns
  - Practices to reduce med errors and DRPs
- PATIENT
  - Pre-admission costing
  - New admission drug review
  - On-going clinical and cost monitoring
  - "Episode of care" case review

Forecast Of The Future

2000	2030
Adult day care $50/day $12,981/yr	Adult day care $220/day $56,100/yr
Home health aide $61/visit $15,743/yr	Home health aide $260/visit $68,000/yr
Assisted living facility $25,300/yr	Assisted living facility $109,300/yr
Nursing home care $44,100/yr	Nursing home care $190,600/yr

Source: American Council of Life Insurer's Report 2000

Pharmacy Reimbursement

Avg Wholesale Price

AWP

AMP

MAC

SPREAD

ASP

EAC

WAC

Only LTC

Diff. between

Estimated Acquisition Cost

Maximum Allowable Cost

MAC 134

AAC .03

.31

Avg. Selling Price

Whole Acqu. Cost

Spread

= (reimbursement − AAC) + rebates

→ Discounts are recognized in AAC

- Rebates must be added into spread

- Spread = Gross Profit (GP)

Avg Manu Price

REDACTED

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Medicaid

STATE	INGREDIENT REIMBURSEMENT	DISPENSING FEE	LTC ADD-ON
Illinois	WAC + 8%/12%	$4.17	No
Minnesota	AWP - 9%	$3.65	Yes $0.30
Tennessee	AWP - 13% (MFN)	$2.50	No
North Carolina	AWP - 10%	$5.60(G) $4.00(B)	No
Rhode Island	WAC + 5%	$3.40 (OP) $2.85(LTC)	No

Medicaid

- No additional reimbursement for extra services (delivery, packaging, etc...)
  - PA study $2.87/rx for LTC services
- Pilot projects for reimbursing for MTMS
  - Washington
  - Wisconsin
  - Mississippi

Medicaid

- Capitation
  - South Carolina $7.00/day
  - New York
- Limits therapeutic choices
- Promotes 2nd class medicine
- No input/control in patient selection

Depakote ER Advantage

Depakote ER 500mg: 1.77 − AWP, 1.41 − ACQ, .36 Spread

Depakote DR 500mg: 1.85 − AWP, 1.48 − ACQ, .37 Spread

ER Disadvantage = .01

OFP – Opportunity for Profit when the preferred product offers a

OFP = ((PPAWP − ACQ) + Rebates) − ((OPAWP − ACQ) + Rebates)

PP – Preferred Product

OP – Other Product in therapeutic class

OFP = (GP of PP) − (GP of OP)

GP = Gross Profit

REDACTED

2002

5

LTC Docs - Exempt from co Pay & Amount of Med Restrictions.

Medicaid

- Maximum # of Rx/month
- Prior Approval (PA)
- Favored Nations (MFN)
- No additional reimbursement for extra services (delivery, packaging, etc...)
- Maximum Allowable Cost (MAC) on generics

Maximum Allowable Cost (MAC)

MAC

- Federal MAC
- State MAC
  - Available from 3 sources
  - Average of WAC

Medicare

- Bill direct to facility
- Prospective pay
- Case mix (RUGS III)
- Capitated rate

REDACTED

2002

6

Insurance



- Pays even worse than Medicaid and Medicare
- AWP - 30% + 1.50

...somebody's gettin' rich ... and it ain't the provider!!

"Helping keep our customers in business in one of our major challenges"

- Profits were Medicare based
- Couldn't stop the spending in time for PPS
- Heavy debt to earnings ratio

Verdict

BANKRUPTCY



Litigation



REDACTED

2002

7

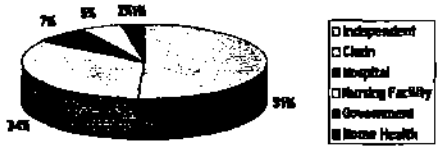
Consolidation

- Predators
- Large providers buy up the competition
  - Driving
    - Pricing
    - Services
    - Contracting



LTC RX

LTC Pharmacy Ownership



LTC Pharmacy Market Share: Nursing Facility Beds

	% of NF	# NF beds	# Total beds
REDACTED	29%	493,684	729,500
REDACTED	16%	274,134	310,000
REDACTED	10.5%	178,206	250,000
REDACTED	9%	153,400	153,400
REDACTED	4%	65,788	65,500
REDACTED	2.5%	45,000	45,000
Everyone else	29%	489,788	7

Source: ASCP data on file, based on 1.8 million NF beds 2001

REDACTED

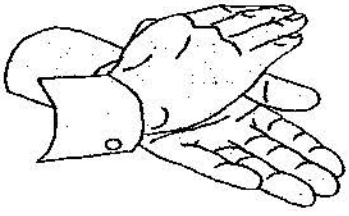
2002

Total Pharmacy LTC Market Share

- Institutional LTC Pharmacy 50%
- Retail drug store 50%



CONGRATULATIONS !!



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2002

9

Market Share

Therapeutic Interchange and Market Share

Abbott Laboratories

Objectives

Upon completion of this session, the attendee should be able to:

- Identify 5 steps for a successful therapeutic interchange program
- List 4 considerations for selecting a preferred product for therapeutic switch
- Describe 3 methods of notifying physicians of a preferred product
- Define "Opportunity for Profit" and its role in monitoring for successful therapeutic switch programs

Advantages of Controlling Market Share

- Contracting
- Rebates
- Reduced Inventory Investment
- Control of Variables in Disease Management

Contracting & Rebates

- Price discounts limited by federally mandated rebates
- Discounts are acceptable for volume purchasing
- Rebates are acceptable if market share goals are attained



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2002

1

Price Discounts & Rebates

- Pharmaceutical Manufacturers must rebate back to state Medicaid an amount = to lowest price anywhere in market
  - Limits amount available to pharmacies
  - Includes rebate amounts
  - Includes incentives if $$ value can be assigned
- OIG is looking at discounts & rebates as inducement (Fraud & Abuse) - no decision yet ... whew!!

Reduced Inventory Investment

- Standardize on 1 or 2 choices within a therapeutic class
- Lower inventory costs
  - Consignment,
  - Improved returns,
  - Special packaging
- *Select product with BEST VALUE*



Value



- Value = What you get for your investment
- Value ≠ Price
- Value = Price x Efficacy x Risk

REDACTED

2002

2

Cost of Drug Therapy

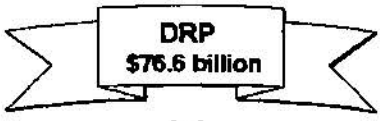
- Total drug cost = (PC+DC) x U +DRP
  - PC = product cost
  - DC = distribution cost
  - U = utilization
  - DRP= drug related problems

Source: Penny, I.R. Total Drug Therapy Cost Control, The Consultant Pharmacist, May 1996

Ambulatory Care Total Drug Cost

PC + DC x U = $84 billion

Source: IMS, 1994



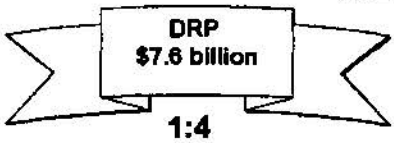
1:1

Source: Bootman L, et al, Arch Int Med 1995

(Without Consultant RPh Involvement) Nursing Homes: Total Drug Cost =

(PC + DC) x U = $2 billion

Source: Nursing Home Drug Sales Audit 1995



1:4

Source: J.Lyle Bootman et al. The Health Care Cost of Drug-Related Morbidity and Mortality in Nursing Facilities. Arch Intern Med, 157, 10/1997

REDACTED

2002

3

(With standard Consultant RPh activity)
Nursing Homes: Total Drug Cost =
(PC + DC) x U = $2 billion

Source: Nursing Home Drug Spkm Audit 1998



1:2

Source: J Lyle Bootman et al, The Health Care Cost of Drug-Related Morbidity and Mortality in Nursing Facilities, Arch Intern Med, 157, 10/1997

Consultant Pharmacists are Responsible for ...



LTC Pharmacists's Role

- Assurance of proper drug utilization
- Minimization of adverse drug related problems
- Reduction of therapeutic failures
- Assurance that the chosen therapy (& associated costs) produces the desired outcome !!

REDACTED

2002

4

The most expensive drug is the one that doesn't work!



Control of Variables in Disease Management

- Choose the best therapeutic alternative
  - metoclopramide vs cisapride
  - escitalopram vs fluoxetine
  - quetiapine vs risperidone
- Outcome data is easy to obtain and manage
  - only 1 set of SE
  - only 1 set of outcome endpoints
- Formulary choices can compliment one another to obtain better outcomes
  - escitalopram(no cP450) & quetiapine (cP450 3A4)

Disadvantages of Controlling Market Share



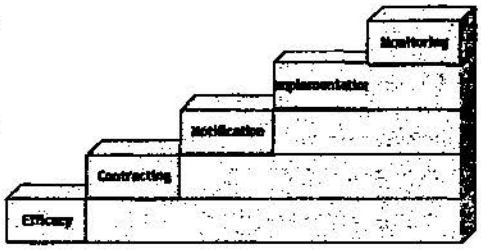
* Alienate physicians
* Irritate nurses (with repetitive order changes)
* Safe-harbor regulations
* Labor Intensive

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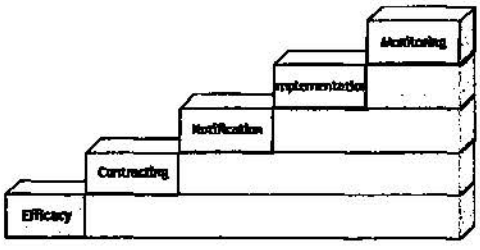
2002

5

5-Step Method for Successful Therapeutic Interchange



5-Step Method for Successful Therapeutic Interchange



Evaluating Therapeutic Efficacy

- Buy-in from clinical pharmacy staff
- Buy-in from physicians
- Must benefit the patient's health outcome and/or quality of life

Best Value doesn't mean Best Price

REDACTED

2002

6

Consultant Pharmacist's Oath

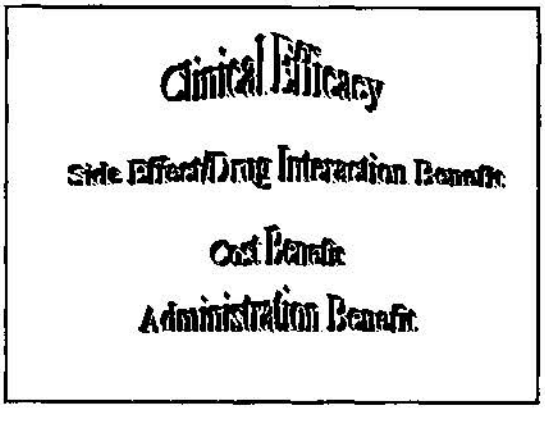
- *"I take responsibility for my patient's medication-related needs and am held accountable for this commitment."*
- *"I ensure my patient's medications are the most appropriate, most effective available, safest possible, and are used correctly."*
- *"I identify, prevent, and resolve medication-related problems that may interfere with goals of therapy."*

Clinical Efficacy

Side Effect/Drug Interaction Benefit

Cost Benefit

Administration Benefit



REDACTED

2002

7

Clinical Efficacy

Summary of Valproic Acid and Divalproate Efficacy in Agitation and Aggression

	N	Design	Outcome (No. improved)
Porsteinsson et al 2001	28*	Placebo-controlled trial	Decreased aggression (17)
Frenchman, 2000	146*	Chart review	Decreased agitation (97)
Sival et al. 1994	23	Chart review	Decreased aggression (6)
Lott et al. 1995	10	Open label	Decreased agitation (9)
Narayan et al. 1997	25*	Chart review	Decreased agitation (13)
Porsteinsson et al. 1997	12	Open label	Decreased agitation (10)

Safety / Drug Interactions

REDACTED

2002

8

Depakote DR and ER Adverse Events



Depakote DR and ER Adverse Events



Divalproex Sodium

Side Effects

- More Common
  - Sedation
  - Gastrointestinal distress (less severe then with other forms of valproate)
  - Tremors (mostly at higher doses)
  - Ataxia (usually dose related)
  - Weight gain
  - Thrombocytopenia (usually mild and dose related)
- Rare
  - Hepatotoxicity
  - Pancreatitis

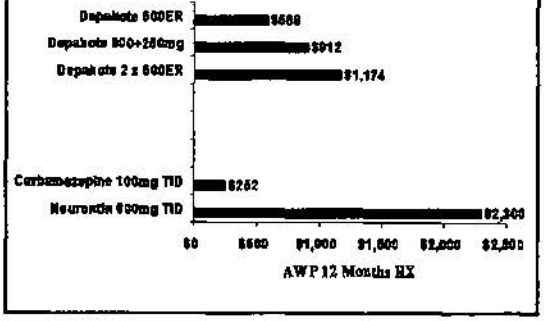
REDACTED

COST

Economic Drug Review

- Product expense (from payor perspective)
  - Depakote ER vs Valproic Acid, Depakote, Neurontin, Carbamazepine
- Preparation expense
  - Ability to open capsule and sprinkle vs crushing
  - Once daily vs multiple administration
- Outcome expense
  - treatment failure, treatment duration
- Adverse reaction expense
  - interactions w/cytochrome P450 system

Annual Cost of Therapy



REDACTED

2002

10

Administration

Dosing Considerations

- 30% of NH residents require some dosage form adjustment for administration
- 1999 new HCFA regs re-define medication error to require adherence to manufacturer's specifications (F 332, F333)



Depakote Dosing Information

Dosage Form	Depakene® (valproic acid)	Depakote® (divalproex sodium)	Depakote ER® (divalproex sodium)
Capsules (250 mg)	X		
Syrup (250 mg/5 mL)	X		
Delayed-release tablets (125 mg, 250 mg, 500mg)		X	
Sprinkle capsules (125 mg)		X	
Extended-release 500 mg tablets; QD Dosing			X

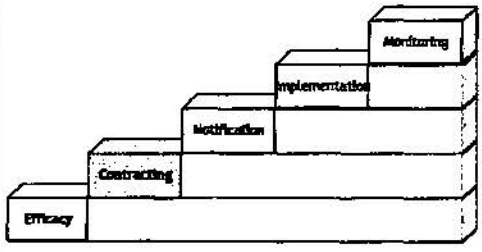
* Divalproex may be preferable to liquid valproate because of its improved gastrointestinal tolerability and dosage flexibility

REDACTED

Initiating Divalproex Therapy

- Initiate 125-250 mg qhs or 125 mg BID
- Increase by 125-250 mg every 3-7 days or until desired clinical response
- Usual range 375-2000 mg/day
  - Usual serum concentration 40-100 µg/mL
- Divalproex is an enteric-coated formulation to minimize gastrointestinal side effects
- Sprinkle capsules for patients who have difficulty swallowing pills

5-Step Method for Successful Therapeutic Interchange



Contract Evaluation



- Purchase Price
  - Spread
    - (AWP - purchase price)
  - MAC'd competitors
  - Return on Investment

REDACTED

Contract Evaluation



- Rebates
  - Market share goals realistic ?
  - Single item market share ?
  - Bundled with other items ?
  - How often are rebates checks provided?
  - Does contract have a ramp-up period?

Depakote ER ADVANTAGE

Depakote ER 500mg		Depakote DR 500mg	
AWP	$ 1.77	AWP	$1.85
ACQ	$ 1.41	ACQ	$1.48
SPREAD	$ 0.36	SPREAD	$0.37



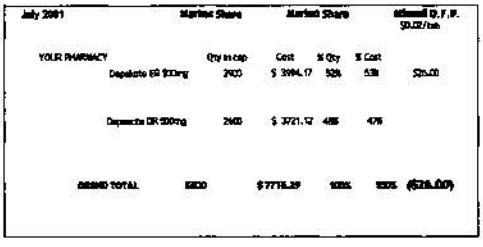
Pricing shown is fictitious and does not reflect actual contract price or

Opportunity for Profit

- *"When the preferred product offers a greater spread between acquisition cost and selling price including rebate than other products in that therapeutic category"*
- OFP = (PP AWP - ACQ - Rebates) - (OP AWP - ACQ - Rebates)
  - OFP = Opportunity for Profit
  - PP = Preferred Product
  - OP = Other Products in therapeutic class

REDACTED

Missed Opportunity for Profit



Capturing the Missed Opportunity for Profit

- Missed OFP = $ 26.00/mo
- Missed OFP = $ 312.00/yr
- Cost of RPh x 1wk = $ 2500.00

NET LOSS/yr = $2812.00



Set Benchmarks

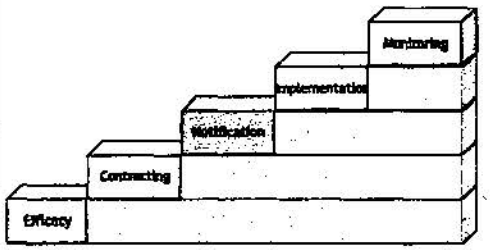
- Evaluate regional market share expectations
- Compare to national/regional standards
- Set Goals & Expectations



REDACTED

2002

5-Step Method for Successful Therapeutic Interchange



Notification

- Consultant DRR Recommendation
- Informative Mailing
  - Physicians
    - Introductory Letter
    - Patient Listing Letter
  - Facility
    - Administrative Introductory Letter
    - Copy of Physician's Letter

Consultant Pharmacist

- Determine appropriate patients prior to notification
- Set up monitoring parameters (GDS, B/P, MMSE, SOB, Dyspepsia, CBC, etc...)
- Provide inservice education to staff & physicians
- Monitor patient for response to therapeutic interchange

REDACTED

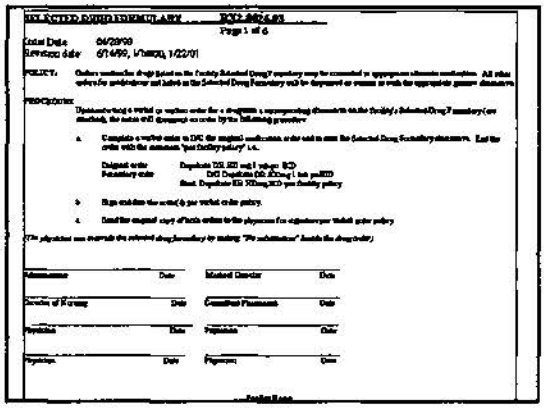
Preferred Product List

- Collaborative practice agreement
  - 35 states allow
  - Each state's requirements /allowances may differ
- Facility policy
  - Signed by:
    - Medical Director
    - DON
    - ADM
    - Consultant Pharmacist
    - Attending MD
- Assures compliance
  - Reduces time
  - Captures re-admits

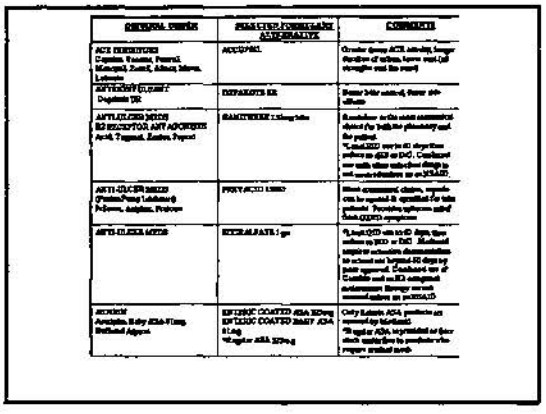


Therapeutic Substitution Formulary

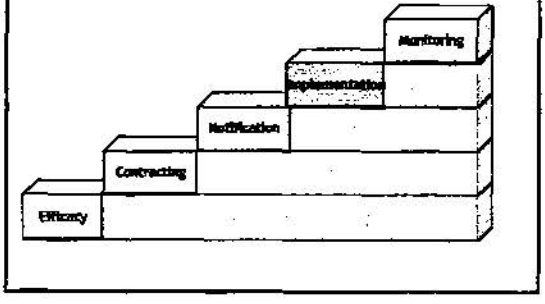
- Improves GM significantly
- Reduces time necessary for formulary maintenance
- Can be used with or without Collaborative Practice Legislation
- Captures new orders and re-admit orders automatically



REDACTED



5-Step Method for Successful Therapeutic Interchange



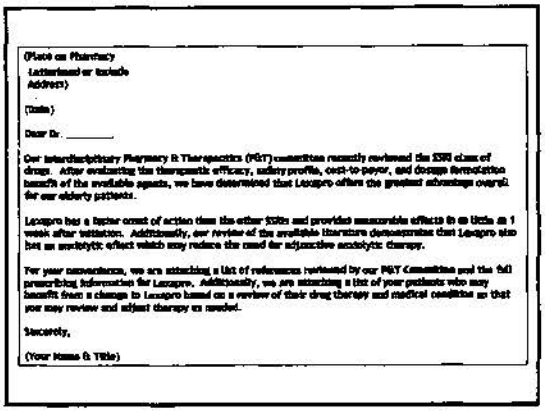
Implementation

- Conversion letter faxed to pharmacy
  - Target date for switch
  - Order change "when current supply is used"
- Consultant drug regimen review
- Notify facility of order change
  - Reminder memo
  - Conversion letter (signed)
    - copy letter for chart
    - write telephone order
    - CHANGE MAR !!

REDACTED

2002

17



(Place on Pharmacy
Letterhead or Include
Address)

(Date)

Dear Dr. _____

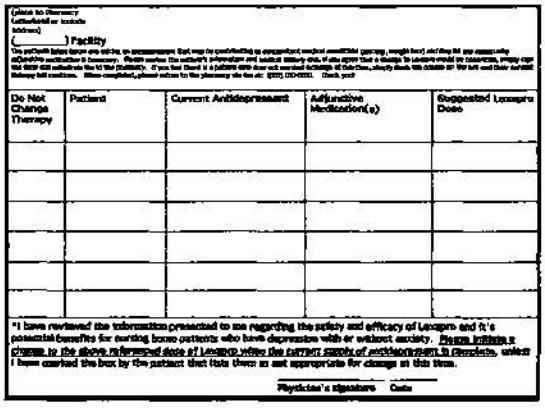
Our Interdisciplinary Pharmacy & Therapeutics (P&T) committee recently reviewed the SSRI class of drugs. After evaluating the therapeutic efficacy, safety profile, cost-to-payor, and dosage formulation benefit of the available agents, we have determined that Lexapro offers the greatest advantage overall for our elderly patients.

Lexapro has a faster onset of action than the other SSRIs and provides measurable effects in as little as 1 week after initiation. Additionally, our review of the available literature demonstrates that Lexapro also has an anxiolytic effect which may reduce the need for adjunctive anxiolytic therapy.

For your convenience, we are attaching a list of references reviewed by our P&T Committee and the full prescribing information for Lexapro. Additionally, we are attaching a list of your patients who may benefit from a change to Lexapro based on a review of their drug therapy and medical condition so that you may review and adjust therapy as needed.

Sincerely,

(Your Name & Title)



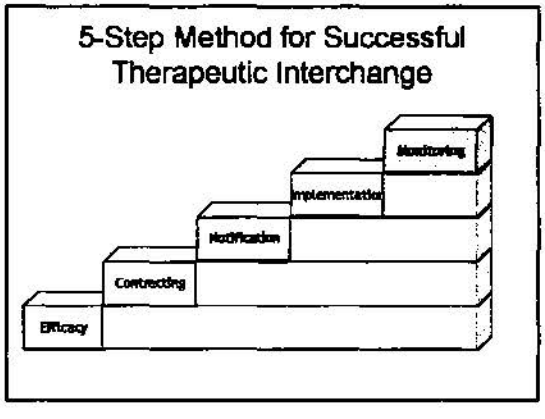
(place on Pharmacy
Letterhead or include
address)

(_____) Facility

Do Not Change Therapy	Patient	Current Antidepressant	Adjunctive Medication(s)	Suggested Lexapro Dose

*I have reviewed the information presented to me regarding the safety and efficacy of Lexapro and it's potential benefits for nursing home patients who have depression with or without anxiety. Please initiate a change to the above referenced dose of Lexapro using the current supply of antidepressant in Pleasant, unless I have marked the box by the patient that lists them as not appropriate for change at this time.

Physician's signature Date



REDACTED

2002

18

Monitoring

- Incorporate monitoring parameters for therapeutic switch into order
- Usually labs or vital signs
  - B/P, Dyspepsia, H/H, Behavior Monitoring, INR, MMSE, GDS
- Have facility report any values outside of acceptable range to MD and Consultant Pharmacist
- Act on information to maintain optimal patient care

Monitoring

- Monthly tracking
  - By facility
  - By pharmacy
  - By consultant
- Prescriptions vs DOT vs Dollars vs Units
  - Rx's from dispensing system
  - Pharmacist's Interventions
  - Consultant Comments

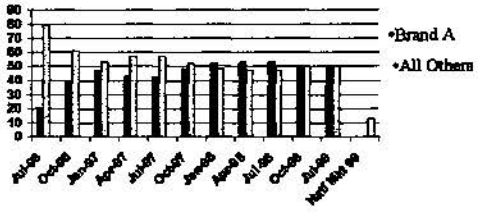
Monitoring

- Audit wholesaler purchases vs rebate data
- Audit market share vs rebate data
- Provide feedback to clinical and dispensing staff
- *Take Action !!!*

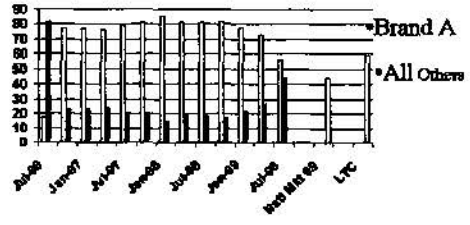


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ACE Inhibitor Market Share



H2 Antagonist Market Share



Extended Release Theophylline Market



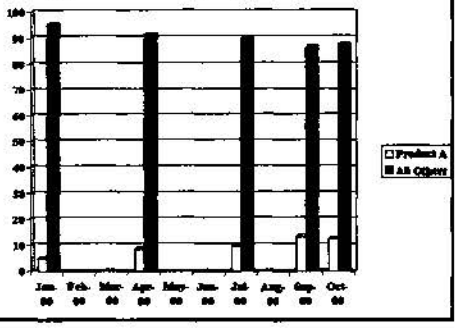
•Brand A
•All Others

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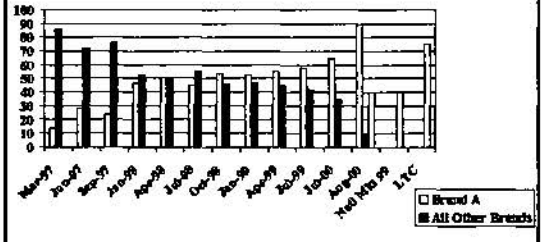
2002

20

Atypical Antipsychotics



Proton Pump Inhibitors



Success Tips

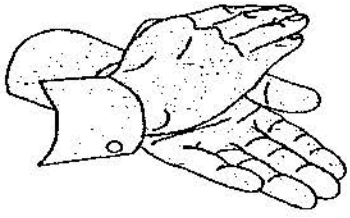
- Products are therapeutically equivalent or selected product is superior
- Product offers a cost savings to payor
- Pharmacists and Physicians have trusting relationship
- High acceptance rate for pharmacist recommendations
- Good tracking methods
- **Primary concern for Optimal Patient Care**

REDACTED

2002

21

CONGRATULATIONS !!



REDACTED

2002

22

Partnering

LTC Partnering



Abbott Laboratories

Objectives

Upon completion of this section the attendee will be able to

- Identify areas where Abbott Pharmaceuticals can assist LTC pharmacies in the performance of their services.
- List the primary factors affecting LTC pharmacy decisions regarding pharmaceuticals.
- Create a plan for marketing Abbott Laboratories' products to the LTC industry.

Partnering

Consultant Pharmacists

- Emphasis on the clinical aspects of pharmaceuticals
- Differentiation of product
- Outcomes data

Partnering

Provider pharmacists

- Information concerning good business strategies and policies
- Profitability of product
- Coverage by payors
- And outcomes data

REDACTED

2002

1

DM → Medical Liaison

Partnering

- Value added services
  - CE programming for LTC employees
  - CE programming for LTC customers
  - Phase III/IV studies
- Co-marketing



Partnering

LTC Pharmacy and Abbott Laboratories working together to bring optimal patient outcomes to the LTC patient



Abbott Laboratories

REDACTED

2002

2



Thinking Outside the Box Exercise

1. Split into groups of 3 or 4. Discuss specific partnering options and value-added services. List below:

2. Outline your individual action plan for account calls and market development.

REDACTED 2002

References

Numeric Identifier _____

MINIMUM DATA SET (MDS) — *VERSION 2.0*

FOR NURSING HOME RESIDENT ASSESSMENT AND CARE SCREENING

BASIC ASSESSMENT TRACKING FORM

Form # CP6038H — Reorder From: MED-PASS, INC. 800-439-8884

SECTION AA. IDENTIFICATION INFORMATION

1.	RESIDENT NAME ⊙	a. (First) b. (Middle Initial) c. (Last) d. (Jr/Sr)
2.	GENDER ⊙	1. Male 2. Female
3.	BIRTHDATE ⊙	Month — Day — Year
4.	RACE/ ETHNICITY ⊙	1. American Indian/Alaskan Native 2. Asian/Pacific Islander 3. Black, not of Hispanic origin 4. Hispanic 5. White, not of Hispanic origin
5.	SOCIAL SECURITY AND MEDICARE NUMBERS ⊙ [C in 1st box if non med. no.]	a. Social Security Number b. Medicare number (or comparable railroad insurance number)
6.	FACILITY PROVIDER NO ⊙	a. State No. b. Federal No.
7.	MEDICAID NO. ["+" if pending, "N" if not a Medicaid recipient] ⊙	
8.	REASONS FOR ASSESSMENT	[Note—Other codes do not apply to this form] a. *Primary reason for assessment* 1. Admission assessment (required by day 14) 2. Annual assessment 3. Significant change in status assessment 4. Significant correction of prior full assessment 5. Quarterly review assessment 10. Significant correction of prior quarterly assessment 0. *NONE OF ABOVE* b. *Codes for assessments required for Medicare PPS or the State* *1. Medicare 5 day assessment* *2. Medicare 30 day assessment* *3. Medicare 60 day assessment* *4. Medicare 90 day assessment* *5. Medicare readmission/return assessment* *6. Other state required assessment* *7. Medicare 14 day assessment* *8. Other Medicare required assessment*

9.	SIGNATURES OF PERSONS WHO COMPLETED A PORTION OF THE ACCOMPANYING ASSESSMENT OR TRACKING FORM		
I certify that the accompanying information accurately reflects resident assessment or tracking information for this resident and that I collected or coordinated collection of this information on the dates specified. To the best of my knowledge, this information was collected in accordance with applicable Medicare and Medicaid requirements. I understand that this information is used as a basis for ensuring that residents receive appropriate and quality care, and as a basis for payment from federal funds. I further understand that payment of such federal funds and continued participation in the government-funded health care programs is conditioned on the accuracy and truthfulness of this information, and that I may be personally subject to or may subject my organization to substantial criminal, civil, and/or administrative penalties for submitting false information. I also certify that I am authorized to submit this information by this facility on its behalf.			
	Signature and Title	Sections	Date
a.			
b.			
c.			
d.			
e.			
f.			
g.			
h.			
i.			
j.			
k.			
l.			

QUALITY INDICATORS

- 1 - Incidence of new fractures
- 2 - Prevalence of falls
- 3 - Prevalence of behavioral symptoms affecting others
- 4 - Prevalence of symptoms of depression
- 5 - Prevalence of symptoms of depression without antidepressant therapy
- 6 - Use of 9 or more different medications
- 7 - Incidence of cognitive impairment
- 8 - Prevalence of bladder or bowel incontinence
- 9 - Prevalence of occasional or frequent bladder or bowel incontinence without a toileting plan
- 10 - Prevalence of indwelling catheters
- ⚑ 11 - Prevalence of fecal impaction
- 12 - Prevalence of urinary tract infections
- 13 - Prevalence of weight loss
- 14 - Prevalence of tube feeding
- ⚑ 15 - Prevalence of dehydration
- 16 - Prevalence of bedfast residents
- 17 - Incidence of decline in late loss ADLs
- 18 - Incidence of decline in ROM
- 19 - Prevalence of antipsychotic use, in the absence of psychotic and related conditions
- 20 - Prevalence of antianxiety/hypnotic use
- 21 - Prevalence of hypnotic use more than two times in last week
- 22 - Prevalence of daily physical restraints
- 23 - Prevalence of little or no activity
- ⚑ 24 - Prevalence of stage 1 - 4 pressure ulcers

⚑ - Identifies QIs that are associated with a sentinel health event.

GENERAL INSTRUCTIONS

Complete this information for submission with all full and quarterly assessments (Admission, Annual, Significant Change, State or Medicare required assessments, or Quarterly Reviews, etc.)

XFM 051699

⊙ - Signifies "answers" that could impact QI items identified by a number in a blue box (e.g., 3).

1 - Numbers (1-24) indicate the specific QI(s) that may be impacted.

Items shaded in GREEN are included in the Medicare PPS RUG-III Grouper. It is recommended that these items be verified for accuracy.
(RUG-III key developed in cooperation with Survey Solutions, Inc., Columbus, Ohio)

⊙ = Key items for computerized resident tracking

☐ = When box blank, must enter number or letter

a. ☐ = When letter in box, check if condition applies

①

Resident _____ Numeric Identifier _____

MINIMUM DATA SET (MDS) — *VERSION 2.0*

FOR NURSING HOME RESIDENT ASSESSMENT AND CARE SCREENING

BACKGROUND (FACE SHEET) INFORMATION AT ADMISSION

SECTION AB. DEMOGRAPHIC INFORMATION

1. DATE OF ENTRY — *Date the stay began. Note — Does not include readmission if record was closed at time of temporary discharge to hospital, etc. In such cases, use prior admission date*

Month ___ Day ___ Year ___

2. ADMITTED FROM (AT ENTRY)
1. Private home/apt. with no home health services
2. Private home/apt. with home health services
3. Board and care/assisted living/group home
4. Nursing home
5. Acute care hospital
6. Psychiatric hospital, MR/DD facility
7. Rehabilitation hospital
8. Other

3. LIVED ALONE (PRIOR TO ENTRY)
0. No
1. Yes
2. In other facility

4. ZIP CODE OF PRIOR PRIMARY RESIDENCE

5. RESIDENTIAL HISTORY 5 YEARS PRIOR TO ENTRY — *(Check all settings resident lived in during 5 years prior to date of entry given in item AB1 above)*
- a. Prior stay at this nursing home
- b. Stay in other nursing home
- c. Other residential facility—board and care home, assisted living, group home
- d. MH/psychiatric setting
- e. MR/DD setting
- f. *NONE OF ABOVE*

6. LIFETIME OCCUPATION(S) [Put '/' between two occupations]

7. EDUCATION (*Highest Level Completed*)
1. No schooling
2. 8th grade/less
3. 9-11 grades
4. High school
5. Technical or trade school
6. Some college
7. Bachelor's degree
8. Graduate degree

8. LANGUAGE — (*Code for correct response*)
a. Primary Language
0. English 1. Spanish 2. French 3. Other
b. If other, specify

9. MENTAL HEALTH HISTORY — Does resident's RECORD indicate any history of mental retardation, mental illness, or developmental disability problem?
0. No 1. Yes

10. CONDITIONS RELATED TO MR/DD STATUS — *(Check all conditions that are related to MR/DD status that were manifested before age 22, and are likely to continue indefinitely)*
- a. Not applicable—no MR/DD (Skip to AB11)

MR/DD with organic condition
- b. Down's syndrome
- c. Autism
- d. Epilepsy
- e. Other organic condition related to MR/DD

- f. MR/DD with no organic condition

11. DATE BACKGROUND INFORMATION COMPLETED

Month ___ Day ___ Year ___

SECTION AC. CUSTOMARY ROUTINE

1. CUSTOMARY ROUTINE (*In year prior to DATE OF ENTRY to this nursing home, or year last in community if now being admitted from another nursing home*) — *(Check all that apply. If all information UNKNOWN, check last box only)*

CYCLE OF DAILY EVENTS
- a. Stays up late at night (e.g., after 9 pm)
- b. Naps regularly during day (at least 1 hour)
- c. Goes out 1+ days a week
- d. Stays busy with hobbies, reading, or fixed daily routine
- e. Spends most of time alone or watching TV
- f. Moves independently indoors (with appliances, if used)
- g. Use of tobacco products at least daily
- h. *NONE OF ABOVE*

EATING PATTERNS
- i. Distinct food preferences
- j. Eats between meals all or most days
- k. Use of alcoholic beverage(s) at least weekly
- l. *NONE OF ABOVE*

ADL PATTERNS
- m. In bed/clothes much of day
- n. Wakens to toilet all or most nights
- o. Has irregular bowel movement pattern
- p. Showers for bathing
- q. Bathing in PM
- r. *NONE OF ABOVE*

INVOLVEMENT PATTERNS
- s. Daily contact with relatives/close friends
- t. Usually attends church, temple, synagogue (etc.)
- u. Finds strength in faith
- v. Daily animal companion/presence
- w. Involved in group activities
- x. *NONE OF ABOVE*

- y. **UNKNOWN**—Resident/family unable to provide information

SECTION AD. FACE SHEET SIGNATURES

SIGNATURES OF PERSONS COMPLETING FACE SHEET:

a. Signature of RN Assessment Coordinator — Date

I certify that the accompanying information accurately reflects resident assessment or tracking information for this resident and that I collected or coordinated collection of this information on the dates specified. To the best of my knowledge, this information was collected in accordance with applicable Medicare and Medicaid requirements. I understand that this information is used as a basis for ensuring that residents receive appropriate and quality care, and as a basis for payment from federal funds. I further understand that payment of such federal funds and continued participation in the government-funded health care programs is conditioned on the accuracy and truthfulness of this information, and that I may be personally subject to or may subject my organization to substantial criminal, civil, and/or administrative penalties for submitting false information. I also certify that I am authorized to submit this information by this facility on its behalf.

b. Signature and Title — Sections — Date

c. — Date

d. — Date

e. — Date

f. — Date

g. — Date

___ = When box blank, must enter number or letter

a. ___ = When letter in box, check if condition applies

Resident _____ Numeric Identifier _____

MINIMUM DATA SET (MDS) — *VERSION 2.0*
FOR NURSING HOME RESIDENT ASSESSMENT AND CARE SCREENING
FULL ASSESSMENT FORM

(Status in last 7 days, unless other time frame indicated)

SECTION A. IDENTIFICATION AND BACKGROUND INFORMATION

1. RESIDENT NAME — a. (First) b. (Middle Initial) c. (Last) d. (Jr/Sr)

2. ROOM NUMBER

3. ASSESSMENT REFERENCE DATE
a. *Last day of MDS observation period* — Month / Day / Year
b. Original (0) or corrected copy of form (enter number of correction)

4a. DATE OF REENTRY — Date of reentry from most recent temporary discharge to a hospital in last 90 days (or since last assessment or admission if less than 90 days) — Month / Day / Year

5. MARITAL STATUS — 1. Never married 2. Married 3. Widowed 4. Separated 5. Divorced

6. MEDICAL RECORD NO.

7. CURRENT PAYMENT SOURCES FOR N.H. STAY — (*Billing Office to indicate; **check all that apply in last 30 days***)
a. Medicaid per diem [a.] f. VA per diem [f.]
b. Medicare per diem [b.] g. Self or family pays for full per diem [g.]
c. Medicare ancillary part A [c.] h. Medicaid resident liability or Medicare co-payment [h.]
d. Medicare ancillary part B [d.] i. Private insurance per diem (including co-payment) [i.]
e. CHAMPUS per diem [e.] j. Other per diem [j.]

8. REASONS FOR ASSESSMENT — [*Note— If this is a discharge or reentry assessment, only a limited subset of MDS items need be completed*]
a. *Primary reason for assessment*
1. Admission assessment (required by day 14)
2. Annual assessment
3. Significant change in status assessment
4. Significant correction of prior full assessment
5. Quarterly review assessment
6. Discharged—return not anticipated
7. Discharged—return anticipated
8. Discharged prior to completing initial assessment
9. Reentry
10. Significant correction of prior quarterly assessment
0. *NONE OF ABOVE*

b. ***Codes for assessments required for Medicare PPS or the State***
1. *Medicare 5 day assessment*
2. *Medicare 30 day assessment*
3. *Medicare 60 day assessment*
4. *Medicare 90 day assessment*
5. *Medicare readmission/return assessment*
6. *Other state required assessment*
7. *Medicare 14 day assessment*
8. *Other Medicare required assessment*

9. RESPONSIBILITY/ LEGAL GUARDIAN — (***Check all that apply***)
a. Legal guardian [a.] d. Durable power attorney/financial [d.]
b. Other legal oversight [b.] e. Family member responsible [e.]
c. Durable power of attorney/health care [c.] f. Patient responsible for self [f.]
g. *NONE OF ABOVE* [g.]

10. ADVANCED DIRECTIVES — (*For those items with supporting **documentation** in the medical record, **check all that apply***)
a. Living will [a.] f. Feeding restrictions [f.]
b. Do not resuscitate [b.] g. Medication restrictions [g.]
c. Do not hospitalize [c.] h. Other treatment restrictions [h.]
d. Organ donation [d.] i. *NONE OF ABOVE* [i.]
e. Autopsy request [e.]

SECTION B. COGNITIVE PATTERNS

1. COMATOSE — (*Persistent vegetative state/no discernible consciousness*) 0. No 4, 5* 1. Yes (**If yes, skip to Section G**)

2. MEMORY — (*Recall of what was learned or known*)
a. Short-term memory OK—seems/appears to recall after 5 minutes 0. Memory OK 1. Memory problem 2, 7
b. Long-term memory OK—seems/appears to recall long past 0. Memory OK. 1. Memory problem 2

3. MEMORY/ RECALL ABILITY — (***Check all that resident was normally able to recall during last 7 days***)
a. Current season [a.] d. That he/she is in a nursing home [d.]
b. Location of own room [b.] e. *NONE OF ABOVE* are recalled [e.]
c. Staff names/faces [c.]

4. COGNITIVE SKILLS FOR DAILY DECISION-MAKING — (*Made decisions regarding tasks of daily life*)
0. *INDEPENDENT*—decisions consistent/reasonable
1. *MODIFIED INDEPENDENCE*—some difficulty in new situations only. 2 7
2. *MODERATELY IMPAIRED*—decisions poor; cues/supervision required. 2 7
3. *SEVERELY IMPAIRED*—never/rarely made decisions. 2, SD 7

5. INDICATORS OF DELIRIUM—PERIODIC DISORDERED THINKING/ AWARENESS — (*Code for behavior in **the last 7 days.**) [**Note: Accurate assessment requires conversations with staff and family who have direct knowledge of resident's behavior over this time**].*
0. Behavior not present
1. Behavior present, not of recent onset
2. Behavior present, over last 7 days appears different from resident's usual functioning (e.g., new onset or worsening)

a. EASILY DISTRACTED—(e.g., difficulty paying attention; gets sidetracked) *1, 17**
b. PERIODS OF ALTERED PERCEPTION OR AWARENESS OF SURROUNDINGS—(e.g., moves lips or talks to someone not present; believes he/she is somewhere else; confuses night and day) *1, 17**
c. EPISODES OF DISORGANIZED SPEECH—(e.g., speech is incoherent, nonsensical, irrelevant, or rambling from subject to subject; loses train of thought) *1, 17**
d. PERIODS OF RESTLESSNESS—(e.g., fidgeting or picking at skin, clothing, napkins, etc; frequent position changes; repetitive physical movements or calling out) *1, 17**
e. PERIODS OF LETHARGY—(e.g., sluggishness; staring into space; difficult to arouse; little body movement) *1, 17**
f. MENTAL FUNCTION VARIES OVER THE COURSE OF THE DAY—(e.g., sometimes better, sometimes worse; behaviors sometimes present, sometimes not) *1, 17**

6. CHANGE IN COGNITIVE STATUS — Resident's cognitive status, skills, or abilities have changed as compared to status of **90 days ago** (or since last assessment if less than 90 days)
0. No change 1. Improved 2. Deteriorated *1, 17**

SECTION C. COMMUNICATION/HEARING PATTERNS

1. HEARING — (*With hearing appliance, if used*)
0. *HEARS ADEQUATELY*—normal talk, TV, phone
1. *MINIMAL DIFFICULTY* when not in quiet setting. 4
2. *HEARS IN SPECIAL SITUATIONS ONLY*—speaker has to adjust tonal quality and speak distinctly. 4
3. *HIGHLY IMPAIRED*/absence of useful hearing. 4

2. COMMUNICATION DEVICES/ TECHNIQUES — (***Check all that apply** during last 7 days*)
a. Hearing aid, present and used [a.]
b. Hearing aid, present and not used regularly [b.]
c. Other receptive comm. techniques used (e.g., lip reading) [c.]
d. *NONE OF ABOVE* [d.]

3. MODES OF EXPRESSION — (***Check all used by resident to make needs known***)
a. Speech [a.] d. Signs/gestures/sounds [d.]
b. Writing messages to express or clarify needs [b.] e. Communication board [e.]
c. American sign language or Braille [c.] f. Other [f.]
g. *NONE OF ABOVE* [g.]

4. MAKING SELF UNDERSTOOD — (*Expressing information content—**however able***)
0. *UNDERSTOOD*
1. *USUALLY UNDERSTOOD*—difficulty finding words or finishing thoughts. 4
2. *SOMETIMES UNDERSTOOD*—ability is limited to making concrete requests. 4
3. *RARELY/NEVER UNDERSTOOD* 4

5. SPEECH CLARITY — (*Code for speech in **the last 7 days***)
0. *CLEAR SPEECH*—distinct, intelligible words
1. *UNCLEAR SPEECH*—slurred, mumbled words
2. *NO SPEECH*—absence of spoken words

6. ABILITY TO UNDERSTAND OTHERS — (*Understanding verbal information content—**however able***)
0. *UNDERSTANDS*
1. *USUALLY UNDERSTANDS*—may miss some part/intent of message. 2, 4
2. *SOMETIMES UNDERSTANDS*—responds adequately to simple, direct communication. 2, 4
3. *RARELY/NEVER UNDERSTANDS* 2, 4

7. CHANGE IN COMMUNICATION/ HEARING — Resident's ability to express, understand, or hear information has changed as compared to status of **90 days ago** (or since last assessment if less than 90 days)
0. No change 1. Improved 2. Deteriorated *17**

☐ = When box blank, must enter number or letter
[a.] = When letter in box, check if condition applies
17 - refer to a RAI manual for clarification*
4, 5* - N1a + N1b + N1c ≤ 1 and B1 = 0

Resident _____ Numeric Identifier _____

SECTION D. VISION PATTERNS

1. VISION

(*Ability to see in adequate light and with glasses if used*)
0. *ADEQUATE*—sees fine detail, including regular print in newspapers/books
1. *IMPAIRED*—sees large print, but not regular print in newspapers/books. *3*
2. *MODERATELY IMPAIRED*—limited vision; not able to see newspaper headlines, but can identify objects. *3*
3. *HIGHLY IMPAIRED*—object identification in question, but eyes appear to follow objects. *3*
4. *SEVERELY IMPAIRED*—no vision or sees only light, colors, or shapes; eyes do not appear to follow objects

2. VISUAL LIMITATIONS/ DIFFICULTIES

a. Side vision problems—decreased peripheral vision (e.g., leaves food on one side of tray, difficulty traveling, bumps into people and objects, misjudges placement of chair when seating self). *3*

b. Experiences any of following: sees halos or rings around lights; sees flashes of light; sees "curtains" over eyes

c. *NONE OF ABOVE*

3. VISUAL APPLIANCES

Glasses; contact lenses; magnifying glass
0. No 1. Yes

SECTION E. MOOD AND BEHAVIOR PATTERNS

1. INDICATORS OF DEPRESSION, ANXIETY, SAD MOOD

(E1a - E1p = 1.2) *8*
(E1n = 1.2) *17**
(E1o = 1.2) *7*

(Code for indicators observed in last 30 days, irrespective of the assumed cause)
0. Indicator not exhibited in last 30 days
1. Indicator of this type exhibited up to five days a week
2. Indicator of this type exhibited daily or almost daily (6, 7 days a week)

VERBAL EXPRESSIONS OF DISTRESS

a. Resident made negative statements—e.g., "*Nothing matters; Would rather be dead; What's the use; Regrets having lived so long; Let me die*" 4.5

b. Repetitive questions—e.g., "*Where do I go; What do I do?*"

c. Repetitive verbalizations—e.g., calling out for help, ("*God help me*")

d. Persistent anger with self or others—e.g., easily annoyed, anger at placement in nursing home; anger at care received

e. Self deprecation—e.g., "*I am nothing; I am of no use to anyone*"

f. Expressions of what appear to be unrealistic fears—e.g., fear of being abandoned, left alone, being with others

g. Recurrent statements that something terrible is about to happen—e.g., believes he or she is about to die, have a heart attack 4.5

h. Repetitive health complaints—e.g., persistently seeks medical attention, obsessive concern with body functions

i. Repetitive anxious complaints/concerns (non-health related) e.g., persistently seeks attention/ reassurance regarding schedules, meals, laundry, clothing, relationship issues

SLEEP-CYCLE ISSUES

j. Unpleasant mood in morning 4.5

k. Insomnia/change in usual sleep pattern

SAD, APATHETIC, ANXIOUS APPEARANCE

l. Sad, pained, worried facial expressions—e.g., furrowed brows

m. Crying, tearfulness

n. Repetitive physical movements—e.g., pacing, hand wringing, restlessness, fidgeting, picking 4.5

LOSS OF INTEREST

o. Withdrawal from activities of interest—e.g., no interest in long standing activities or being with family/friends 4.5

p. Reduced social interaction 4.5

2. MOOD PERSISTENCE

One or more indicators of depressed, sad or anxious mood were not easily altered by attempts to "cheer up", console, or reassure the resident over last 7 days
0. No mood indicators 1. Indicators present, easily altered. *8,* 4.5 2. Indicators present, not easily altered. *8,* 4.5

3. CHANGE IN MOOD

Resident's mood status has changed as compared to status of 90 days ago (or since last assessment if less than 90 days)
0. No change 1. Improved 2. Deteriorated *1, 17**

4. BEHAVIORAL SYMPTOMS

(A) ***Behavioral symptom frequency in last 7 days***
0. Behavior not exhibited in last 7 days
1. Behavior of this type occurred 1 to 3 days in last 7 days
2. Behavior of this type occurred 4 to 6 days, but less than daily
3. Behavior of this type occurred daily

(B) ***Behavioral symptom alterability in last 7 days***
0. Behavior not present OR behavior was easily altered
1. Behavior was not easily altered

	(A)	(B)
a. WANDERING (moved with no rational purpose, seemingly oblivious to needs or safety) *9, 11*		
b. VERBALLY ABUSIVE BEHAVIORAL SYMPTOMS (others were threatened, screamed at, cursed at) *9,* 3		
c. PHYSICALLY ABUSIVE BEHAVIORAL SYMPTOMS (others were hit, shoved, scratched, sexually abused) *9,* 3		
d. SOCIALLY INAPPROPRIATE/DISRUPTIVE BEHAVIORAL SYMPTOMS (made disruptive sounds, noisiness, screaming, self-abusive acts, sexual behavior or disrobing in public, smeared/threw food/feces, hoarding, rummaged through others' belongings) *9,* 3		
e. RESISTS CARE (resisted taking medications/ injections, ADL assistance, or eating) *9,* 4.5		

5. CHANGE IN BEHAVIORAL SYMPTOMS

Resident's behavior status has changed as compared to status of 90 days ago (or since last assessment if less than 90 days)
0. No change 1. Improved *9* 2. Deteriorated *1, 17**

SECTION F. PSYCHOSOCIAL WELL-BEING

1. SENSE OF INITIATIVE/ INVOLVEMENT

a. At ease interacting with others
b. At ease doing planned or structured activities
c. At ease doing self-initiated activities
d. Establishes own goals *7*
e. Pursues involvement in life of facility (e.g., makes/keeps friends; involved in group activities; responds positively to new activities; assists at religious services)
f. Accepts invitations into most group activities
g. *NONE OF ABOVE*

2. UNSETTLED RELATIONSHIPS

a. Covert/open conflict with or repeated criticism of staff *7*
b. Unhappy with roommate *7*
c. Unhappy with residents other than roommate *7*
d. Openly expresses conflict/anger with family/friends *7*
e. Absence of personal contact with family/friends
f. Recent loss of close family member/friend
g. Does not adjust easily to change in routines
h. *NONE OF ABOVE*

3. PAST ROLES

a. Strong identification with past roles and life status *7*
b. Expresses sadness/anger/empty feeling over lost roles/status *7*
c. Resident perceives that daily routine (customary routine, activities) is very different from prior pattern in the community *7*
d. *NONE OF ABOVE*

SECTION G. PHYSICAL FUNCTIONING AND STRUCTURAL PROBLEMS

1. (A) ADL SELF-PERFORMANCE—(***Code for resident's PERFORMANCE OVER ALL SHIFTS during last 7 days—Not including setup***)

0. *INDEPENDENT*—No help or oversight —OR— Help/oversight provided only 1 or 2 times during last 7 days
1. *SUPERVISION*—Oversight, encouragement or cueing provided 3 or more times during last 7 days —OR— Supervision (3 or more times) plus physical assistance provided only 1 or 2 times during last 7 days
2. *LIMITED ASSISTANCE*—Resident highly involved in activity; received physical help in guided maneuvering of limbs or other nonweight bearing assistance 3 or more times —OR—More help provided only 1 or 2 times during last 7 days
3. *EXTENSIVE ASSISTANCE*—While resident performed part of activity, over last 7-day period, help of following type(s) provided 3 or more times:
— Weight-bearing support
— Full staff performance during part (but not all) of last 7 days
4. *TOTAL DEPENDENCE*—Full staff performance of activity during entire 7 days
8. *ACTIVITY DID NOT OCCUR* during entire 7 days

(B) ADL SUPPORT PROVIDED—(***Code for MOST SUPPORT PROVIDED OVER ALL SHIFTS during last 7 days; code regardless of resident's self-performance classification***)

0. No *setup* or physical help from staff
1. Setup help only
2. One person physical assist
3. Two+ persons physical assist
8. ADL activity itself did not occur during entire 7 days

			(A) SELF-PERF	(B) SUPPORT
a.	BED MOBILITY	How resident moves to and from lying position, turns side to side, and positions body while in bed 1,2,3,4 = *5A* 2,3,4,8 = *16* 17		
b.	TRANSFER	How resident moves between surfaces—to/from: bed, chair, wheelchair, standing position (EXCLUDE to/from bath/toilet) 1,2,3,4 = *5A* 17		
c.	WALK IN ROOM	How resident walks between locations in his/her room 1,2,3,4 = *5A*		
d.	WALK IN CORRIDOR	How resident walks in corridor on unit 1,2,3,4 = *5A*		
e.	LOCOMOTION ON UNIT	How resident moves between locations in his/her room and adjacent corridor on same floor. If in wheelchair, self-sufficiency once in chair 1,2,3,4 = *5A*		
f.	LOCOMOTION OFF UNIT	How resident moves to and returns from off unit locations (e.g., areas set aside for dining, activities, or treatments). If facility has only one floor, how resident moves to and from distant areas on the floor. If in wheelchair, self-sufficiency once in chair 1,2,3,4 = *5A*		
g.	DRESSING	How resident puts on, fastens, and takes off all items of street clothing, including donning/removing prosthesis 1,2,3,4 = *5A*		
h.	EATING	How resident eats and drinks (regardless of skill). Includes intake of nourishment by other means (e.g., tube feeding, total parenteral nutrition) 1,2,3,4 = *5A* 17		
i.	TOILET USE	How resident uses the toilet room (or commode, bedpan, urinal); transfer on/off toilet, cleanses, changes pad, manages ostomy or catheter, adjusts clothes 1,2,3,4 = *5A* 17		
j.	PERSONAL HYGIENE	How resident maintains personal hygiene, including combing hair, brushing teeth, shaving, applying makeup, washing/drying face, hands, and perineum (EXCLUDE baths and showers) 1,2,3,4 = *5A*		

17 - refer to a RAI manual for clarification

Resident _____ Numeric Identifier _____

2. BATHING — How resident takes full-body bath/shower, sponge bath, and transfers in/out of tub/shower (EXCLUDE washing of back and hair.) *Code for most dependent in self-performance and support.*
(A) BATHING SELF-PERFORMANCE codes appear below (A) (B)
0. Independent—No help provided
1. Supervision—Oversight help only *5.4*
2. Physical help limited to transfer only *5.4*
3. Physical help in part of bathing activity *5.4*
4. Total dependence *5.4*
8. Activity itself did not occur during entire 7 days
(Bathing support codes are as defined in Item 1, code B above)

3. TEST FOR BALANCE (see training manual)
(Code for ability during test in the last 7 days)
0. Maintained position as required in test
1. Unsteady, but able to rebalance self without physical support
2. Partial physical support during test; or stands (sits) but does not follow directions for test
3. Not able to attempt test without physical help
a. Balance while standing
b. Balance while sitting—position, trunk control *17**

4. FUNCTIONAL LIMITATION IN RANGE OF MOTION (see training manual)
(Code for limitations during last 7 days that interfered with daily functions or placed resident at risk of injury)
(A) *RANGE OF MOTION*: 0. No limitation; ☐ 1. Limitation on one side; ☐ 2. Limitation on both sides
(B) *VOLUNTARY MOVEMENT*: 0. No loss; 1. Partial loss; 2. Full loss

	(A)	(B)
a. Neck 18		
b. Arm—including shoulder or elbow 18		
c. Hand—including wrist or fingers 18		
d. Leg—including hip or knee 18		
e. Foot—including ankle or toes 18		
f. Other limitation or loss 18		

5. MODES OF LOCOMOTION *(Check all that apply during last 7 days)*
a. Cane/walker/crutch [a.] — b. Wheeled self [b.] — c. Other person wheeled [c.] — d. Wheelchair primary mode of locomotion [d.] — e. *NONE OF ABOVE* [e.]

6. MODES OF TRANSFER *(Check all that apply during last 7 days)*
a. Bedfast all or most of time *16* 16 [a.] — b. Bed rails used for bed mobility or transfer [b.] — c. Lifted manually [c.] — d. Lifted mechanically [d.] — e. Transfer aid (e.g., slide board, trapeze, cane, walker, brace) [e.] — f. *NONE OF ABOVE* [f.]

7. TASK SEGMENTATION Some or all of ADL activities were broken into subtasks during last 7 days so that resident could perform them
0. No 1. Yes

8. ADL FUNCTIONAL REHABILITATION POTENTIAL
a. Resident believes he/she is capable of increased independence in at least some ADLs *5.4* [a.]
b. Direct care staff believe resident is capable of increased independence in at least some ADLs *5.4* [b.]
c. Resident able to perform tasks/activity but is very slow [c.]
d. Difference in ADL Self-Performance or ADL Support, comparing mornings to evenings [d.]
e. *NONE OF ABOVE* [e.]

9. CHANGE IN ADL FUNCTION Resident's ADL self-performance status has changed as compared to status of **90 days ago** (or since last assessment if less than 90 days)
0. No change 1. Improved 2. Deteriorated

SECTION H. CONTINENCE IN LAST 14 DAYS

1. CONTINENCE SELF-CONTROL CATEGORIES
(Code for resident's PERFORMANCE OVER ALL SHIFTS)
0. *CONTINENT*—Complete control *[includes use of indwelling urinary catheter or ostomy device that does not leak urine or stool]*
1. *USUALLY CONTINENT*—BLADDER, incontinent episodes once a week or less; BOWEL, less than weekly
☐ 2. *OCCASIONALLY INCONTINENT*—BLADDER, 2 or more times a week but not daily; BOWEL, once a week
☐ 3. *FREQUENTLY INCONTINENT*—BLADDER, tended to be incontinent daily, but some control present (e.g., on day shift); BOWEL, 2-3 times a week
☐ 4. *INCONTINENT*—Had inadequate control BLADDER, multiple daily episodes; BOWEL, all (or almost all) of the time

a. BOWEL CONTINENCE — Control of bowel movement, with appliance or bowel continence programs, if employed 1,2,3,4 = *16* 3.4=8 2.3=9*

b. BLADDER CONTINENCE — Control of urinary bladder function (if dribbles, volume insufficient to soak through underpants), with appliances (e.g., foley) or continence programs, if employed 2,3,4 = *6* 3.4=8 2.3=9*

2. BOWEL ELIMINATION PATTERN
a. Bowel elimination pattern regular—at least one movement every three days [a.] — b. Constipation *17** [b.] — c. Diarrhea [c.] — d. Fecal impaction *17** 11 [d.] — e. *NONE OF ABOVE* [e.]

3. APPLIANCES AND PROGRAMS
a. Any scheduled toileting plan [a.] — b. Bladder retraining program [b.] — c. External (condom) catheter *6* [c.] — d. Indwelling catheter *6* 10 [d.] — e. Intermittent catheter *6* [e.] — f. Did not use toilet room/commode/urinal [f.] — g. Pads/briefs used *6* [g.] — h. Enemas/irrigation [h.] — i. Ostomy present [i.] — j. *NONE OF ABOVE* [j.]

4. CHANGE IN URINARY CONTINENCE Resident's urinary continence has changed as compared to status of **90 days ago** (or since last assessment if less than 90 days)
0. No change 1. Improved 2. Deteriorated

SECTION I. DISEASE DIAGNOSES

Check only those diseases that have a relationship to current ADL status, cognitive status, mood and behavior status, medical treatments, nursing monitoring, or risk of death. (Do not list inactive diagnoses)

1. DISEASES *(If none apply, CHECK the NONE OF ABOVE box)*

ENDOCRINE/METABOLIC/NUTRITIONAL
a. Diabetes mellitus [a.]
b. Hyperthyroidism [b.]
c. Hypothyroidism [c.]

HEART/CIRCULATION
d. Arteriosclerotic heart disease (ASHD) [d.]
e. Cardiac dysrhythmias [e.]
f. Congestive heart failure [f.]
g. Deep vein thrombosis [g.]
h. Hypertension [h.]
i. Hypotension *17** [i.]
j. Peripheral vascular disease *16* [j.]
k. Other cardiovascular disease [k.]

MUSCULOSKELETAL
l. Arthritis [l.]
m. Hip fracture [m.]
n. Missing limb (e.g., amputation) [n.]
o. Osteoporosis [o.]
p. Pathological bone fracture [p.]

NEUROLOGICAL
q. Alzheimer's disease [q.]
r. Aphasia [r.]
s. Cerebral palsy [s.]
t. Cerebrovascular accident (stroke) [t.]
u. Dementia other than Alzheimer's disease [u.]
v. Hemiplegia/Hemiparesis [v.]
w. Multiple sclerosis [w.]
x. Paraplegia [x.]
y. Parkinson's disease [y.]
z. Quadriplegia [z.]
aa. Seizure disorder [aa.]
bb. Transient ischemic attack (TIA) [bb.]
cc. Traumatic brain injury [cc.]

PSYCHIATRIC/MOOD
dd. Anxiety disorder [dd.]
ee. Depression *17** [ee.]
ff. Manic depression (bipolar disease) [ff.]
gg. Schizophrenia [gg.]

PULMONARY
hh. Asthma [hh.]
ii. Emphysema/COPD [ii.]

SENSORY
jj. Cataracts *3* [jj.]
kk. Diabetic retinopathy [kk.]
ll. Glaucoma *3* [ll.]
mm. Macular degeneration [mm.]

OTHER
nn. Allergies [nn.]
oo. Anemia [oo.]
pp. Cancer [pp.]
qq. Renal failure [qq.]
rr. *NONE OF ABOVE* [rr.]

2. INFECTIONS *(If none apply, CHECK the NONE OF ABOVE box)*
a. Antibiotic resistant infection (e.g., Methicillin resistant staph) [a.]
b. Clostridium difficile (c. diff.) [b.]
c. Conjunctivitis [c.]
d. HIV infection [d.]
e. Pneumonia [e.]
f. Respiratory infection [f.]
g. Septicemia [g.]
h. Sexually transmitted diseases [h.]
i. Tuberculosis [i.]
j. Urinary tract infection in last 30 days *14* 12 [j.]
k. Viral hepatitis [k.]
l. Wound infection [l.]
m. *NONE OF ABOVE* [m.]

3. OTHER CURRENT OR MORE DETAILED DIAGNOSES AND ICD-9 CODES
a. _____ •
b. _____ •
c. _____ •
d. _____ •
e. _____ •
276.5 = 14, 15

SECTION J. HEALTH CONDITIONS

1. PROBLEM CONDITIONS *(Check all problems present in last 7 days unless other time frame is indicated)*

INDICATORS OF FLUID STATUS
a. Weight gain or loss of 3 or more pounds within a 7 day period. *14* [a.]
b. Inability to lie flat due to shortness of breath [b.]
c. Dehydrated; output exceeds input *14* 15 [c.]
d. Insufficient fluid; did NOT consume all/almost all liquids provided during last 3 days. *14* [d.]

OTHER
e. Delusions [e.]
f. Dizziness/Vertigo *11,17** [f.]
g. Edema [g.]
h. Fever *14* [h.]
i. Hallucinations *17** [i.]
j. Internal bleeding *14* [j.]
k. Recurrent lung aspirations in last 90 days. *17** [k.]
l. Shortness of breath [l.]
m. Syncope (fainting) *17** [m.]
n. Unsteady gait *17** [n.]
o. Vomiting [o.]
p. *NONE OF ABOVE* [p.]

17 - refer to a RAI manual for clarification* 9* - H3a or H3b not checked

Resident _____ Numeric Identifier _____

2. PAIN SYMPTOMS (*Code the highest level of pain present in the last 7 days*)
- a. FREQUENCY with which resident complains or shows evidence of pain: 0. No pain (*skip to J4*) 1. Pain less than daily 2. Pain daily
- b. INTENSITY of pain: 1. Mild pain 2. Moderate pain 3. Times when pain is horrible or excruciating

3. PAIN SITE (*If pain present, check all sites that apply in last 7 days*)
- a. Back pain
- b. Bone pain
- c. Chest pain while doing usual activities
- d. Headache
- e. Hip pain
- f. Incisional pain
- g. Joint pain (other than hip)
- h. Soft tissue pain (e.g., lesion, muscle)
- i. Stomach pain
- j. Other

4. ACCIDENTS (*Check all that apply*)
- a. Fell in past 30 days *11,17** 2
- b. Fell in past 31-180 days *11,17**
- c. Hip fracture in last 180 days *17** 1
- d. Other fracture in last 180 days 1
- e. *NONE OF ABOVE*

5. STABILITY OF CONDITIONS
- a. Conditions/diseases make resident's cognitive, ADL, mood or behavior patterns unstable—(fluctuating, precarious, or deteriorating)
- b. Resident experiencing an acute episode or a flare-up of a recurrent or chronic problem
- c. End-stage disease, 6 or fewer months to live
- d. *NONE OF ABOVE*

SECTION K. ORAL/NUTRITIONAL STATUS

1. ORAL PROBLEMS
- a. Chewing problem
- b. Swallowing problem *17**
- c. Mouth pain *15*
- d. *NONE OF ABOVE*

2. HEIGHT AND WEIGHT *Record (a.) height in inches and (b.) weight in pounds. Base weight on most recent measure in last 30 days; measure weight consistently in accord with standard facility practice—e.g., in a.m. after voiding, before meal, with shoes off, and in nightclothes*
a. HT (in.) b. WT (lb.)

3. WEIGHT CHANGE
- a. Weight loss—5 % or more in last 30 days; or 10 % or more in last 180 days. 0. No 1. Yes *12* 4.5.13
- b. Weight gain—5 % or more in last 30 days; or 10 % or more in last 180 days. 0. No 1. Yes

4. NUTRITIONAL PROBLEMS
- a. Complains about the taste of many foods *12*
- b. Regular or repetitive complaints of hunger
- c. Leaves 25% or more of food uneaten at most meals *12*
- d. *NONE OF ABOVE*

5. NUTRITIONAL APPROACHES (*Check all that apply in last 7 days*)
- a. Parenteral/IV *12,14*
- b. Feeding tube *13,14* 14
- c. Mechanically altered diet *12*
- d. Syringe (oral feeding) *12*
- e. Therapeutic diet *12*
- f. Dietary supplement between meals
- g. Plate guard, stabilized built-up utensil, etc.
- h. On a planned weight change program
- i. *NONE OF ABOVE*

6. PARENTERAL OR ENTERAL INTAKE (*Skip to Section L if neither 5a nor 5b is checked*)
- a. Code the proportion of total calories the resident received through parenteral or tube feedings in the last 7 days: 0. None 1. 1% to 25% 2. 26% to 50% 3. 51% to 75% 4. 76% to 100%
- b. Code the average fluid intake per day by IV or tube in last 7 days: 0. None 1. 1 to 500 cc/day 2. 501 to 1000 cc/day 3. 1001 to 1500 cc/day 4. 1501 to 2000 cc/day 5. 2001 or more cc/day

SECTION L. ORAL/DENTAL STATUS

1. ORAL STATUS AND DISEASE PREVENTION
- a. Debris (soft, easily movable substances) present in mouth prior to going to bed at night *15*
- b. Has dentures or removable bridge
- c. Some/all natural teeth lost—does not have or does not use dentures (or partial plates) *15*
- d. Broken, loose, or carious teeth *15*
- e. Inflamed gums (gingiva); swollen or bleeding gums; oral abscesses; ulcers or rashes *15*
- f. Daily cleaning of teeth/dentures or daily mouth care—by resident or staff. Not ✓ = *15*
- g. *NONE OF ABOVE*

SECTION M. SKIN CONDITION

1. ULCERS (Due to any cause) (*Record the number of ulcers at each ulcer stage—regardless of cause. If none present at a stage, record "0" (zero). Code all that apply during last 7 days. Code 9 = 9 or more.) [Requires full body exam.]* — Number at Stage
- a. Stage 1. A persistent area of skin redness (without a break in the skin) that does not disappear when pressure is relieved.
- b. Stage 2. A partial thickness loss of skin layers that presents clinically as an abrasion, blister, or shallow crater.
- c. Stage 3. A full thickness of skin is lost, exposing the subcutaneous tissues - presents as a deep crater with or without undermining adjacent tissue.
- d. Stage 4. A full thickness of skin and subcutaneous tissue is lost, exposing muscle or bone.

2. TYPE OF ULCER 2,3,4 = *12* 1,2,3,4 = *16*
(*For each type of ulcer, code for the highest stage in the last 7 days using scale in item M1—i.e., 0=none; stages 1, 2, 3, 4*)
- a. Pressure ulcer—any lesion caused by pressure resulting in damage of underlying tissue 0 - 24
- b. Stasis ulcer—open lesion caused by poor circulation in the lower extremities

3. HISTORY OF RESOLVED ULCERS Resident had an ulcer that was resolved or cured in LAST 90 DAYS. 0. No 1. Yes *16*

4. OTHER SKIN PROBLEMS OR LESIONS PRESENT (*Check all that apply during last 7 days*)
- a. Abrasions, bruises
- b. Burns (second or third degree)
- c. Open lesions other than ulcers, rashes, cuts (e.g., cancer lesions)
- d. Rashes—e.g., intertrigo, eczema, drug rash, heat rash, herpes zoster
- e. Skin desensitized to pain or pressure *16*
- f. Skin tears or cuts (other than surgery)
- g. Surgical wounds
- h. *NONE OF ABOVE*

5. SKIN TREATMENTS (*Check all that apply during last 7 days*)
- a. Pressure relieving device(s) for chair
- b. Pressure relieving device(s) for bed
- c. Turning/repositioning program
- d. Nutrition or hydration intervention to manage skin problems
- e. Ulcer care
- f. Surgical wound care
- g. Application of dressings (with or without topical medications) other than to feet
- h. Application of ointments/medications (other than to feet)
- i. Other preventative or protective skin care (other than to feet)
- j. *NONE OF ABOVE*

6. FOOT PROBLEMS AND CARE (*Check all that apply during last 7 days*)
- a. Resident has one or more foot problems—e.g., corns, callouses, bunions, hammer toes, overlapping toes, pain, structural problems
- b. Infection of the foot—e.g., cellulitis, purulent drainage
- c. Open lesions on the foot
- d. Nails/calluses trimmed during last 90 days
- e. Received preventative or protective foot care (e.g., used special shoes, inserts, pads, toe separators)
- f. Application of dressings (with or without topical medications)
- g. *NONE OF ABOVE*

SECTION N. ACTIVITY PURSUIT PATTERNS

1. TIME AWAKE (*Check appropriate time periods over last 7 days*) Resident awake all or most of time (i.e., naps no more than one hour per time period) in the:
- a. Morning 2 *10B* 4.5*
- b. Afternoon 4.5*
- c. Evening 4.5*
- d. *NONE OF ABOVE* 4.5

(If resident is comatose, skip to Section O)

2. AVERAGE TIME INVOLVED IN ACTIVITIES (When awake and not receiving treatments or ADL care)
0. Most—more than 2/3 of time 2 *10B*
1. Some—from 1/3 to 2/3 of time
2. Little—less than 1/3 of time *10A* 23
3. None *10A* 23

3. PREFERRED ACTIVITY SETTINGS (*Check all settings in which activities are preferred*)
- a. Own room
- b. Day/activity room
- c. Inside NH/off unit
- d. Outside facility
- e. *NONE OF ABOVE*

4. GENERAL ACTIVITY PREFERENCES (adapted to resident's current abilities) (*Check all PREFERENCES whether or not activity is currently available to resident*)
- a. Cards/other games
- b. Crafts/arts
- c. Exercise/sports
- d. Music
- e. Reading/writing
- f. Spiritual/religious activities
- g. Trips/shopping
- h. Walking/wheeling outdoors
- i. Watching TV
- j. Gardening or plants
- k. Talking or conversing
- l. Helping others
- m. *NONE OF ABOVE*

17 - refer to a RAI manual for clarification* 2 = Two items required to trigger

4.5* - N1a + N1b + N1c ≤ 1 and B1 = 0 MDS 2.0 September, 20

Resident _____ Numeric Identifier _____

5. PREFERS CHANGE IN DAILY ROUTINE

Code for resident preferences in daily routines
0. No change 1. Slight change *104* 2. Major change *104*

a. Type of activities in which resident is currently involved
b. Extent of resident involvement in activities

SECTION O. MEDICATIONS

1. NUMBER OF MEDICATIONS (*Record the number of different medications used in the last 7 days; enter "0" if none used*) 0-6

2. NEW MEDICATIONS (*Resident currently receiving medications that were initiated during the last 90 days*)
0. No 1. Yes

3. INJECTIONS (*Record the number of DAYS injections of any type received during the last 7 days; enter "0" if none used*)

4. DAYS RECEIVED THE FOLLOWING MEDICATION (*Record the number of DAYS during last 7 days; enter "0" if not used. Note—enter "1" for long-acting meds used less than weekly*)

a. Antipsychotic 1-7= ✱17* 0-1=19
b. Antianxiety 1-7= *11*, ✱17* 1=20
c. Antidepressant 1-7= *11*,✱17* 0=5
d. Hypnotic 0-1=20 >2=21
e. Diuretic 1-7= *14*

SECTION P. SPECIAL TREATMENTS AND PROCEDURES

1. SPECIAL TREATMENTS, PROCEDURES, AND PROGRAMS

a. **SPECIAL CARE**—*Check treatments or programs received during the last 14 days*

TREATMENTS
a. Chemotherapy
b. Dialysis
c. IV medication
d. Intake/output
e. Monitoring acute medical condition
f. Ostomy care
g. Oxygen therapy
h. Radiation
i. Suctioning
j. Tracheostomy care
k. Transfusions

PROGRAMS
l. Ventilator or respirator
m. Alcohol/drug treatment program
n. Alzheimer's/dementia special care unit
o. Hospice care
p. Pediatric unit
q. Respite care
r. Training in skills required to return to the community (e.g., taking medications, house work, shopping, transportation, ADLs)
s. *NONE OF ABOVE*

b. **THERAPIES** - *Record the number of days and total minutes each of the following therapies was administered (for at least 15 minutes a day) in the last 7 calendar days (Enter 0 if none or less than 15 min. daily)*
[Note—count only post admission therapies]
(A) = # of days administered for 15 minutes or more
(B) = total # of minutes provided in last 7 days

	DAYS (A)	MIN (B)
a. Speech - language pathology and audiology services		
b. Occupational therapy		
c. Physical therapy		
d. Respiratory therapy		
e. Psychological therapy (by any licensed mental health professional)		

2. INTERVENTION PROGRAMS FOR MOOD, BEHAVIOR, COGNITIVE LOSS (*Check all interventions or strategies used in last 7 days*—no matter where received)

a. Special behavior symptom evaluation program
b. Evaluation by a licensed mental health specialist in last 90 days
c. Group therapy
d. Resident-specific deliberate changes in the environment to address mood/behavior patterns—e.g., providing bureau in which to rummage
e. Reorientation—e.g., cueing
f. *NONE OF ABOVE*

3. NURSING REHABILITATION/ RESTORATIVE CARE *Record the NUMBER OF DAYS each of the following rehabilitation or restorative techniques or practices was provided to the resident for more than or equal to 15 minutes per day in the last 7 days (Enter 0 if none or less than 15 min. daily.)*

a. Range of motion (passive)
b. Range of motion (active)
c. Splint or brace assistance
TRAINING AND SKILL PRACTICE IN:
d. Bed mobility
e. Transfer
f. Walking
g. Dressing or grooming
h. Eating or swallowing
i. Amputation/prosthesis care
j. Communication
k. Other

✱ = One of these three items, plus at least one other item required to trigger

17 - refer to a RAI manual for clarification*

4. DEVICES AND RESTRAINTS (*Use the following codes for last 7 days:*)
0. Not used
1. Used less than daily
2. Used daily

Bed rails
a. — Full bed rails on all open sides of bed
b. — Other types of side rails used (e.g., half rail, one side)
c. Trunk restraint 1,2 = *11,18* 2 = *16* 22
d. Limb restraint 1,2 = *18* 22
e. Chair prevents rising 1,2 = *18* 22

5. HOSPITAL STAY(S) Record number of times resident was admitted to hospital with an overnight stay in last 90 days (or since last assessment if less than 90 days). (*Enter 0 if no hospital admissions*)

6. EMERGENCY ROOM (ER) VISIT(S) Record number of times resident visited ER without an overnight stay in last 90 days (or since last assessment if less than 90 days). (*Enter 0 if no ER visits*)

7. PHYSICIAN VISITS In the **LAST 14 DAYS** (or since admission if less than 14 days in facility) how many days has the physician (or authorized assistant or practitioner) examined the resident? (*Enter 0 if none*)

8. PHYSICIAN ORDERS In the **LAST 14 DAYS** (or since admission if less than 14 days in facility) how many days has the physician (or authorized assistant or practitioner) changed the resident's orders? *Do not include order renewals without change.* (*Enter 0 if none*)

9. ABNORMAL LAB VALUES Has the resident had any abnormal lab values during the last 90 days (or since admission)?
0. No 1. Yes

SECTION Q. DISCHARGE POTENTIAL AND OVERALL STATUS

1. DISCHARGE POTENTIAL

a. Resident expresses/indicates preference to return to the community
0. No 1. Yes

b. Resident has a support person who is positive towards discharge
0. No 1. Yes

c. Stay projected to be of a short duration— discharge projected within 90 days (do not include expected discharge due to death)
0. No 2. Within 31-90 days
1. Within 30 days 3. Discharge status uncertain

2. OVERALL CHANGE IN CARE NEEDS Resident's overall self sufficiency has changed significantly as compared to status of 90 days ago (or since last assessment if less than 90 days)
0. No change 1. Improved—receives fewer supports, needs less restrictive level of care 2. Deteriorated—receives more support

SECTION R. ASSESSMENT INFORMATION

1. PARTICIPATION IN ASSESSMENT

a. Resident: 0. No 1. Yes
b. Family: 0. No 1. Yes 2. No family
c. Significant other: 0. No 1. Yes 2. None

2. SIGNATURE OF PERSON COORDINATING THE ASSESSMENT:

a. Signature of RN Assessment Coordinator (sign on above line)

b. Date RN Assessment Coordinator signed as complete ___ Month ___ Day ____ Year

Resident _____ Numeric Identifier _____

SECTION T. THERAPY SUPPLEMENT FOR MEDICARE PPS

1. SPECIAL TREATMENTS AND PROCEDURES

a. **RECREATION THERAPY**—*Enter number of days and total minutes of recreation therapy administered (for at least 15 minutes a day) in the last 7 days (Enter 0 if none)*

	DAYS (A)	MIN (B)
(A) = # of days administered for 15 minutes or more (B) = total # of minutes provided in last 7 days		

Skip unless this is a Medicare 5 day or Medicare readmission/return assessment.

b. **ORDERED THERAPIES**—*Has physician ordered any of following therapies to begin in FIRST 14 days of stay—physical therapy, occupational therapy, or speech pathology service?*
0. No 1. Yes

If not ordered, skip to item 2

c. Through day 15, provide an estimate of the number of days when at least 1 therapy service can be expected to have been delivered.

d. Through day 15, provide an estimate of the number of therapy minutes (across the therapies) that can be expected to be delivered?

2. WALKING WHEN MOST SELF SUFFICIENT

Complete item 2 if ADL self-performance score for TRANSFER (G.1.b.A) is 0,1,2, or 3 AND at least one of the following are present:
- Resident received physical therapy involving gait training (P.1.b.c)
- Physical therapy was ordered for the resident involving gait training (T.1.b)
- Resident received nursing rehabilitation for walking (P.3.f)
- Physical therapy involving walking has been discontinued within the past 180 days

Skip to item 3 if resident did not walk in last 7 days

(FOR FOLLOWING FIVE ITEMS, BASE CODING ON THE EPISODE WHEN THE RESIDENT WALKED THE FARTHEST WITHOUT SITTING DOWN. INCLUDE WALKING DURING REHABILITATION SESSIONS.)

a. **Furthest distance walked** without sitting down during this episode.

0. 150+ feet
1. 51-149 feet
2. 26-50 feet
3. 10-25 feet
4. Less than 10 feet

b. **Time walked** without sitting down during this episode.

0. 1-2 minutes
1. 3-4 minutes
2. 5-10 minutes
3. 11-15 minutes
4. 16-30 minutes
5. 31+ minutes

c. **Self-Performance in walking** during this episode.

0. *INDEPENDENT*—No help or oversight
1. *SUPERVISION*—Oversight, encouragement or cueing provided
2. *LIMITED ASSISTANCE*—Resident highly involved in walking; received physical help in guided maneuvering of limbs or other nonweight bearing assistance
3. *EXTENSIVE ASSISTANCE*—Resident received weight bearing assistance while walking

d. **Walking support provided** associated with this episode (code regardless of resident's self-performance classification).

0. No setup or physical help from staff
1. Setup help only
2. One person physical assist
3. Two+ persons physical assist

e. **Parallel bars** used by resident in association with this episode.

0. No 1. Yes

3. CASE MIX GROUP

Medicare [ ][ ][ ][ ][ ] State [ ][ ][ ][ ][ ]

Resident _____ Numeric Identifier _____

SECTION U. MEDICATIONS – CASE MIX DEMO

List all medications that the resident **received** during the last 7 days. Include scheduled medications that are used regularly, but less than weekly.

1. Medication Name and Dose Ordered. Record the name of the medication and dose ordered.
2. Route of Administration (RA). Code the Route of Administration using the following list:

1 = by mouth (PO)	5 = subcutaneous (SQ)	8 = inhalation
2 = sub lingual (SL)	6 = rectal (R)	9 = enteral tube
3 = intramuscular (IM)	7 = topical	10 = other
4 = intravenous (IV)		

3. Frequency. Code the number of times per day, week, or month the medication is administered using the following list:

PR = (PRN) as necessary	2D = (BID) two times daily (includes every 12 hrs)	QO = every other day
1H = (QH) every hour		4W = 4 times each week
2H = (Q2H) every two hours	3D = (TID) three times daily	5W = five times each week
3H = (Q3H) every three hours	4D = (QID) four times daily	6W = six times each week
4H = (Q4H) every four hours	5D = five times daily	1M = (Q month) once every month
6H = (Q6H) every six hours	1W = (Q week) once each wk	2M = twice every month
8H = (Q8H) every eight hours	2W = two times every week	C = continuous
1D = (QD or HS) once daily	3W = three times every week	O = other

4. Amount Administered (AA). Record the number of tablets, capsules, suppositories, or liquid (any route) **per dose** administered to the resident. Code 999 for topicals, eye drops, inhalants and oral medications that need to be dissolved in water.
5. PRN-number of days (PRN-n). If the frequency code for the medication is "PR", record the number of times during the last 7 days each PRN medication was given. Code STAT medications as PRNs given once.
6. NDC Codes. Enter the National Drug Code for each medication given. Be sure to enter the correct NDC code for the drug name, strength, and form. The NDC code must match the drug dispensed by the pharmacy.

1. Medication Name and Dose Ordered	2. RA	3. Freq	4. AA	5. PRN-n	6. NDC Codes

Numeric Identifier _____

SECTION V. RESIDENT ASSESSMENT PROTOCOL SUMMARY

Resident's Name:	Medical Record No.:

1. Check if RAP is triggered.
2. For each triggered RAP, use the RAP guidelines to identify areas needing further assessment. Document relevant assessment information regarding the resident's status.
   - Describe:
     - — Nature of the condition (may include presence or lack of objective data and subjective complaints).
     - — Complications and risk factors that affect your decision to proceed to care planning.
     - — Factors that must be considered in developing individualized care plan interventions.
     - — Need for referrals/further evaluation by appropriate health professionals.
   - Documentation should support your decision-making regarding whether to proceed with a care plan for a triggered RAP and the type(s) of care plan interventions that are appropriate for a particular resident.
   - Documentation may appear anywhere in the clinical record (e.g., progress notes, consults, flowsheets, etc.).
3. Indicate under the Location of RAP Assessment Documentation column where information related to the RAP assessment can be found.
4. For each triggered RAP, indicate whether a new care plan, care plan revision, or continuation of current care plan is necessary to address the problem(s) identified in your assessment. The Care Planning Decision column must be completed within 7 days of completing the RAI (MDS and RAPs).

A. RAP PROBLEM AREA	(a) Check if triggered	Location and Date of RAP Assessment Documentation	(b) Care Planning Decision—check if addressed in care plan
1. DELIRIUM			
2. COGNITIVE LOSS			
3. VISUAL FUNCTION			
4. COMMUNICATION			
5. ADL FUNCTIONAL/ REHABILITATION POTENTIAL			
6. URINARY INCONTINENCE AND INDWELLING CATHETER			
7. PSYCHOSOCIAL WELL-BEING			
8. MOOD STATE			
9. BEHAVIORAL SYMPTOMS			
10. ACTIVITIES			
11. FALLS			
12. NUTRITIONAL STATUS			
13. FEEDING TUBES			
14. DEHYDRATION/FLUID MAINTENANCE			
15. DENTAL CARE			
16. PRESSURE ULCERS			
17. PSYCHOTROPIC DRUG USE			
18. PHYSICAL RESTRAINTS			

B.

1. Signature of RN Coordinator for RAP Assessment Process

2. ☐☐ — ☐☐ — ☐☐☐☐ (Month — Day — Year)

3. Signature of Person Completing Care Planning Decision

4. ☐☐ — ☐☐ — ☐☐☐☐ (Month — Day — Year)

Sample **Exhibit 269**

Run Date: 1/7/1999 2:53:52 pm

Report 2
Facility Quality Indicator Profile

Report Period: 1/1/1998 to 12/31/1998

Facility: REDACTED

Facility Login ID: T44

Data Submitted By: 1/5/1999

Domain/Quality Indicator	# in Num	# in Denom	Facility Percent	Comparison Group Percent	Percentile Rank
Accidents					
1. Incidence of new fractures	1	159	0.6	0.9	27
2. Prevalence of falls	47	177	26.6	20.4	92
Behavior/Emotional Patterns					
3. Prevalence of behavioral symptoms affecting others	29	177	16.4	19.9	8
High risk	24	100	24.0	26.0	6
Low risk	5	77	6.5	7.4	51
4. Prevalence of symptoms of depression	19	177	10.7	20.7	8
5. Prevalence of symptoms of depression without antidepressant therapy	5	177	2.8	10.0	0
Clinical Management					
6. Use of 9 or more different medications	82	177	46.3	34.6	100
Cognitive Patterns					
7. Incidence of cognitive impairment	6	47	12.8	9.1	89
Elimination/Incontinence					
8. Prevalence of bladder or bowel incontinence	60	163	36.8	39.6	13
High risk	19	37	51.4	47.6	62
Low risk	41	126	32.5	36.3	14
9. Prevalence of occasional or frequent bladder or bowel incontinence without toileting plan	22	64	34.4	22.6	81
10. Prevalence of indwelling catheter	10	177	5.6	7.4	14
11. Prevalence of fecal impaction	1	177	0.6	0.8	31
Infection Control					
12. Prevalence of urinary tract infections	32	177	18.1	9.7	100
Nutrition/Eating					
13. Prevalence of weight loss	29	177	16.4	10.6	100
14. Prevalence of tube feeding	5	177	2.8	2.7	70
15. Prevalence of dehydration	0	177	0.0	0.5	50

Designed and Implemented by the Center for Health Systems Research and Analysis. U.W. - Madison
for the HCFA Standard Automation System Analytic Reporting System (beta-test)

Sample **Exhibit 269 (continued)**

Run Date: 1/7/1999 2:53:52 pm

Report 2
Facility Quality Indicator Profile

Report Period: 1/1/1998 to 12/31/1998

Facility: REDACTED

Facility Login ID: T44

Data Submitted By: 1/5/1999

Domain/Quality Indicator	# in Num	# in Denom	Facility Percent	Comparison Group Percent	Percentile Rank
Physical Functioning					
16. Prevalence of bedfast residents	11	177	6.2	2.1	100
17. Incidence of decline in late loss ADLs	18	108	16.7	17.5	61
18. Incidence of decline in ROM	72	120	60.0	14.3	95
Psychotropic Drug Use					
19. Prevalence of antipsychotic use, in the absence of psychotic or related conditions	19	169	11.2	11.2	61
High risk	5	22	22.7	29.9	50
Low risk	14	147	9.5	7.4	77
20. Prevalence of antianxiety/hypnotic use	37	169	21.9	15.2	100
21. Prevalence of hynotic use more than two times in last week	12	177	6.8	2.6	100
Quality of Life					
22. Prevalence of daily physical restraints	7	177	4.0	8.7	13
23. Prevalence of little or no activity	64	177	36.2	18.0	93
Skin Care					
24. Prevalence of stage 1-4 pressure ulcers	17	177	9.6	7.5	82
High risk	8	68	11.8	11.5	7
Low risk	9	109	8.3	4.0	100

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REDACTED

Glossary

Activities of Daily Living (ADLs)
Functions required to be able to live independently, which include: Eating, Bathing, Grooming, Transferring, Toileting, and Transferring.

Acute Care
Care for a person with a single episode of a short-term illness or with an exacerbation of a chronic condition.

Administrator
Person responsible for the overall operation of a health care facility. A term most associated with hospitals and nursing homes. May be called the *Program Director* in community based facilities.

Adult Foster Home (AFH)
Private residence where up to 5 non-related elderly or disabled people may live in order to receive room, board, and personal care. Care provider must live in the residence full time. Care providers are not required to be medically licensed or certified.

Alzheimer's Unit
Provides medical and custodial care for individuals suffering from Alzheimer's disease.

American Association of Homes and Services for the Aged (AAHSA)
An organization representing nursing homes and assisted living facilities. Membership is primarily made up of not-for-profit facilities.

American Health Care Association (AHCA)
An organization representing nursing homes. Membership is primarily made up of for-profit facilities.

American Society of Consultant Pharmacists (ASCP)
An organization representing pharmacists who provide prescription services and consulting services to the long-term care industry.

American Medical Directors Association (AMDA)
The organization representing physicians who are medical directors of nursing homes.

American Geriatrics Society (AGS)
An organization comprised of any healthcare professional who is engaged in providing care and/or services to the long-term care environment. Includes physicians, nurses, social workers, and pharmacists.

Ancillary Services
Hospital services other than room, board, and professional services. They may include x-ray, laboratory, or anesthesia.

Assisted Living Facility (ALF)
Facility with over 5 residents who live in individual apartments or room. Meals, organized activities, medication management, and some assistance with dressing and personal care provided by hired staff. Care staff not required to be licensed or certified. Minimal supervision by RN or non at all. Social model.

Assisted Living Federation of America (ALFA)
An organization representing assisted living facilities.

Balanced Budget Act (BBA) of 1997
A Congressional act that introduced Medicare + Choice, an option that was intended to reduce Medicare costs. The act allows beneficiaries who have Medicare A & B to choose risk-based HMO plans, fee-for-service plans, or Medical Savings Accounts.

Beds
Term used to describe the capacity of a facility. Used in hospitals and nursing homes. Not an acceptable term in community based facilities. (*See units*)

Beneficiary
A person designated by an insuring organization as eligible to receive insurance benefits.

Bingo Card
A form of modified unit dose packaging, also referred to as blister pack or punch card.

Bundling
A contractual arrangement in which a seller provides several products at a discount. The products may be related, possibly from another manufacturer or unrelated, such as drug and non-drug products.

Care Plan
A plan that identifies the resident's care needs, describes the strategy for providing services to meet those needs, documents treatment goals, and objectives, outlines the criteria for terminating specified interventions, and documents the resident's progress in meeting goals and objectives.

Care Staff
A loosely used term to refer to the staff providing physical care in all levels of care. May or may not be licensed or certified.

Case Manager
An experienced professional (e.g., nurse, doctor, or social worker) who works with patients, providers, and insurers to coordinate all services necessary to provide the patient with a plan of medically necessary and appropriate health care.

Client
Current term often used in place of the term patient, especially in community based care facilities, and facilities for the mentally retarded or developmentally disabled.

Closed Formulary
A formulary that restricts prescriptions exclusively to the approved drug list. Emphasis may be placed on generic substitutions and step therapy protocols.

REDACTED

Center for Medicare and Medicaid Services (CMS)
A Federal Agency under the Department of Health and Human Services (HHS), which administers the Medicare program and oversees the states' management of the Medicaid program. (Formerly Health Care Finance Administration-HCFA)

Certified Medication Assistant (CMA)
A person who has worked for a specified period of time as a CAN then completed and passed a standardized program in basic medication administration. May not administer injections or IVs. Not recognized in all the states.

Certified Nursing Assistant (CNA)
A person who has completed and passed a standardized certification program in basic care. Provides assistance with activities of daily living (ADLs).

Community
See *Facility*.

Community Based Care
Term used for facilities other than hospitals and nursing homes. Includes ALF, AFH, RCF.

Delegation
Allows non-licensed non-certified staff to perform some duties traditionally done by licensed nurses. Requires teaching and supervision by an RN.

Diagnosis Related Groups (DRGs)
A system of classification for inpatient hospital services based on principle diagnosis, secondary diagnosis, surgical procedures, age, sex, and presence of complications. This system of classification is used as a financing mechanism to reimburse hospital and selected other providers for services rendered.

Director of Nursing
The person who is responsible for all nursing care provided. Required in hospitals and nursing homes. Must be a registered nurse. Also know as a Director of Nursing Services (DNS).

Disease Management
An information based process that provides an integrated, multi-disciplinary approach to the prevention, diagnosis, management, and treatment of various diseases. The goal is to optimize the clinical and economic outcome of care for a specific disease state of diagnosis.

Drug Regimen Review (DRR)
A review of the record of each patient in the long-term care facility to identify drug therapy problems or irregularities. DRRs are conducted by consultant pharmacists, and must be made in writing. (Also known as Drug Utilization Review-DUR).

Facility
The building or environment where residents live. A more acceptable term replacing the word *institution*. Now being replaced by the term *Community*.

Fee-for-Service Plan
A method of reimbursement in which providers are paid a "reasonable or customary" fee for a unit of service. Included are comprehensive first-dollar coverage, arrangements with deductibles and co-payments, or plans using utilization reviews and mandatory second opinions.

Formulary
An exclusive list of drugs for which a third-party payer will provide reimbursement. A formulary usually includes lower-priced entries in a multiple source category, and will often exclude higher-priced, branded products.

Health Care Coordinator
A loosely defined term often used in community based facilities to refer to the person responsible for overseeing the care provided to the residents. This person may or may not be licensed or certified.

Hospice
A facility or program engaged in providing palliative and supportive care of the terminally ill, and licensed, certified or otherwise pursuant to the law of jurisdiction in which services are received.

Intermediate Care Facility (ICF)
See Nursing Facility (NF)

Long-Term Care
Assistance and care of persons with chronic disabilities who require help with the activities of daily living or who suffer from cognitive impairment. Long-term care's goal is to help people with disabilities be as independent as possible; thus it is focused more on caring than on curing.

Long-Term Care Provider
Any organization that provides long-term health care. The description applies equally to a single nursing home or home health agency, a nursing home chain, or a large integrated system that contains a combination of long-term care services, including sub-acute care, skilled nursing care, and home care.

Managed Care
A system of healthcare delivery that influences utilization and cost of services and measure performance. The goal is a system that delivers value by giving people access to high-quality, cost-effective healthcare. A systemic approach, which seeks to ensure the provision of the right healthcare at the right time, place, and cost. (Also know as Managed Costs)

Medicaid
A federal program, partially funded by individual states, that provides medical benefits to certain low-income individuals. Each state under broad federal guidelines, determines what benefits are covered, who is eligible and how much providers will be paid.

Medical Director
A physician who assumes some administrative responsibilities in hospitals and nursing homes. Not required in community based facilities. Is paid for his role as medical director and must sign documents and attend quarterly meetings.

Medical Model
Refers to physician centered philosophy of care found in hospitals and nursing homes. All care is provided under the direct orders of a physician.

Medical Savings Account
A method of reimbursement in which the beneficiary is allotted a fixed amount of money to spend on health care. Allows the beneficiary to control the selection of providers and therapies.

REDACTED

Medicare
A federally funded program that uses tax dollars to reimburse providers for health care services rendered to the elderly, ages 65 and over. The major benefits of this legislation include physician services, hospital care, home care, and extended care facility coverage for a defined period of time. This program is voluntary and is financed through Social Security deductions from employee-employer payrolls. It is handled through nation trust funds. Part A covers hospital and skilled nursing facility costs. Part V, for which there is a monthly premium, covers physician services and certain outpatient procedures. While it is governed at the federal level, claims are processed through insurance companies that serve as fiscal intermediaries.

Medicare + Choice
An option introduced by the Balanced Budget Act of 1997 that was inteded to reduce Medicare costs. The act allows beneficiaries who have Medicare parts A & B to choose risk-based HMO plans, fee-for-service plans, or Medical Savings Accounts.

Minimum Data Set (MDS)
A CMS assessment tool containing more than 100 items that is filled out by nursing staff when a patient is admitted to a nursing facility. It is completed quarterly and upon a significant change in the resident's condition. It captures a patient's medical condition, functional status, sensory and physical impairment, nutrition, psychosocial status, dental status, activity level and rehabilitation potential. It is based both on staff observation and on previous written reports filed on the patient.

Morbidity (morbidity rate)
1. An actuarial determination of the incidence and severity of sickness and accidents in a well-defined class or classes of people. 2. The actual state of being diseased. 3. An actuarial determination of the death rate in a given population in a given period.

Open Formulary
A formulary that allows physicians to prescribe as they see fit, whether or not the drug is on the approved list.

Outcome
The result of a certain course of therapy, measured in terms of health impact and costs.

Patient
Consumer of health care. Term still used in some medical model facilities. Not an acceptable term in community based facilities (see *Resident or Client*).

Pharmacy and Therapeutics Committee (P&T)
An organized panel of consulting physicians, attending physicians, pharmacists, the director of nursing, and the long-term care administrator, who function as an advisory panel to the facility or plan regarding the safe and effective use of prescription medications.

Pharmacy Provider
A company that contracts to supply pharmacy services to a health care provider.

Prior Authorization (PA)
The process of obtaining approval to reimburse for a service or medication.

Program Director
A loosely defined term referring to the person responsible for the overall operations of a community based facility. (See *Administrator*).

Prospective Payment System (PPS)
The system for payment of Medicare Skilled Nursing Facility care. Pays for a day of care on an all-inclusive basis. The case mix adjusted payment includes all routine, pharmaceutical ancillary and capital related costs for each skilled day of care.

Residential Care Facility (RCF)
Facility with over 5 residents. Meals, organized activities, medication management, and some assistance with dressing and personal care provided by hired staff. Care staff not required to be licensed or certified. Minimal supervision or none by RN.

Resident
Person who lives in a health care fadcility. Term used in nursing homes and community based facilities. (See *Patient or Client*).

Resource Utilization Group (RUGs)
The classification system that is being used as part of the Prospective Payment System (PPS) for Skilled Nursing Facility care (SNF). The RUGs III classification system is based upon nursing and therapy resource use across 44 different patient categories.

Restricted Formulary
A formulary that restricts the number of drug choices in a particular class. May have lower co-pays for preferred products and higher co-pays for non-preferred drugs.

Retirement Facility
Facility providing individual apartment living with organized activities, meals, security, and limited or no health care services. No licensed nursing services.

Skilled Nursing Facility (SNF)
Facility providing skilled nursing care for elderly, disabled, and chronically ill patients.

Step Therapy
A procedure that requires physicians to use less expensive therapies in patient treatment before going on to more extensive interventions.

Social Model
Refers to client centered health care. Client directs his/her own health care and maintains the right to remain autonomous. Opposite of Medical Model.

Sub Acute Facility
Merges the intensity of hospital based services with the operation of a nursing facility to reduce the cost of caring for seriously ill patients., The goal of sub-acute care is to stabilize patients requiring cardiac care, pain management, extensive wound care or other types of labor intensive care so they can be moved to a less care-intensive facility.

Therapeutic Interchange or Substitution
The dispensing by a pharmacist of a therapeutically equivalent product without event-specific approval of the physician. This practice is common in hospitals and/or formulary- based programs for a limited number of selected rugs. Approval is generally provided by the P&T Committee. This practice will become more common in the long-term care facilities as PPS is enacted.

Third Party Payer
A public or private organization that pays for or underwrites coverage for healthcare expense4s or another entity, usually an employer (i.e. Blue Cross, Blue Shield; Medicare; Medicaid; commercial insurers).

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Transitional Care Unit (TCU)
Provides high level skilled nursing care for more acutely ill patients transitioning from hospital setting. Also know as a "step-down unit".

Units
Apartments. Current term used to describe the capacity of an assisted living facility. (See *Beds*).

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Reference Guide For CMS F-Tags

Issue	F-Tag
Antianxiety Agents	F329
Antidepressant Agents	F329
Antipsychotic Agents	F329
Antipsychotics - initial therapy	F330
Antipsychotics - gradual dose reductions	F331
Chemical Restraints	F222
Consultant Pharmacist requirements	F427
Controlled Drug - record keeping	F427
Drugs Potentially Inappropriate in Elderly	F329/F429
Drug Regimen Review	F428
DRR - report to DON & Medical Director	F429
DRR - report must be acted upon	F430
Hypnotic Agents	F329

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Reference Guide For CMS F-Tags

Issue	F-Tag
Medication Change Notification	F157
Labeling of Medications	F431
Medication Errors	F332
Significant Medication Errors	F331
Medication Pass Observation	F331
Medication Storage	F432
Parenteral/Enteral Nutrition	F328
Pharmacy Services	F425
QAA Committee	F520
Sedative/Hypnotic Agents	F329
Self-administration of Drugs	F176
Side Effect Documentation	F272
Unnecessary Drugs	F329

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SPECIAL ARTICLE

Explicit Criteria for Determining Potentially Inappropriate Medication Use by the Elderly

An Update

Mark H. Beers, MD

This study updates and expands explicit criteria defining potentially inappropriate medication use by the elderly. Additional goals were to address whether adverse outcomes were likely to be clinically severe and to incorporate clinical information on diagnoses when available. These criteria are meant to serve epidemiological studies, drug utilization review systems, health care providers, and educational efforts. Consensus from a panel of 6 nationally recognized experts on the appropriate use of medication in the elderly was sought. The expert panel agreed on the validity of 28 criteria describing the potentially inappropriate use of medication by general populations of the elderly as well as 35 criteria defining potentially inappropriate medication use in older persons known to have any of 15 common medical conditions. Updated, expanded, and more generally applicable criteria are now available to help identify inappropriate use of medications in elderly populations. These criteria define medications that should generally be avoided in the ambulatory elderly, doses or frequencies of administrations that should generally not be exceeded, and medications that should be avoided in older persons known to have any of several common conditions.

Arch Intern Med. 1997;157:1531-1536

In 1991, researchers[1] at the University of California, Los Angeles published the first explicit criteria identifying inappropriate medication use in nursing home residents. Thus, the criteria were designed to apply to only the frailest and sickest elderly populations. Those criteria were meant to serve researchers evaluating the quality of prescribing, drug utilization review systems, and educational efforts. They were designed to evaluate medication use in the absence of clinical information on diagnoses because of the relative inaccuracy of such information in nursing home records. The criteria have now been used as the basis for several research studies.[2-4]

At the time they were created, the criteria filled a void in pharmacoepidemiological methods.[5] However, even when they were first published, the authors cautioned that updating and expansion would be needed. The growing need for such criteria has led to their application in ways that they were never intended to be used. For example, although the original criteria were developed for the frailest elderly—those residing in nursing homes—they have been used to evaluate prescribing in noninstitutionalized elderly populations.[6-8] Additionally, the original criteria have been modified by most who have used them. Some have selected a subset of the criteria that they believed identified the most serious prescribing problems, since the criteria did not rate the potential severity of outcomes. Since the creation of the criteria, new medications have come to the marketplace that were not considered during the original development process and new scientific information has become available about the effects and side effects of many medications in older populations. Finally, the availability of clinical information in drug utilization review and research databases has increased so that accurate information on concurrent diagnosis is sometimes available. For all these reasons, the criteria must be reevaluated.

From the Division of Geriatric Medicine, Allegheny University of the Health Sciences, Presidential City, Philadelphia, Pa.

Table 1. Final Criteria: Independent of Diagnoses*

Summary of Prescribing Concern	Applicable Medications†	High Severity
Propoxyphene should generally be avoided in the elderly. It offers few analgesic advantages over acetaminophen, yet has the side effects of other narcotic drugs.	Propoxyphene and combination products	No
Of all available nonsteroidal, anti-inflammatory drugs, indomethacin produces the most central nervous system side effects and should, therefore, be avoided in the elderly.	Indomethacin (Indocin, Indocin SR)	No
Phenylbutazone may produce serious hematological side effects and should not be used in elderly patients.	Phenylbutazone (Butazolidin)	No
Pentazocine is a narcotic analgesic that causes more central nervous system side effects, including confusion and hallucinations, more commonly than other narcotic drugs. Additionally, it is a mixed agonist and antagonist. For both reasons, its use should generally be avoided in the elderly.	Pentazocine (Talwin)	Yes
Trimethobenzamide is one of the least effective antiemetic drugs, yet it can cause extrapyramidal side effects. When possible, it should be avoided in the elderly.	Trimethobenzamide (Tigan)	No
Most muscle relaxants and antispasmodic drugs are poorly tolerated by the elderly, leading to anticholinergic side effects, sedation, and weakness. Additionally, their effectiveness at doses tolerated by the elderly is questionable. Whenever possible, they should not be used by the elderly.	Methocarbamol (Robaxin), carisoprodol (Soma), orphenadrine (Norflex), chlorzoxazone (Parafon Forte), metaxalone (Skelaxin), and cyclobenzaprine (Flexeril)	No
Benzodiazepine hypnotic has an extremely long half-life in the elderly (often days), producing prolonged sedation and increasing the incidence of falls and fractures. Medium- or short-acting benzodiazepines are preferable.	Flurazepam (Dalmane)	Yes
Because of its strong anticholinergic and sedating properties, amitriptyline is rarely the antidepressant of choice for the elderly.	Amitriptyline (Elavil), chlordiazepoxide-amitriptyline (Limbitrol), and perphenazine-amitriptyline (Triavil)	Yes
Because of its strong anticholinergic and sedating properties, doxepin is rarely the antidepressant of choice for the elderly.	Doxepin (Sinequan)	Yes
Meprobamate is a highly addictive and sedating anxiolytic. Avoid in elderly patients. Those using meprobamate for prolonged periods may be addicted and may need to be withdrawn slowly.	Meprobamate (Miltown, Equanil)	Yes if recently started‡
Because of increased sensitivity to benzodiazepines in the elderly, smaller doses may be effective as well as safer. Total daily doses should rarely exceed the following suggested maximums:	Lorazepam (Ativan), 3 mg; oxazepam (Serax), 60 mg; alprazolam (Xanax), 2 mg; temazepam (Restoril), 15 mg; zolpidem (Ambien), 5 mg; triazolam (Halcion), 0.25 mg	No
Chlordiazepoxide and diazepam have a long half-life in the elderly (often several days), producing prolonged sedation and increasing the risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required.	Chlordiazepoxide (Librium), chlordiazepoxide-amitriptyline (Limbitrol), clidinium-chlordiazepoxide (Librax), and diazepam (Valium)	Yes
Disopyramide, of all antiarrhythmic drugs, is the most potent negative inotrope and therefore may induce heart failure in the elderly. It is also strongly anticholinergic. When appropriate, other antiarrhythmic drugs should be used.	Disopyramide (Norpace, Norpace CR)	Yes
Because of decreased renal clearance of digoxin, doses in the elderly should rarely exceed 0.125 mg daily, except when treating atrial arrhythmias.	Digoxin (Lanoxin)	Yes if recently started‡
Dipyridamole frequently causes orthostatic hypotension in the elderly. It has been proven beneficial only in patients with artificial heart valves. Whenever possible, its use in the elderly should be avoided.	Dipyridamole (Persantine)	No
Methyldopa may cause bradycardia and exacerbate depression in the elderly. Alternate treatments for hypertension are generally preferred.	Methyldopa (Aldomet); methyldopa/hydrochlorothiazide (Aldoril)	Yes if recently started‡
Reserpine imposes unnecessary risk in the elderly, inducing depression, impotence, sedation, and orthostatic hypotension. Safer alternatives exist.	Reserpine (Serpasil); reserpine hydrochlorothiazide (Hydropres)	No
Chlorpropamide has a prolonged half-life in the elderly and can cause prolonged and serious hypoglycemia. Additionally, it is the only oral hypoglycemic agent that causes SIADH. Avoid in the elderly.	Chlorpropamide (Diabinese)	Yes
Gastrointestinal antispasmodic drugs are highly anticholinergic and generally produce substantial toxic effects in the elderly. Additionally, their effectiveness at doses tolerated by the elderly is questionable. All these drugs are best avoided in the elderly, especially for long-term use.	Dicyclomine (Bentyl); hyoscyamine (Levsin, Levsinex); propantheline (Pro-Banthine); belladonna alkaloids (Donnatal and others); and clidinium-chlordiazepoxide (Librax)	Yes
All nonprescription and many prescription antihistamines have potent anticholinergic properties. Many cough and cold preparations are available without antihistamines, and these are safer substitutes in the elderly.	Examples include single and combination preparations containing chlorpheniramine (Chlor-Trimeton), diphenhydramine (Benadryl), hydroxyzine (Vistaril, Atarax), cyproheptadine (Periactin), promethazine (Phenergan), triprolidine, and dexchlorpheniramine (Polaramine)	No

(Continued)

Table 2. Final Criteria Considering Diagnoses*

Disease and Condition	Drug†	Alert	High Severity
Heart failure	Disopyramide	Negative inotrope. May worsen heart failure.	Yes
	Drugs with high sodium content (such as sodium alginate, bicarbonate, biphosphate, citrate, phosphate, salicylate, and sulfate)	Large sodium load, leading to fluid retention. May worsen heart failure.	No
Diabetes	β-Blockers (limited to people with diabetes taking oral hypoglycemics or insulin)	May block hypoglycemic symptoms in people with diabetes receiving treatment.	No
	Corticosteroids (limited to recently started use)	May worsen diabetic control.	No
Hypertension	Diet pills; amphetamines	May elevate blood pressure.	Yes
Chronic obstructive pulmonary disease	β-Blockers	May worsen respiratory function in persons with chronic obstructive pulmonary disease.	Yes
	Sedative/hypnotics	May slow respirations and increase carbon dioxide retention in persons with severe chronic obstructive pulmonary disease.	Yes
Asthma	β-Blockers	May worsen respiratory function in persons with chronic obstructive pulmonary disease.	Yes
Ulcers	NSAIDs	May exacerbate ulcer disease, gastritis, and GERD.	Yes
	Aspirin (>325 mg)	May exacerbate ulcer disease, gastritis, and GERD.	No
	Potassium supplements (all)	May cause gastric irritation with symptoms similar to ulcer disease.	No
Seizures or epilepsy	Clozapine, thioridazine, thiothixene, and chlorprothixene	Lower seizure threshold.	No
	Metoclopramide	May worsen peripheral arterial blood flow and precipitate claudication.	Yes
Peripheral vascular disease	β-Blockers	May worsen peripheral arterial blood flow and precipitate claudication.	Yes
Blood-clotting disorders, limited to those receiving anticoagulant therapy	Aspirin	May cause bleeding in those using anticoagulants.	Yes
	NSAIDs	May cause bleeding in those using anticoagulants.	Yes
	Dipyridamole and ticlopidine	May cause bleeding in those using anticoagulants.	Yes
BPH	Anticholinergic antihistamines	Anticholinergic drugs may impair micturition and cause obstruction in persons with BPH.	Yes
	Gastrointestinal antispasmodic drugs	Anticholinergic drugs may impair micturition and cause obstruction in persons with BPH.	Yes
	Muscle relaxants	Anticholinergic drugs may impair micturition and cause obstruction in persons with BPH.	No
	Narcotic drugs (including propoxyphene)	Narcotic drugs may impair micturition and cause obstruction in persons with BPH.	No
	Flavoxate, oxybutynin	Bladder relaxants may cause obstruction in persons with BPH	No
	Belladonnol	Anticholinergic bladder relaxants may cause obstruction in persons with BPH.	No
	Anticholinergic antidepressant drugs	Anticholinergic drugs may impair micturition and cause obstruction in persons with BPH.	Yes
Incontinence	α-Blockers	α-Blockers relax the external bladder sphincter and may cause incontinence.	No
Constipation	Anticholinergic drugs	Will worsen constipation.	No
	Narcotic drugs	Will worsen constipation.	No
	Tricyclic antidepressant drugs	May worsen constipation.	Yes
Syncope or falls	β-Blockers	Negative chronotrope and inotrope. May precipitate syncope in susceptible persons.	No
	Long-acting benzodiazepine drugs	May contribute to falls.	Yes
Arrhythmias	Tricyclic antidepressant drugs	May induce arrhythmias.	Yes if started recently‡
Insomnia	Decongestants	May cause or worsen insomnia.	No
	Theophylline	May cause or worsen insomnia.	No
	Desipramine, SSRIs, methylphenidate, and MAOIs	May cause or worsen insomnia.	No
	β-Agonists	May cause or worsen insomnia	No

*It is important to note that most package circulars produced by drug manufacturers do not include language identical to the statements presented herein. Although the adverse effects that these drugs can produce are generally listed in the package circulars, these as well as warnings and contraindications must be approved by regulatory agencies and in general are not based on consensus or surveys. NSAIDs indicates nonsteroidal anti-inflammatory drugs; GERD, gastroesophageal reflux disease; BPH, benign prostatic hyperplasia; SSRIs, selective serotonin reuptake inhibitors; and MAOIs, monoamine oxidase inhibitors.

†Dose limits are total daily dose.

‡Panelists believed that the severity of adverse reaction would be substantially greater when these drugs were recently started. In general, the greatest risk would be within about a 1-month period.

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ORIGINAL INVESTIGATION

The Health Care Cost of Drug-Related Morbidity and Mortality in Nursing Facilities

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Background: Preventable drug-related morbidity and mortality within nursing facilities represent a serious problem urgently requiring expert medical attention. The health care costs of drug-related problems can be both immense and avoidable. However, the research to date has been narrow in scope, focusing on the drug costs avoided and failing to consider the wider range of possible negative outcomes and potential drug-related problems.

Objectives: To develop a model of therapeutic outcomes resulting from drug therapy within nursing facilities, to estimate the magnitude of the cost of drug-related morbidity and mortality within nursing facilities in the United States, and to assess the impact of pharmacist-conducted, federally mandated, monthly, retrospective review of nursing facility residents' drug regimens in reducing the cost of drug-related morbidity and mortality.

Methods: Using decision analysis techniques, a probability pathway model was developed to estimate the cost of drug-related problems within nursing facilities. An expert panel consisting of consultant pharmacists and physicians with practice experience in nursing facilities and geriatric care was surveyed to determine conditional probabilities of therapeutic outcomes attributable to drug therapy. Health care utilization and associated costs derived from negative therapeutic outcomes were estimated.

Results: Baseline estimates indicate that the cost of drug-related morbidity and mortality with the services of consultant pharmacists was $4 billion compared with $7.6 billion without the services of consultant pharmacists.

Conclusions: Drug-related morbidity and mortality in nursing facilities represent a serious economic problem. For every dollar spent on drugs in nursing facilities, $1.33 in health care resources are consumed in the treatment of drug-related problems. With the current federally mandated drug regimen review, it is estimated that consultant pharmacists help to reduce health care resources attributed to drug-related problems in nursing facilities by $3.6 billion.

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MEDICATIONS ARE prescribed to nursing facility residents for the treatment of disease with the intent of achieving an optimal therapeutic outcome. In the past, *optimal therapeutic outcome* has been defined as "the right drug, for the right patient, at the right time."[1] More recently, optimal therapeutic outcome implies the absence of drug-related problems (DRPs).[2] A *DRP* is defined as an event or circumstance involving a patient's drug treatment that actually or potentially interferes with the achievement of an optimal outcome.[2] Eight categories of DRPs have been identified (**Table 1**).[3]

Unresolved and/or unrecognized DRPs may manifest as drug-related morbidity and, if left untreated, may eventually lead to drug-related mortality. Although it is recognized that some drug-related morbidity and mortality is due to patient peculiarity and is therefore unavoidable, there is considerable evidence that a large proportion of drug-related morbidity is preventable.[2-7]

Preventable drug-related morbidity within nursing facilities may be the result of a number of factors, including inappropriate prescribing by the physician or inappropriate monitoring by the pharmacist.[2] Viewing the cause of drug-related morbidity and mortality within this context, Manasse[5,6] suggests that it be considered a "disease" whose clinical, epidemiological, and economic impact should be measured. Thus, drug-related morbidity and mortality within nursing facilities can be assessed using cost-of-illness methods, providing a baseline measurement against which new interventions may be evaluated.[8]

physician visits. The direct cost of drug-related morbidity and mortality within nursing facilities, both with and without the services of a consultant pharmacist, was estimated by multiplying the number of health services used as a result of negative therapeutic outcomes by the estimated unit cost of each service. All calculations were based on 41 million nursing facility physician encounters, which conservatively assumes 2 initial physician encounters per month for each of the 1.7 million nursing facility residents. This estimate was based on consultations with clinical faculty, consultant pharmacists, and physicians practicing in nursing facilities.

COST DEFINITIONS

The rising cost, frequency, and duration of nursing facility care is a major concern to third-party payers of health care. Therefore, the perspective taken in the study was that of a third-party payer and every attempt was made to obtain values reflecting this perspective. Monetary values were identified from previous published reports and available statistical reports (**Table 2**). A value of $27.01 was used as the average prescription cost.[19] The cost of both an initial and subsequent nursing facility physician visit was conservatively estimated at $61.00. This value represents the national average allowed by Medicare for reimbursement to physicians.[20] The cost of an ED visit was taken from a review of recent articles reporting an average cost of ED visit of $360.00.[11,21-23] The cost of a hospital admission ($5415.00) was estimated from the American Hospital Association's 1992 hospital statistics,[24] multiplying the average length of stay by the adjusted total expense per inpatient day and adjusted for inflation to 1995 dollars. Additionally, this method of calculation has been used in previous estimations of the cost of drug-related hospital admissions.[11,25] The average cost of an allied health care professional visit (eg, dietitian, physical therapist) was estimated as $75.00 based on a survey of local charges. For the purposes of this research, the average cost of a consultant pharmacist's services was based on a fee of $10.00 per health care encounter. It should be noted that consultant pharmacists are not reimbursed per patient encounter. However, failure to include some economic value of pharmacist services assumes that no cost is associated with such services, thus biasing our total cost estimates. The average cost per laboratory and radiology procedure ($100.00) was also estimated using the 1995 HealthCare Consultants' *Physicians' Fee Guide*.[26] For estimating the costs associated with the outcome of death, it was assumed that deaths were preceded by a hospital admission.[11,22] The indirect costs of lost productivity or intangible costs were not included in this analysis because of the perspective taken and the average age of the population.

The ultimate outcome or resolution of drug-related morbidity and mortality may require a series of health care encounters. Thus, the costs associated with the final pathway must reflect all previous health care encounters. For example, additional prescription therapy would imply a preceding prescriber contact. As such, the cost of managing a treatment failure due to a DRP may include the cost of an initial physician visit, an initial prescription for the offending drug, and then a revisit by the physician (which may or may not lead to an additional prescription, an ED visit, or a laboratory or radiology procedure). Alternatively, a new medical problem may require hospitalization for management, which includes not only the cost of the hospital stay but also the initial physician visit and prescription along with a revisit by the physician and an ED visit.

STATISTICAL ANALYSIS

Descriptive statistics were calculated for all items with the results used in estimating the probabilities associated with the various points of the pathway probability model. The Student *t* test was used to test for differences across probability estimates between the 2 groups of panel experts (consultant pharmacists and physicians). Panel responses were tabulated and statistical analyses performed using computer software (Microsoft EXCEL, version 7.0, Microsoft Corp, Redmond, Wash).

SENSITIVITY ANALYSES

The cost-of-illness model was evaluated for its sensitivity to key components of the model based on 3 sensitivity analyses. These sensitivity analyses were chosen because of their potential impact on the decision process, and the analyses target the key probability estimates of the decision process. The first 2 sensitivity analyses accounted for possible differences in the distribution of residents among the various outcomes provided by the 2 groups of expert panel members. Specifically, the first 2 sensitivity analyses used the different estimates of outcomes provided by physician and pharmacist panel members. The third sensitivity analysis increased the proportion of physician visits resulting in the initiation of drug therapy to 60%. We believed that this was a reasonable assumption, given the estimates provided by our panel members and information from the medical literature.[11]

cant economic consequences of preventable drug-related morbidity and mortality in nursing facilities. However, given the current emphasis on cost containment within the health care system, it is necessary to justify the economic outlay demanded by such services.

The pharmacy and medical literature is replete with the results of research pertaining to the impact of consultant pharmacists on inappropriate medication use in nursing facilities.[12-18] Although the contribution of these studies is recognized, most have been narrow in scope (ie, measuring only drug costs avoided), failing to consider the range of possible negative outcomes (therapeutic failure, new medical problem, or a combination of the 2) and the range of potential DRPs.[2,3] An analysis of the direct costs of illness associated with drug-related morbidity and mortality in nursing facilities requires that a wide range of possible negative outcomes and potential DRPs be incorporated.

Preventable drug-related morbidity and mortality represent a dire medical problem that urgently requires expert attention.[2] The extent to which negative therapeutic outcomes can be minimized within nursing facilities would then represent the value of that expert attention. This study uses cost-of-illness methods to estimate

Table 2. Cost of Health Care Resource Utilization*

Outcome	Cost, $								
	Health Care Visit	Prescription	Additional Health Care Visit	Additional Prescription	ED Visit	Hospital Admission	Laboratory or Radiology Procedure	Allied Health Care Professional Visit	Total
No additional treatment	61.00	27.01	...	...	...	...	...	...	88.01
Practitioner visit	61.00	27.01	61.00	...	...	...	...	...	149.01
Additional treatment	61.00	27.01	61.00	27.01	...	...	...	...	176.02
ED visit	61.00	27.01	61.00	...	360.00	...	...	...	509.01
Hospital admission	61.00	27.01	61.00	...	360.00	5415.00	...	...	5924.01
Additional laboratory or radiology procedure	61.00	27.01	...	...	...	...	100.00	...	188.01
Death	61.00	27.01	61.00	...	360.00	5415.00	...	...	5924.01
Allied health care professional visit	61.00	27.01	61.00	...	...	...	...	75.00	224.01
Optimal outcome	61.00	27.01	...	...	...	...	...	...	88.01
No drug therapy	61.00	...	...	...	...	...	...	...	61.00

*When calculating the cost of health care resource utilization with the services of consultant pharmacists, a $10 initial consultation fee was assumed and included. ED indicates emergency department; ellipses, no costs were incurred in particular scenario.

to occur in 4% to 7% of cases involving negative therapeutic outcomes. Finally, deaths attributed to negative therapeutic outcomes were estimated to occur in 2% to 4% of nursing facility residents.

COST OF DRUG-RELATED MORBIDITY AND MORTALITY

Using the estimated 41 million annual nursing facility encounters, the baseline estimate of the cost of drug-related morbidity and mortality without the services of consultant pharmacists is $7.6 billion ($3.2 billion, treatment failure; $2.3 billion, new medical problem; and $2.1 billion, both treatment failure and new medical problem) (**Table 6**). With consultant pharmacists providing the federally mandated retrospective review of each nursing facility resident's drug regimen, the estimated cost of drug-related morbidity and mortality is $4 billion ($1.6 billion, treatment failure; $1.3 billion, new medical problem; and $1.1 billion, both treatment failure and new medical problem).

With the services of consultant pharmacists, there will be an estimated 9.6 million optimal therapeutic outcomes compared with 6.7 million without consultant pharmacists. Conversely, with the services of consultant pharmacists, it is estimated that 6.4 million suboptimal outcomes (2.7 million, treatment failure; 2.4 million, new medical problem; and 1.3 million, both treatment failure and new medical problem) occur compared with 9.3 million (4.2 million, treatment failure; 3 million, new medical problem; and 2.1 million, both treatment failure and new medical problem) without the services of consultant pharmacists.

SENSITIVITY ANALYSES

Table 6 provides a comparison of the cost-of-illness estimates derived from the 3 sensitivity analyses, as well as the baseline estimate. The first 2 sensitivity analyses evaluated the sensitivity of the model to possible differences in the outcomes provided by the 2 expert panel groups. As Table 6 depicts, some variation in the cost-of-illness estimates exists between physicians and pharmacists and between physicians' and pharmacists' estimates and baseline. However, all 3 estimates provide similar or identical values for the difference in costs with and without consultant pharmacists ($3.6, $3.4, and $3.6 billion). Based on the outcome estimates provided by physician panel members, the estimated cost of drug-related morbidity and mortality is $3.3 billion ($1.4 billion, treatment failure; $1.2 billion, new medical problem; and $0.7 billion, both treatment failure and new medical problem) with the services of consultant pharmacists. Without consultant pharmacist services in nursing facilities, the estimated cost of drug-related morbidity and mortality is $6.7 billion ($2.8 billion, treatment failure; $2.2 billion, new medical problem; and $1.7 billion, both treatment failure and new medical problem).

Table 3. Expert Panel Demographics

Statistic	Responses, Mean (SD)		
	Pharmacist	Physician	Total
No. of nursing facilities	5.00 (5.44)	1.61 (1.24)	3.42 (4.22)
No. of total nursing facility beds	592.00 (616.67)	215.80 (221.83)	417.30 (495.72)
Years practicing in nursing facility	10.80 (6.17)	9.88 (4.89)	10.38 (5.53)
No. of nursing facility visits per month	1.60 (1.61)	9.78 (8.61)	5.40 (7.45)
Time devoted to nursing facilities, %	56.00 (34.63)	44.62 (39.85)	50.71 (36.49)
Health care encounters resulting in drug therapy initiation, %	45.53 (27.57)	30.38 (10.90)	38.50 (22.22)

ing to the initiation of therapy increases the estimated cost of drug-related morbidity and mortality. Specifically, the estimated cost of drug-related morbidity and mortality is $6 billion ($2.4 billion, treatment failure; $2 billion, new medical problem; and $1.6 billion, both treatment failure and new medical problem) with the services of consultant pharmacists. Without consultant pharmacist services in nursing facilities, the estimated cost of drug-related morbidity and mortality is $11.5 billion ($4.8 billion, treatment failure; $3.5 billion, new medical problem; and $3.2 billion, both treatment failure and new medical problem).

COMMENT

The cost estimates presented in this study of drug-related morbidity and mortality in nursing facilities represent a significant economic outlay of our nation's health care resources. The cost estimates of drug-related morbidity and mortality with the services of consultant pharmacists range from a low of $3.3 billion to a high of $6.0 billion. Without consultant pharmacists' services, cost estimates range from $6.7 billion to $11.5 billion.

The difference between the 2 baseline estimates, $3.6 billion, represents the drug-related morbidity and mortality costs that may be avoided with the services of consultant pharmacists through retrospective drug regimen reviews. This represents a 54% reduction in the cost of drug-related morbidity and mortality within nursing facilities, which is remarkably similar to the impact of pharmaceutical care on the cost of drug-related morbidity and mortality in the ambulatory setting estimated by Johnson and Bootman.[4,11]

To put these costs into perspective, however, the costs of DRPs should be compared with the total expenditure for drug products within long-term care nursing facilities. It is estimated that approximately $3 billion is spent annually for drug therapy in nursing facilities,[9] indicating that the estimated health care cost of drug-related morbidity and mortality exceeds the original outlay for drugs by $1 billion. In other words, for every dollar spent on drugs in nursing facilities, $1.33 is consumed in the treatment of drug-related morbidity and mortality. This ratio is higher than that reported by Johnson and Bootman[4,11] for the ambulatory setting (1:1). This higher ratio can be explained by a number of factors. First, nursing facility residents consume, on average, a greater number of prescription medications, thus increasing the potential for DRPs. Additionally, in contrast to their ambulatory counterparts, nursing facility residents are placed at higher risk of DRPs because of the physiological effects of aging that alter the ability to metabolize certain drug products. Finally, another factor leading to the greater cost of drug-related morbidity and mortality is that once a DRP has occurred in the nursing home patient, there is a greater intensity of care required to treat the DRP. This could be the result of a more severe reaction experienced by the frail elderly or the higher costs of care that occur within the institutional setting.

The results of the 3 sensitivity analyses demonstrated that the cost-of-illness estimates were relatively insensitive to variations in the estimates of the distribution of residents among the various outcomes used in this research. Estimates provided by physicians and pharmacists varied little from each other as well as from the overall estimate. However, variations in the number of physician visits resulting in the initiation of drug therapy had a significant impact on the cost-of-illness estimate as well as the number of optimal therapeutic outcomes attained. A modest increase in the proportion of visits resulting in drug therapy brought about a 50% increase in the cost-of-illness estimate. Finally, because the scope of this research was broad, the costs estimated are significantly higher than those in previous reports.[17,18]

There are significant limitations and assumptions involved in this research. Most importantly, this research is limited by the lack of empirical data concerning the clinical outcomes associated with drug therapy in the nursing facility setting. These data are essential in determining the true health care cost of DRPs in nursing facilities. Additional research is needed to provide these data. However, the use of clinical experts to gather data is considered acceptable.[24,25] Overall, the impact of this possible limitation is reduced because of the following: when the probabilities of negative therapeutic outcomes and DRPs were compared between groups of panel members (physicians and pharmacists), the responses were very consistent and no significant differences were detected; and the expert panel did not provide responses biased toward the consultant pharmacist alternative since the probabilities derived from the expert panel demonstrated only a modest effect for consultant pharmacists on the proportion of optimal therapeutic outcomes attained.

Additional limitations are that the model used to assess the 2 alternatives was conceptual and the probabilities attached to the outcomes as well as costs were estimations. Therefore, the results of this research represent estimations of the true costs of drug-related morbidity and mortality. However, the estimates were provided by a panel of experienced practitioners, including both pharmacists and physicians, with diverse backgrounds practicing throughout the country.

In conclusion, this research represents a significant advancement in the economic analysis of the cost of drug-related morbidity and mortality in nursing facilities and the impact of consultant pharmacists in reducing these costs. Previous attempts to evaluate the health-care cost of DRPs have been narrow in scope (ie, measuring only the drug costs avoided), failing to consider the range of possible negative outcomes (therapeutic failure, new medical problem, or a combination of the 2) and potential DRPs. This research represents an improvement over previous research endeavors in that it simultaneously incorporates clinical and economic effects of drug therapy in the nursing facility setting.

The serious nature of the provision of drug therapy in nursing facilities is highlighted by the results of this analysis. Under the current federally mandated drug regimen review, the cost of drug-related morbidity and mor-

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OUTCOMES BASED THERAPEUTIC INTERCHANGE: AN ACE INHIBITOR INTERCHANGE PROGRAM

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Sonya Sengson

Objective: To evaluate the impact of a consultant pharmacist therapeutic intervention program for ACE inhibitors on both patient outcomes and market share of preferred product.
Design: Data was collected retrospectively and included measurements prior to and following the therapeutic interchange.
Setting and Participants: Patients taking an ACE inhibitor who resided in long-term care facilities in Georgia that were consulted to by the staff of United Pharmacy Services.
Main Outcome Measures: Blood pressures were recorded at one week intervals for three weeks prior to and following conversions. Additionally, physician-recorded symptoms of CHF were recorded during one month post conversion. Percent market share of ACE inhibitors was measured prior to conversion and one month post conversion.
Results: Of the 131 patients included in the retrospective review, none of the patients had to stop therapy as a result of a change in clinical status. No patient in the data sampling had any symptoms of CHF documented during the month before or the month after conversion to quinapril. The mean blood pressure recordings did not change after conversion. Market share of the preferred ACE inhibitor, quinapril increased from 3% to 44% during the conversion period.
Conclusions: Pharmacist-driven voluntary therapeutic interchange of ACE inhibitors resulted in significant change in market share of preferred agent without noticeable change in blood pressure or symptoms of CHF in the residents of selected long-term care facilities.
Abbreviations: ACE = angiotensin-converting enzyme; CHF = congestive heart failure.
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Two of the primary considerations in the selection of medications for patients are patient response (or outcome) and cost. These reasons are the driving forces behind many programs being developed to monitor and evaluate the outcomes of patient care interventions, especially those outcomes directly resulting from pharmacist interventions.[1] The long-term care environment, which focuses on cost-containment, places pharmacists in an ideal position to lead the health care team in both the selection and monitoring of the optimal medication for individual patients on the basis of their specific medical conditions.[2]

In the past, the availability (or non-availability) of a medication on a pre-determined formulary was usually the only strategy implemented to manage drug costs.[3] However, the management of drug costs in this manner provided only a limited degree of total cost control. When the primary focus is on product and distribution costs (with no consideration for costs associated with therapeutic failure and adverse events) any formulary will achieve only limited success (Figure 1). The focus of pharmaceutical care must be the management of appropriate utilization and the avoidance or reduction of therapeutic failures and adverse reactions. Traditional formularies also have failed to consider patient outcomes from therapy as part of the formulary (drug selection) process.[3] Consequently, fiscal savings in the pharmacy budget may likely be spent twofold or threefold in other departmental budgets.[4]

PREFERRED MEDICATION LISTS

In order to improve patient outcomes, many organizations, including United Pharmacy Services, Inc. (UPS), are changing from the rigidity of traditional formulary systems to a list of "preferred medications." Under this classification system, medications are identified as being preferred, acceptable, or unacceptable as the primary medication selected. This system is similar to a traditional formulary, as there is still a primary agent desired for utilization; however, the preferred agent's selection is not based on cost alone. Several clinical and economic factors

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Assessment Committee (QAAC). At that time the medical director and consultant pharmacist discussed any concerns and clarified questions about implementation. The list was then sent to attending physicians for their approval and signature. By signing the preferred agent list, each physician established a collaborative protocol agreement with the pharmacy care team so that the dispensing pharmacist can change the original order to the preferred agent. The pharmacist would then have the responsibility, acting as the agent of the physician, to notify the nursing facility staff of the interchange so that all records would be updated. This notification is through a verbal order form, which is also sent to the physician's office to be signed. In addition, monitoring parameters are also determined and procedures are implemented so that both the physician and consultant pharmacist are notified immediately if the monitored criteria fall outside the pre-determined parameters.

ACE Inhibitor Selection

Quinapril was selected as the preferred ACE inhibitor because no ACE inhibitor demonstrated a significant clinical advantage over the others and there was a significant cost savings derived from economy-of-scale buying incentives with this drug. The need for a preferred ACE inhibitor was initially determined by a desire to reduce the variety of agents being used (Figure 2) and the belief that this would increase the nurses' familiarity with medications, because there would be a fewer number of agents in this class. Another significant factor was the once-a-day dose schedule, which would reduce the total number of medication doses administered on a daily basis compared with the older ACE inhibitors dosed two or more times per day. By converting patients to quinapril, we anticipated that they would receive the same therapeutic response and clinical outcome as with their previous ACE inhibitor,[16] the nursing staff would have to administer fewer doses each day, and the pharmacy would have a lower investment in inventory. A table of equivalent ACE inhibitor conversions was developed for converting patients to quinapril (Table 4). The doses were based on initial dose recommendations adapted from *Facts and Comparisons* and the pharmacist's clinical experience and judgment.

Benchmarking and Program Implementation

Prior to the selection of quinapril as the preferred ACE inhibitor, the utilization of ACE inhibitors was examined (Figure 2) to establish a benchmark. This examination revealed that three agents accounted for 79% of the ACE inhibitor use, with enalapril accounting for the highest use at 35%. However, on further examination it was determined that 31% of the ordered ACE inhibitors were dosed multiple times a day. This was an important factor in our selection criteria. The reduction of doses may reduce nursing medication administration time in general and, in some cases, may eliminate entire medication passes for individual patients. This theoretical timesaving would be an important factor in obtaining nursing staff support for this conversion program. If successful, it would allow them to invest their time in other patient care activities, rather than simply administering medications to patients.

In April 1996, three UPS consultant pharmacists began requesting that physicians convert patients to once-a-day quinapril therapy in four long-term care facilities. This was done as a pilot program to obtain sample physician responses and to assess the overall comfort and acceptance of the conversion. During the pilot program, 79 recommendations were made to switch from the current ACE inhibitor to quinapril, of which 58 were accepted (73.4%). Of the 21 recommendations not accepted by physicians, 10 were refused without reason, nine expressed concern over change in disease control, and two were patients who were receiving high-dose enalapril therapy (40 mg/day) and the physician did not feel comfortable with the conversion.

However, since these facilities were selected because of good physician–pharmacist relationships and a higher-than-average physician acceptance rate in general, it was thought that a more modest overall conversion rate of approximately 60%–70% should be expected when the program was implemented on a larger scale. In July and August 1996, all UPS consultant pharmacists

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basis of ease of access to retrospective data in the medical records. Data were collected for 131 patients, on the basis of convenience. This represented 16% of patients who were converted to quinapril. Thirteen of the 823 patients receiving an ACE inhibitor were receiving quinapril at start of the conversion, leaving 810 patients with the opportunity for the conversion.

Prior to being converted to quinapril, the 131 patients sampled had a mean length of ACE inhibitor therapy of 14.3 months. The range of treatment length extended from less than one month to 54 months at the pre-conversion dose and dose schedule. When converted, the mean starting dose of quinapril was 12.5 mg (range, 2.5–40 mg), with all doses being administered once a day; 40 (30.5%) were receiving ACE inhibitor therapy two or three times per day prior to conversion. One patient was receiving lisinopril on a twice-a-day schedule, and quinapril was initiated at an equivalent dose to lisinopril and at a twice-a-day schedule.

None of the 131 patients had to stop therapy as a result of a change in clinical status. No patient in the data sampling had any symptoms of CHF documented during the month before or the month following the conversion to quinapril. The mean blood pressure recordings, which were primarily collected by certified nursing assistants, also did not change after the conversion. The mean systolic pressure, for the sample of 131 patients, was 131.2 mmHG at three weeks before and 130.9 mmHG three weeks after the change. The mean diastolic blood pressure was 73.1 mmHG three weeks before and 72.7 mmHg three weeks after the change.

Discussion

This was one of the first outcomes projects conducted by UPS in which all consultant pharmacists were included in the intervention and data collection. As a result, one limitation in the process was that all consultant pharmacists were not proceeding at the same rate and at the same time. Each consultant implemented the conversion over a period of several months. While this allowed each one to reach a comfort level before aggressively proceeding, it increased the difficulties associated with retrospective data collection and record availability. Another limitation involved the actual data collection. Because the facility staffs were not actively participating in data collection, they did not strive to assure that records were complete and available. Also by collecting the data several months after the conversion, questionable or missing data could not be re-collected. Missing information was the primary reason that only a sampling of patients were selected for data analysis. The blood pressure readings used for calculating the mean values were those recorded on the

TABLE 3. ACE Inhibitor Conversion Guidelines

ACE Inhibitor	ACE Ratio	Other ACE Dosage Equivalent to 10mg of Quinapril*
Ramipril: quinapril	1:4	2.5 mg ramipril
Captopril: quinapril	5:1	50 mg captopril
Benazepril: quinapril	1:1	10 mg benazepril
Fosinopril: quinapril	1:1	10 mg fosinopril
Moexipril: quinapril	1:1.5	7.5 mg moexipril
Enalapril: quinapril	1:2	5 mg enalapril
Lisinopril: quinapril	1:1	10 mg lisinopril

Adapted from Facts and Comparisons: Angiotensin-Converting Enzyme Inhibitors, Initial Dose Recommendations.
*When appropriate, rounded to nearest available dosage strength.

TABLE 4. Indications for Use of ACE Inhibitor for Study Group of Patients

Indication for Use	No. of Patients (n=131)	% of Patients
Congestive heart failure	18	14
Hypertension	75	57
Hypertension and congestive heart failure	38	29

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U.S. v. Abbott Laboratories

program is the key to a successful program. Clear and frequent communication between pharmacists and physicians, nurses, and the direct care staff, as well as an organized and well-planned process, is essential for a successful program.

While some physicians may object to programs such as this because of concern over prescribing authority or patient differences that they believe pharmacists may not be able to determine,[24] our experience is that this is not the case. Through this program of voluntary interchange of ACE inhibitors, pharmacists were able to determine therapeutic equivalence and manage the implementation of a conversion program in a clinical setting. Although patients in the data sampling did not have changes in blood pressure based on MAR recordings, physician-identified CHF symptoms, or ACE inhibitor dose adjustments within the first three weeks after the conversion, the program cannot assess whether the clinical outcomes observed were associated with the conversion. Further research will be needed to assess the impact of this program on clinical and economic outcomes.

While the future of long-term care pharmacy may significantly change under a prospective payment system, managed care, or any reimbursement model, the role of the pharmacist to assure the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life will not change. This is how the consultant pharmacist of the next millennium will survive—by implementing programs and treatment strategies that assure both clinical effectiveness and cost efficiency to both the patients and the payers.

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Special Report

The Pharmacy Benefit in the Year 2001: Experts See Problems and Discuss Solutions

Robert McCarthy, PhD, Valerie Ottarsh, MPH, CSW

The millennium has come and gone. We've had a presidential election and we've had the Supreme Court "legitimize" the appointment of a president. Now for the issues that hit home: Will there be a Medicare drug benefit? Will anything be done to abate the ever-increasing pharmacy spend? Is Big Pharma superseding the HMO in the "Big Book of Consumer Demonology"? These and other issues are weighed and considered by our panel of expert prognosticators. Here now are their predictions of things to watch—and to watch out for—during the coming year.

Joseph M. Sinopoli, RPh
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Editorial Advisory Board member of Drug Benefit Trends

More Tiers, More Therapeutic Substitution, More Red Ink?

I'm afraid I see a continuing trend of premium increases at managed care organizations. At the same time—and I'm sure payers aren't going to be happy to hear this—too many MCOs are operating in the red and cannot continue to do so for very long.

It's a question of survival. MCOs in the red that have to increase premiums are being confronted by MCOs in the black that see an opportunity to low-ball premiums. While the object of those in the black is plain old economic piracy, the effect may be deleterious across the industry. Obviously, those MCOs in the red will be in worse shape if they lose members and clients—but those currently in the black who play that game may find themselves squeezed between higher medical costs and lower revenues.

We're also seeing some pharmacy-risk arrangements being removed from physician-provider contracts. Physician groups are increasingly unwilling to go at-risk for pharmacy cost and utilization. This means risk travels upstream to the managed care organizations, whose pharmacy spend then goes up. We're already looking, as we did last year, at a pharmacy benefit cost increase of between 15% and 18%.

There will be an increasing pullback of managed care from Medicare and Medicaid products. Plans have been burnt; the reimbursements have been inadequate. Plans staying in those businesses will be increasingly conscious of the cost of pharmaceuticals. Here's a hint to the pharmaceutical companies: when introducing new products or when repricing old ones, please consider lower average wholesale prices (AWPs)—especially if your drug is in a crowded therapeutic class. Lower AWPs may be what it takes to get your drug prescribed.

Speaking of pharmaceutical companies, I look for more in the way of mergers and acquisitions. For us in the MCO business, such mergers are often equal to less competitive pharmaceutical pricing. I also am looking for more in the way of state-mandated coverage—for infertility, diabetes disease management, and so forth.

In addition, I expect drug companies to increase their spending on outcomes studies and pharmacoeconomics. In order to sell into a crowded therapeutic class, increase share, and increase profits, the pharmaceutical companies will have to supply data.

We're going to see more MCOs going to "legal" therapeutic substitution; that is, increased efforts to drive utilization toward specific drug class members in an effort to save dollars, whether via rebates or lower AWPs. Look for a lot more switching and a lot more working with physicians to prescribe the preferred product than ever before.

We'll see a fourth tier in formularies. There will be deductibles before you even get to the copays. You'll see bigger percentage deductions from AWP and more drugs not covered. If the plan member wants noncovered drugs, he or she must pay the entire cost. There'll be more NDC lockouts with drugs not covered. It's touchy, it gets to member satisfaction—but the big, big imperative is controlling the pharmacy spend.

There will be some very good, but very expensive, new biotech products. I think managed care organizations will

Dr McCarthy, a freelance journalist, writes the monthly Managed Care Matters column. Ms Ottarsh is a health care consultant working in New York City.

ing will intensify during the next 12 months—especially in the face of likely political gridlock in Washington. Several states have tried to take some action on pricing—particularly, the border states, both north and south. What Maine, for instance, has been trying to do, while understandable from a political perspective, is unlikely to be successful enough to provide anybody any benefit; practical impact is extremely low. (See Legal Matters, page 17)

On the federal front, Congress has already passed the Medicine Equity and Drug Safety Act that authorizes the reimportation and resale of exported pharmaceuticals; however, the regulations needed to support it will probably take at least 2 years to write and implement. And I would surmise those regulations will be written in such a way as to prevent what the pharmaceutical industry would describe as the "worst excesses" of parallel trade into the United States.

From a practical point of view, I don't see any conceivable state or federal action posing any real threat to business as usual for the pharmaceutical industry. The new Congress won't change that, and given how politically wounded the new president will be, real radical change is implausible.

With regard to the pharmacy benefit, the continued thrust from managed care organizations will center on trying to control pharmacy costs by means of a multitier formulary strategy. Already 30% to 35% of managed care lives have a multitier formulary in place, and by next year, those figures will be well over 50%. I think we'll also see copay amounts increasing, with copay differentials increasing across the tiers in addition to the more expected increased differential between brand and generic copays. I'm not sure any of those strategies have had much impact on the pharmaceutical industry; they've impacted the consumer, who has so far opted to absorb the increased costs.

We'll also see some targeted action centered on particular therapeutic areas. The proton pump inhibitor (PPI) class will definitely see some cost-control action. With *Prilosec* going off patent, we can expect to see a major battle around MCOs struggling to switch patients to a generic version and AstraZeneca looking to switch those patients to its PPI. In fact, the MCO strategy now is to switch PPI patients to *Prilosec*, take a hit in the short term, and when *Prilosec* goes off patent, to drive those *Prilosec* patients over to the generic version.

Another possible battleground involves COX-2s. Pharmacia and Pfizer will be releasing their follow-up COX-2 product in 2002, which they think will be very big. But I think the managed care view is that there is a lot of inappropriate use of these agents. There are patients and conditions for which NSAIDs and even OTCs would do the job just as well and for far less cost.

With regard to the pharmacy spend, most of what the pharmaceutical companies say is true; it's mostly being driven by utilization, not pricing. The industry has told the truth on that issue, which is an important stake to put in the ground. But if you look from the payers' point of view, pharmacy costs have been increasing by 15% to 18% for several years now—and no one thinks that's going to change anytime soon. Some payers are about to reach a critical-mass moment: when their drug costs actually surpass their inpatient costs. That's going to be an important psychological milestone; it's going to concentrate minds. Will it concentrate them enough to enable MCOs to go to employers and say, look, let's really do something? That's another matter.

And yet I would think that pharmacy costs increasing at 15% to 18% per annum is simply not sustainable. What ultimately might result is employers throwing up their hands and getting out of the health care benefit business. But I don't see that happening in the short-term and, in the meantime, other things might occur to change the equation.

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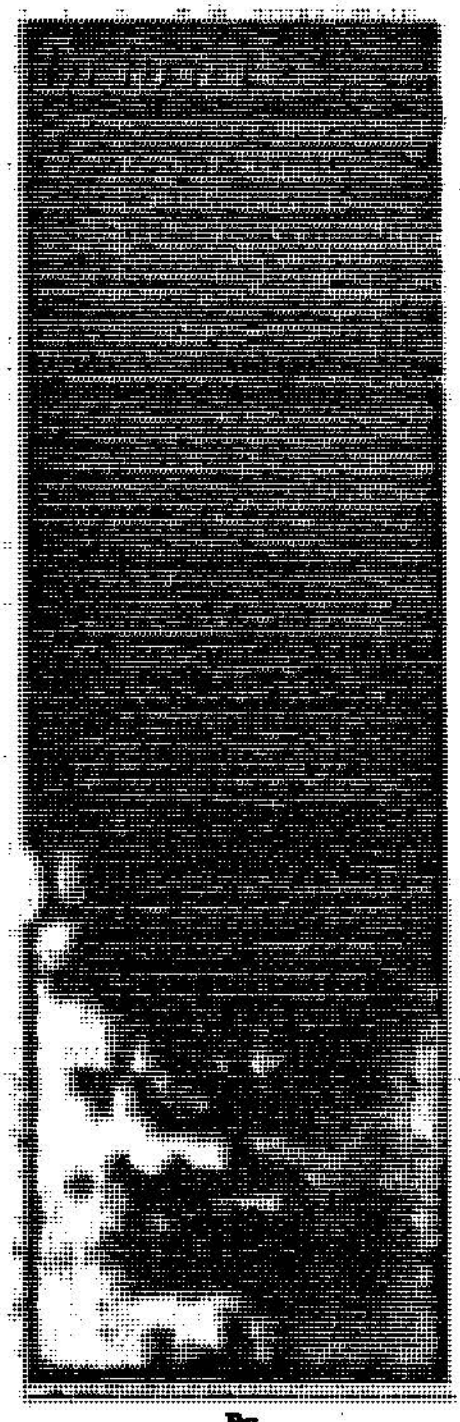
Injectables Get the Pharmacy Benefit Treatment

Bad press for pharmaceutical manufacturers is likely to remain because of the increasingly prevalent perception that prices are too high. The response from manufacturers has to be a demonstration of value: the price may be high, but look at what we're able to treat and to cure that wasn't treatable or curable just a short time ago. This message has to get to consumers. Consumers, not managed care or federal and state governments, are the ones now screaming the loudest about the price of medicines. I suspect we'll see some sort of direct-to-consumer messages concerning the value of particular drug products.

I also think the big push on the payer side will be how to implement the reimportation legislation. I think there will be more focus on reimportation as a strategy to help control the pharmacy spend, but there has to be an assessment of how, and whether, this legislation can be implemented. That's going to take a lot of time and energy.

As for a Medicare drug benefit, I believe we'll see something—regardless of who the president is. Something will

Nursing home ADEs: Largely preventable



By
Michael F. Conlan

There are about 20,000 fatal or life-threatening adverse drug events among the 350,000 ADEs that take place at the nation's nursing homes annually, according to a research team that called its estimates "likely to be conservative." The researchers said half of all the ADEs are preventable, including 80% of the most serious ones.

They based their conclusions on a study of 2,916 residents of 18 Massachusetts nursing homes. About three-fourths of residents were women; the



in 17,000 U.S. nursing homes. An average resident uses six different medications, and 20% take 10 or more.

R. Tim Webster, executive director of the American Society of Consultant Pharmacists (ASCP), called the study "valuable" and said that it "supports our assertion that adverse drug events and other medication-related problems are a significant national health policy issue. It's especially acute for the elderly, wherever they reside."

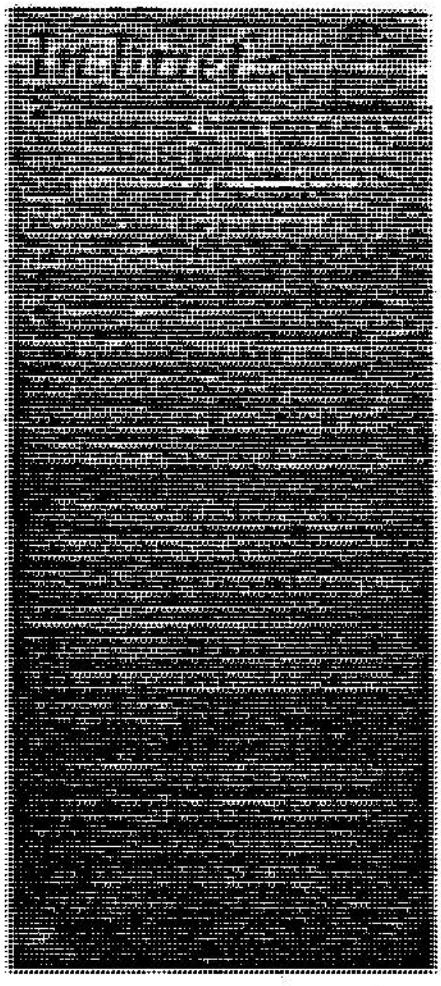
Webster called for research into medication problems associated with the growing number of seniors residing in assisted-living facilities. "Given the fact that nursing home residents are closely monitored and that well-established medication-use systems are in place in nursing facilities, it stands to reason that the scope of the problem among seniors in assisted-living and ambulatory populations is significantly higher," he told *Drug Topics for Consultant Pharmacists*.

The Massachusetts study findings were reported in the Aug. 1 issue of the *American Journal of Medicine*. The re-

Amy C. Edmondson, Ph.D.; and David W. Bates, M.D., of Harvard University.

"This study points out that it's not just a small list of so-called bad drugs in the elderly that we need to be concerned about. It's the whole range of drugs," Gurwitz said. "However, we have identified some drug categories that appear to cause more problems than others. We're not saying people shouldn't be on these drugs. We're saying that sometimes providers are not

Corporatization: Is it good for consultant pharmacy?



By
Joseph Breu
Based in Chicago, the author writes frequently on pharmacy-related issues.

Where once there used to be a lot of mom and pop consultant pharmacists, today corporatization through consolidation is the order of the day. It's a "fait accompli," in the words of R. Tim Webster, Sc.D., executive director of the American Society of Consultant Pharmacists (ASCP). The question is, What impact is it having on pharmacists and on nursing homes and patient care?

The answer varies depending on who is asked. Some will say it has cost some pharmacists their jobs and increased the pressure on consulting pharmacists to do more with less. Others claim there are several benefits, such as the greater information resources that the large companies can provide and some of the initiatives that they undertake.

And while a lot of small companies have been gobbled up by the large concerns, other small and medium-sized pharmacies are finding a niche and gaining business by responding to local conditions and offering some of the services that the big companies do not.

"There are quite a number of smaller, independently owned local or regional pharmacies that are getting their footing in the market, and they are growing quickly because of their entrepreneurial drive. And that's true not only with regard to nursing homes but in assisted living and in the ambulatory elderly market as well," noted Webster. Nonetheless, he added, it is true that the nursing home segment of the industry is now dominated by large, publicly held corporations, both in terms of the number of facilities and the number of patients served.

"Consolidation is a fact; it's extant; it exists today," Webster said. And it is having effects on consultant pharmacists and on the way they practice, say observers.

"One of the big impacts that I have seen from consolidation is stress on staff," observed Lynn Williams, R.Ph., v.p. of Learning Solutions in Boulder, Colo., a firm that provides educational services to pharmacists and other health-care personnel in long-term care (LTC).

"Staff is being asked to do more with less because the financial resources for pharmacy have been decreased," she said. "It takes a lot of financial resources for those companies to buy out pharmacies and the LTC facilities, and a number of them have gone bankrupt because they've gotten themselves into too much debt just when reimbursement from Medicare has decreased."

One of the reasons for that, according to Webster, was the implementation in 1998 of a prospective payment system (PPS) for nursing home care provided under Medicare. "When payment for drugs is wrapped in an all-inclusive per diem that's paid to the nursing facility, that focuses people's attention on managing the cost of that service component so the facility can live within the constraints of the finite per diem payment," he said. "That has led pharmacists to focus more on cost-containment rather than optimizing drug therapy."

One who believes that the companies and nursing homes should have foreseen the challenges of PPS is Gene Memoli Jr., R.Ph., v.p. of pharmaceutical care for The Medicine Center Pharmacies, a group of independent pharmacies in New England. "The large companies were not prepared properly for PPS," Memoli said. "They knew it was coming and they were generating huge profits before PPS, but they didn't put anything aside for it. So when it hit, they got hit financially. Now, they look at everything from a cost perspective. They're cutting their staffs and consolidating their pharmacies, in turn increasing the workloads of the consultant pharmacists."

Memoli is also critical of the large

Wanted: Consultants in geriatric health care

Consultant pharmacists are in demand. A shortage of geriatricians, the physicians who specialize in treating elderly patients, has led to a need for other health professionals with expertise in geriatrics.

"There is a shortage [of geriatricians], and it's severe," confirmed Kathleen DiGangi of the American Geriatrics Society's Foundation for Health in Aging. Currently, there are about 9,500 certified geriatricians in the United States, and that's less than half the number necessary to meet the needs of the elderly population.

"There's going to be an unprecedented need for pharmacists with knowledge of [geriatric pharmacy]," said Jon Bernhoft, R.Ph., a consultant pharmacist and owner of Sequim Plaza Pharmacy in Sequim, Wash.

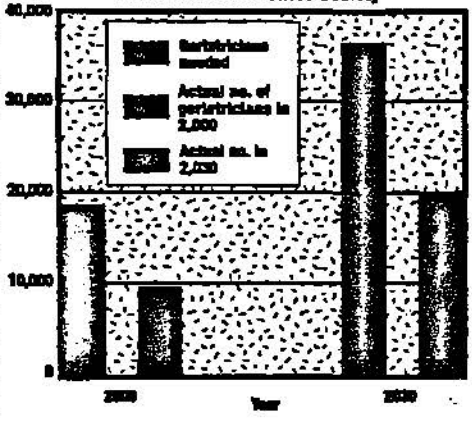
According to Tom Clark, R.Ph., M.H.S., director of professional affairs at the American Society of Consultant Pharmacists (ASCP), older adults have a decreased ability to metabolize and excrete drugs. Liver and kidney functions are often impaired, and altered protein binding and volume of distribution (becoming more hydrophyllic) may also occur. All of these changes can lead to increased susceptibility to drug interactions and adverse reactions. He explained that pharmacists fresh out of school, as well as established pharmacists looking for a career change, will most likely need additional training before entering consultant pharmacy.

Excellent communication skills, problem-solving skills, and knowledge of geriatric pharmacotherapy are essential for any consultant pharmacist, said Clark. Being able to communicate effectively is especially critical, he noted, because geriatrics is a highly interdisciplinary field. "It really takes a team of people to get [the elderly] the care that they need," he said. Consultant pharmacists "have to be able to present issues and problems in a nonthreatening way. Most of our members have generally developed pretty good relationships with physicians."

Bernhoft, who provides chart-review and drug-regimen review services to local long-term care facilities, agreed. He estimated that 80% to 90% of the physicians he consults with appreciate his help.

While knowledge of geriatric pharmacotherapy is essential for consultants, there are other issues they need to be familiar with as well. Clark pointed out that there are numerous regulations pharmacists should understand. These regulations vary from state to state and by type of facility.

Adapted from statistics compiled by the American Geriatrics Society



A relatively recent development is the Minimum Data Set, or MDS, a comprehensive assessment instrument that has been in use for about 10 years. The MDS "has become increasingly more important," said Bernhoft.

The MDS is a tool upon which reimbursement is based, and an inaccurate MDS can result in Medicare fraud, Clark cautioned. As if all that weren't enough, he said, independent consultant pharmacists have to become proficient in marketing, contracts, pricing, and time management. Fortunately, there are several good references available, and many can be obtained through ASCP. The organization also offers an on-line review course to prepare for the Commission for Certification in Geriatric Pharmacy's certification exam. Pharmacists who pass the exam may use the title Certified Geriatric Pharmacist or C.G.P. Clark said there are now more than 500 pharmacists who have qualified for certification.

ASCP has developed several traineeships for consultants seeking further education in specific areas. These include wound care, Alzheimer's/dementia, Parkinson's disease, and psychiatric and behavioral disorders. The traineeships allow a small number of pharmacists to receive five days of intensive training at selected medical centers. While all of these educational programs are extremely valuable, Clark said, "the best way for someone to learn [how to consult] is to hook up with someone who's doing it." He recommended spending six to 12 months shadowing an established consultant.

Susan Klem, B.S., C.G.P., regional clinical director, Great Lakes and Great Plains Region, for Omnicare, echoed Clark's views. She added that some universities also have geriatric certification programs, including one that Omnicare helped create at Ferris State University in Big Rapids, Mich.

Klem believes some physicians are satisfied if patients are stable, and they may be reluctant to make therapy changes purely for improved quality of life. This age bias, which implies older adults stop living after a certain age, is unfounded, she said. "We have people getting married at 100 years old."

By
Jillene Magill-Lewis, R.Ph.
Based in Washington State, the author writes frequently on health-related subjects.

Studies: Crisis Looms in Long-Term Care

As more Americans grow older, the rate of increase for acute care services, primarily hospital care and physicians' services, will drop. At the same time, however, expenditures for long-term care will increase sharply, according to a recent study.

The study and other recent research into the issue of long-term care shows that America is heading for a crisis as the population ages. Providing health care for older Americans will become more costly and the burden will fall on all health care providers and public policy experts to develop solutions to the problem, experts say.

Americans who are 50 years and older are responsible for about 58% of all health care spending, 61% of all over-the-counter drug spending, and 74% of all prescription drug expenditures, says Ken Dychtwald, the president and CEO of AGE Wave LLC, a company in Emeryville, Calif., that advises corporations on age-related trends, and the author of *Age Power, How The 21st Century Will Be Ruled By The New Old*, (J. P. Tarcher Inc., Los Angeles, 1999).

What's more, baby boomers are demanding consumers. They will present in pharmacies and physician offices with heart disease, orthopedic impairments, diabetes, digestive disorders, and adult cancer, among other conditions, Dychtwald says. He believes the health care system is ill prepared to deal with the coming onslaught. Out of the 126 medical schools in the United States, only three have departments of geriatrics, and less than 2% of physicians graduating this year have taken a rotation in geriatric care, he says.

Among all Americans, 13% are currently over the age of 65. Within 30 years, 20% will be over age 65, according to population projections from the U.S. Census Bureau.

Health care for those in the last two years of life is particularly costly, according to a study, "Longevity Has Implications for Health Care Financing," published in *The New England Journal of Medicine*, May 11. Authors Brenda C. Spillman of the Urban Institute, in Washington, D.C., and James Lubitz of the federal Health Care Financing Administration (HCFA), in Washington, D.C., used data from Medicare and national surveys to estimate expenditures on health care according to age at death.

Spending increases with the age at death because of steep increases in nursing home care, and the costs of long-term care at the end of life are less likely to be covered by Medicare or private insurance than are the costs of acute care, Spillman and Lubitz report. The total expenditure for all health care services from age 65 until death is $164,505, in 1996 dollars, they say. Total spending from age 65 until death rises substantially with longevity, from $31,181 for people who die at 65 to more than $200,000 for those who die at age 90 or older.

"Our simulations show that increased longevity after the age of 65 may have a small effect on expenditures for acute care, if present trends continue, but will have a larger effect on expenditures for long-term care and, consequently, on total health care spending for the elderly," says Spillman.

The patterns identified in the study could result in a greater financial burden for elderly people and their families as well as for Medicaid programs as the population ages, says Judith Feder, dean of policy studies at Georgetown University in Washington, D.C.

The fact that nearly a third of long-term care costs are paid out of pocket by patients "reflects the absence of an insurance system, public or private, that spreads the financial risk of needing long-term care," Feder says. "In its place is a system that protects people only if they are impoverished." The average annual cost of nursing home care is more than $40,000, resulting in a substantial financial burden for people who need to purchase such care," she says.

Feder and others believe the financial dilemma implied in these figures should be addressed through a series of public policy initiatives, including increased public support of the financing of long-term care. "I don't believe these issues can be addressed through private long-term care insurance," she says, "because the people who need financial protection the most often cannot afford or even subscribe to this type of insurance."

"Long-term care matters to many Americans of all ages and affects spending by public programs. Legislative support is needed to enhance public financing of this service."

—Judith Feder, Georgetown University

Many financial planners believe that Americans should save money during their working years to pay for long-term care if needed. But Feder counters that the purpose of insurance is to pay for expensive and unpredictable costs. "That's what long-term care is, and that's why this is a public policy issue," she says.

Many seniors needing long-term care today do not have the money to pay for it, a public policy dilemma that could have catastrophic implications for millions of Americans as our society ages, says Feder.

(Continued on page 14)

D.C., and Marlene Niefeld, a research associate at the institute, describe an "imperative change (in public support for long-term care) to assure adequate services at an acceptable cost." Their findings also were published in *Health Affairs*, May 1.

Using public money to supplement private insurance is not the answer, says Feder. "Realistically, subsidizing private insurance just helps those people who are already capable of helping themselves," she says. "It would be better to use that money to provide care to people who need help the most."

Long-term care should be financed in the same manner as acute care, relying on insurance to spread risk, she says. Although 39% of people age 65 and over will need some nursing home care before they die, almost half will require less than a year of care, while about a fifth will require five years or more. "Public discussion all too often assumes that a need for long-term care is an inevitable part of aging and that saving is therefore the right strategy to address it," says Feder. "With costs so varied and unpredictable, savings will be inadequate and inefficient. Insurance makes more sense."

—Reported and written by Marian Sipkoff, in Gettysburg, Pa.

Experts Offer Ideas for Public Financing of LTC

Expanded public financing of long-term care would entail a major shift in how the costs of LTC would be shared by society, says David Kennell, a researcher with Lewin-VHI Inc., a health care research organization in Fairfax, Va. Kennell has studied the issue of long-term care for the federal Department of Health and Human Services in Washington, D.C. "In evaluating public insurance models, it is important to assess not only who benefits, but who pays," Kennell says. "The distribution of the cost burden will depend upon the specific taxes and financing mechanisms used to generate the revenue needed to pay for public benefits."

About 50% of all long-term care costs are borne privately by the individuals who use care, primarily through private payments for nursing home care, Kennell says. The remaining 50% of formal long-term care costs is borne by the public sector, in particular the Medicaid program, which pays 38% of the cost. Medicaid costs are paid out of federal and state general revenue, primarily income taxes.

A social insurance approach, modeled on Social Security and Medicare, would finance benefits for beneficiaries from payroll taxes on current workers. Under social insurance, workers would pay into the system during their working years, and draw benefits from the system when they need long-term care as they age. "Like Social Security and Medicare, a social insurance approach to financing long-term care would be built upon social pacts between successive generations of workers," Kennell says.

Broader-based financing mechanisms also have been proposed to finance a public insurance program for long-term care, Kennell says. Increased taxes on unearned income and increases in payroll taxes would distribute costs more evenly across all age groups, since individuals over age 55 hold the vast majority of the nation's financial assets and earn the majority of unearned income, he says. Also, the government might consider taxing the Social Security benefits of beneficiaries who have high incomes, he adds.

"Like private insurance, a public insurance program would reduce the costs to most individuals who needed long-term care services and increase costs to those who paid into the system, but never used benefits," Kennell says. "Unlike private insurance, however, participation in the insurance risk pool would be mandatory, not optional. In addition, a public program is likely to include an income redistribution component, in which premium costs are income related, while benefits for all eligible recipients would be equal."

The advantages of public financing for long-term care include the following, according to Kennell and others:

Universal access. All persons who needed long-term care would be provided access to care without regard to their ability to pay. Persons with long-standing chronic conditions would not be denied access to care simply because they were uninsurable, and discriminatory policies against poor patients would be minimized.

Equity. All persons would be entitled to the same standard benefit, regardless of their economic position. Under the current system, patients who pay for care themselves often receive better quality of care than Medicaid patients do, experts say. Wealthier individuals could still purchase additional services not covered under the public program, but the basic standard of care would be raised for everyone. Also, since the program would be federally financed, current differences in access and quality among states would diminish.

Protection against catastrophic costs. Since all persons would be covered under a public program, all individuals would be protected from the risk of being impoverished by catastrophic long-term care costs. This protection would be provided to all elderly individuals, not just those who can afford to buy insurance privately.

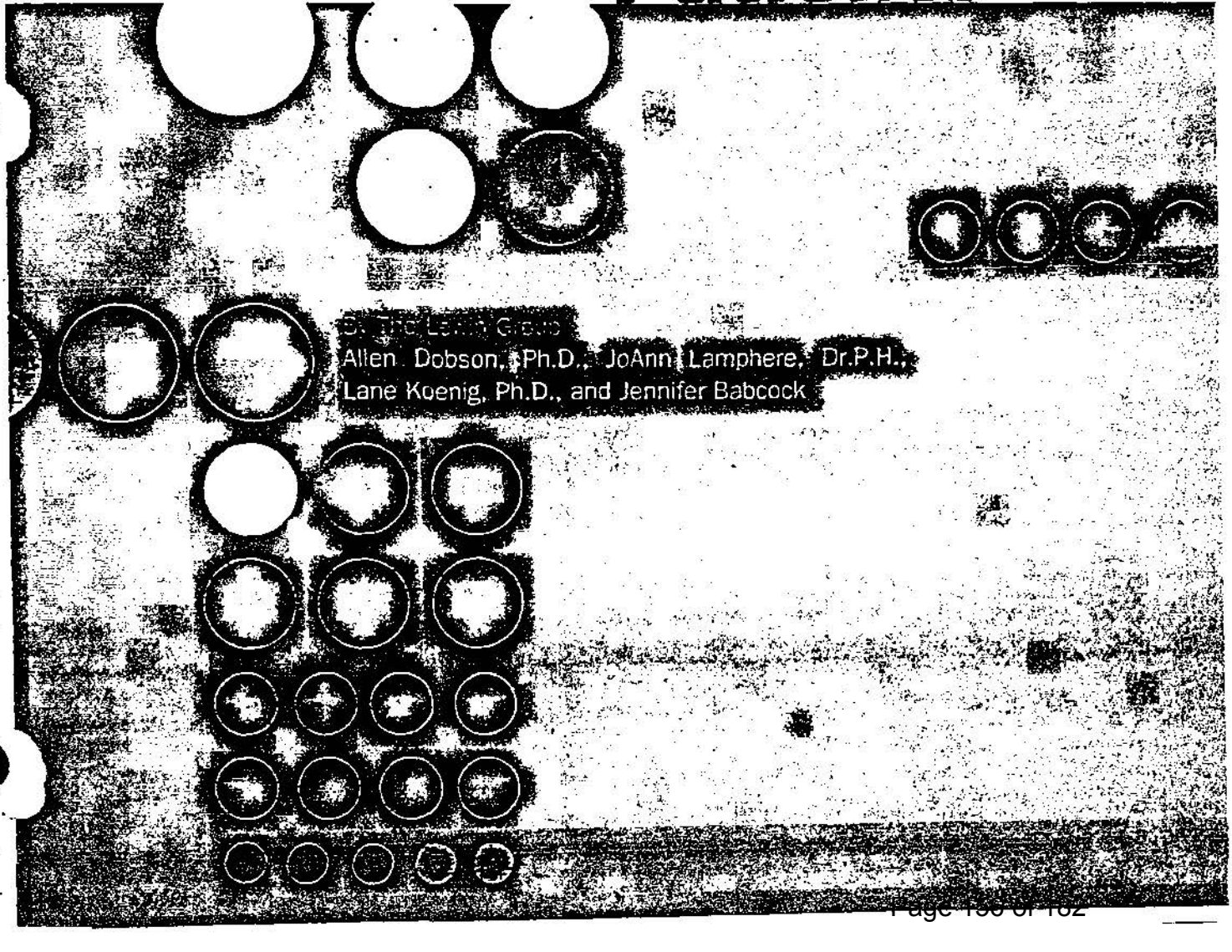
Dedicated financing. Since a public long-term care program would be financed by taxes devoted exclusively to the purpose of financing long-term care, the financial stability of the program would be increased.

Broad-based insurance. All taxpayers or workers would be required to pay taxes to finance the system. This universal insurance risk pool would mean that the costs of long-term care would be spread across a broad group of users.

Administrative efficiency. Compared with private insurance systems, public programs, such as Social Security and Medicare, are so large that they have low administrative costs relative to the amount of premiums paid.

—MS

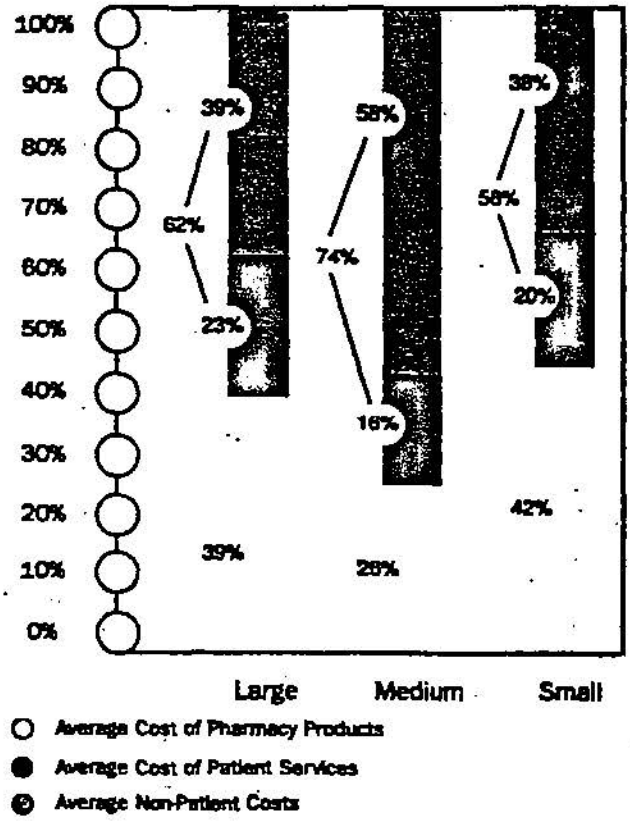
Impact of Proposed AWP Reductions on the Provision of Home Drug Therapies to Medicare and Medicaid Patients



Allen Dobson, Ph.D., JoAnn Lamphere, Dr.P.H.,
Lane Koenig, Ph.D., and Jennifer Babcock

Exhibit 1

Estimated Distribution of Average Total Cost of Providing Respiratory Therapy and Infusion Drugs in the Home to Medicare and Medicaid Patients, by Company Size



provide ongoing professional services integral to quality patient care under current payment arrangements.

The Department of Health and Human Services announced on May 31, 2000 that it is moving administratively to reduce Medicare payments for select drug therapies. For Medicare Part B claims, DHHS intends to pay the "average wholesale catalog price," compiled by the Department of Justice and recommended for state Medicaid programs. Although First Data Bank (FDB) recalculated wholesale drug prices for nearly 400 national drug codes, the method used by FDB has not been made publicly available. Resulting Medicare drug payment changes are scheduled to become effective October 1, 2000.

The Lewin Group has completed its analysis of data collected from mail and telephone surveys of providers. The following is a report of what was learned through this effort.

Analysis and Approach

STUDY OBJECTIVES

The Lewin Group conducted a study for the American Association for Homecare during July-August 2000 that estimated the cost structure of providing respiratory and infusion drug therapies in the home setting and the financial impact of adopting proposed reductions in Medicare Part B and Medicaid reimbursement for these drugs. As part of this study, The Lewin Group assessed the potential effect of these reimbursement changes on Medicare and Medicaid patients who receive drug therapies in the home.

SAMPLE

Data were obtained from 12 providers of home medical equipment and pharmaceutical services, specifically respiratory and infusion therapies, who completed a written survey instrument and a telephone interview. The sample is believed to be generally representative of home pharmaceutical companies nationally. Sampled companies range in size from less than $1 million to $1 billion annual net revenue and serve Medicare and Medicaid patients in all geographic regions throughout the United States.

The sample was stratified by size of companies' volume of business. Small firms were defined as those with less than $5 million total annual revenue; large firms were those with $30 million or more in total annual revenue; and mid-sized firms were in-between.

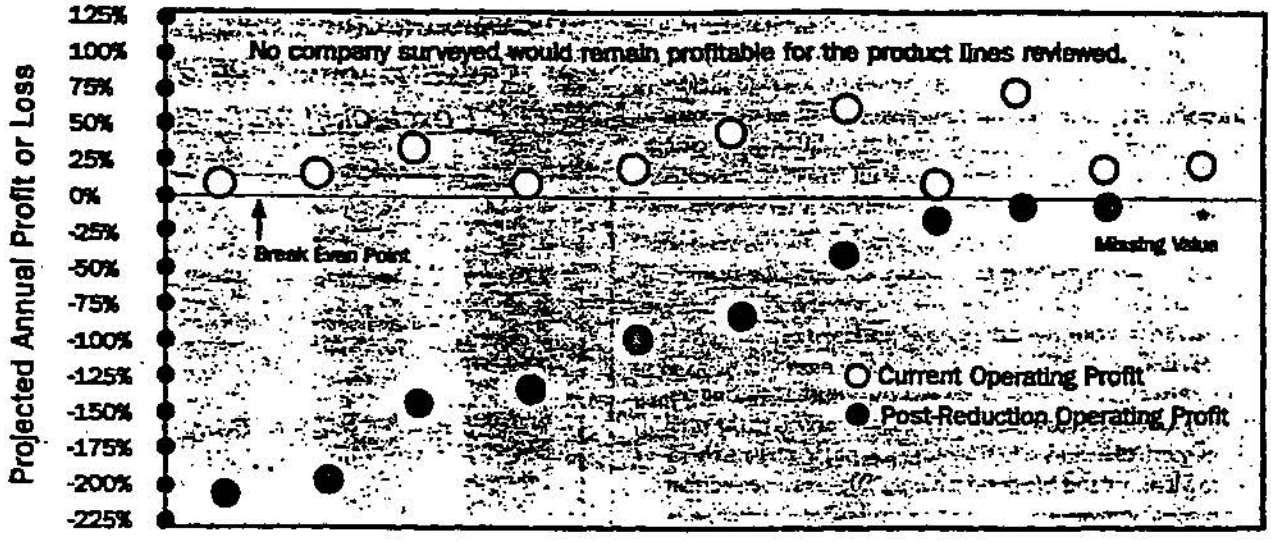
SURVEY DESIGN

The cost survey, designed in conjunction with industry financial experts, sought to calibrate the cost structure of the industry as it pertains to the provision of respiratory and infusion drug therapies in the home setting to Medicare and Medicaid patients. A chief financial officer (or designee) from each participating company completed the mail-in cost survey and participated in an extensive follow-up telephone interview.

The Lewin cost survey identified major categories of professional services that accompany the provision of drug therapies in the home (such as pharmacy, patient management, delivery, and others) and other corporate costs. Revenue and cost data were provided by surveyed companies and then proportionately allocated to the business unit providing respiratory and infusion services to patients whose care is covered by Medicare or Medicaid. Estimates of AWP reductions were derived for approximately 50 drug categories listed in First Data Bank's compilation of drugs that would be affected by new pricing data (as of June 2, 2000), as communicated in a Department of Justice letter to State Medicaid directors. In addition to financial data, the survey and follow-up telephone interviews posed open-ended questions concerning the provider's assessment of the business impact of proposed AWP reductions in the Medicare and Medicaid sectors for those drug therapies under review. Finally, participants provided their perceptions of the consequences in terms of

Exhibit 3

Estimated Initial Financial Impact of AWP Reductions for Respiratory and Infusion Drug Therapies to Medicare and Medicaid Patients at Home by Individual Company



- No company surveyed would remain profitable for the provision of home respiratory and infusion drug therapies to Medicare and Medicaid patients should the proposed AWP reductions be implemented. The estimated initial financial loss to companies as a result of proposed reductions ranges from 2 percent to 214 percent (Exhibit 3). If bad debt costs are excluded from financial loss estimates, only two companies expect to show any profit from Medicare and Medicaid services after AWP reductions (Exhibit 4). Note: in both Exhibits 3 and 4, sampled companies are arrayed in order of expected loss, not by size of company.
- The companies projecting the greatest percentage losses are those that are the largest and which have operations in many states. Two-thirds of the largest companies and three-quarters of mid-sized companies expect to experience a 50+ percent loss on studied services should proposed AWP reductions be adopted for the Medicare and Medicaid programs.
- Most of the companies with the greatest projected negative impact are those which serve a high proportion (>75 percent) of Medicare patients in their respiratory and/or infusion service areas.

IMPACT ON MEDICARE AND MEDICAID BENEFICIARIES

- Medicare and Medicaid beneficiaries' access to respiratory and infusion drug therapies is expected to diminish should AWP reductions be adopted. Firms indicate they will reduce exposure in certain public sector markets. Companies report that they will be forced to curtail accepting new Medicare and Medicaid patients. Several companies assert they will exit the Medicare and Medicaid markets altogether.
- Quality may be jeopardized as companies limit ongoing patient monitoring and reduce staff.
- Ironically, Medicare patient costs could increase should proposed AWP reductions be adopted. Said one pharmacist, "I could serve patients one whole year for what it will cost Medicare for a day when they end up in the emergency room" [because of reduced access to in-home services]. In addition, some companies report they may stop accepting assignment for Medicare patients, thus increasing costs to the patient.

It is important for public policymakers to grasp the financial realities of the health care industry that provides respiratory and infusion services to Medicare and Medicaid patients in the home. Companies in this study's sample serve Medicaid patients in 31 states. Due to revenue losses from Medicaid AWP reductions for respiratory and infusion drug therapies, companies report they have begun curtailing acceptance of new Medicaid referrals, not accepting

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ORIGINAL CONTRIBUTION

Adverse Events Associated With Prescription Drug Cost-Sharing Among Poor and Elderly Persons

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Context Rising costs of medications and inequities in access have sparked calls for drug policy reform in the United States and Canada. Control of drug expenditures by prescription cost-sharing for elderly persons and poor persons is a contentious issue because little is known about the health impact in these subgroups.

Objectives To determine (1) the impact of introducing prescription drug cost-sharing on use of essential and less essential drugs among elderly persons and welfare recipients and (2) rates of emergency department (ED) visits and serious adverse events associated with reductions in drug use before and after policy implementation.

Design and Setting Interrupted time-series analysis of data from 32 months before and 17 months after introduction of a prescription coinsurance and deductible cost-sharing policy in Quebec in 1996. Separate 10-month prepolicy control and postpolicy cohort studies were conducted to estimate the impact of the drug reform on adverse events.

Participants A random sample of 93 950 elderly persons and 55 333 adult welfare medication recipients.

Main Outcome Measures Mean daily number of essential and less essential drugs used per month, ED visits, and serious adverse events (hospitalization, nursing home admission, and mortality) before and after policy introduction.

Results After cost-sharing was introduced, use of essential drugs decreased by 9.12% (95% confidence interval [CI], 8.7%-9.6%) in elderly persons and by 14.42% (95% CI, 13.3%-15.6%) in welfare recipients; use of less essential drugs decreased by 15.14% (95% CI, 14.4%-15.9%) and 22.39% (95% CI, 20.9%-23.9%), respectively. The rate (per 10 000 person-months) of serious adverse events associated with reductions in use of essential drugs increased from 5.8 in the prepolicy control cohort to 12.6 in the postpolicy cohort in elderly persons (a net increase of 6.8 [95% CI, 5.6-8.0]) and from 14.7 to 27.6 in welfare recipients (a net increase of 12.9 [95% CI, 10.2-15.5]). Emergency department visit rates related to reductions in the use of essential drugs also increased by 14.2 (95% CI, 8.5-19.9) per 10 000 person-months in elderly persons (prepolicy control cohort, 32.9; postpolicy cohort, 47.1) and by 54.2 (95% CI, 33.5-74.8) among welfare recipients (prepolicy control cohort, 69.6; postpolicy cohort, 123.8). These increases were primarily due to an increase in the proportion of recipients who reduced their use of essential drugs. Reductions in the use of less essential drugs were not associated with an increase in risk of adverse events or ED visits.

Conclusions In our study, increased cost-sharing for prescription drugs in elderly persons and welfare recipients was followed by reductions in use of essential drugs and a higher rate of serious adverse events and ED visits associated with these reductions.

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RISING COSTS OF MEDICATIONS and inequities in access to medication have sparked calls for drug policy reform in the United States and Canada.[1,2] One of the most contentious issues is the introduction of cost-sharing to control drug expenditures. Cost-sharing is intended to deter the use of drug therapies that do little to improve health.[3-5] But cost-effectiveness rests on the assumption that individuals will have the capacity to pay for essential drugs and that they will make rational choices about which drugs to use and abandon. Otherwise, the use of essential drugs will be curtailed to control drug expenditures and short-term savings in the drug budget may be offset by downstream costs in the

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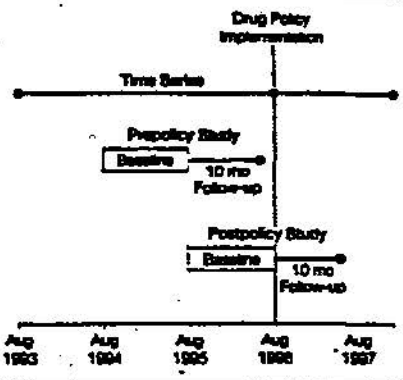
ies were conducted in comparable 10-month periods before (August 1995 to 1996) and after (August 1996-1997) policy implementation (FIGURE 1). The prepolicy control study provided an estimate of the expected rate of adverse events due to reductions in drug use prior to policy implementation. The estimation of an expected rate was important because even when drugs are free, individuals will experience adverse drug events due to injudicious reductions in needed therapy, because of forgetfulness, adverse effects, or misperceptions about the importance of drug treatment.[27] The difference in the rate in the prepolicy control study vs the postpolicy study was used to estimate the impact of the drug reform on adverse events. This approach had several advantages. First, it voided biases related to ecological fallacy[28] because changes in drug use were linked at the level of the individual with the occurrence of adverse events and ED visits. Second, it provided a means of isolating the effect of the drug policy from other health care policies that were implemented in the same 4-year period that may have reduced the rate of ED visits and hospitalizations, unrelated to prescription drug use (hospital closures and reallocation of service locations). Finally, the prepolicy and postpolicy cohort study approach verified the assumption that the primary impact of cost-sharing would be to increase the prevalence of reductions of drug use rather than changing the "biological risk" associated with rationing or stopping therapy. Thus, the studies were designed to estimate both the risk and the population attributable fraction or the share of adverse events and ED visits due to reductions in drug use, in the prepolicy and postpolicy periods.

For this analysis, study populations were limited to regular recipients of essential or less essential drugs, defined as persons who had a supply of the respective medication in each of the 12 months prior to the follow-up period or new users with a minimum of 6 months of continuous use.

Data Sources

Four provincial health databases, validated in previous research,[29-31] were linked by unique encrypted health numbers. The beneficiary demographic database provided data on drug plan eligibility, death, and beneficiary characteristics. The prescription claims database, which includes the drug, quantity, date, and duration for each prescription dispensed from community-based pharmacies, was used to measure medication use. The physician claims database, which includes the date, type, and location of service delivery (eg, inpatient, emergency, clinic), was used to measure ED visits and hospitalization-institutionalization. The hospitalization database was used to validate claims-based measures of hospitalization-institutionalization.

Figure 1. Time Series and Prepolicy Control and Postpolicy Cohort Design



The first 3 months of the time series and of an individual's enrollment in the public plan were excluded because prescriptions filled prior to these dates were unknown and created artificially low values for monthly drug use. The month immediately prior to policy implementation also was excluded because of possible prescription stockpiling.

Prescription Drug Use

The number of drugs available each day was calculated from prescription claims records using methods developed to convert the date, drug, and duration of prescriptions dispensed into a drug-by-day matrix.[32] In each of the 53 months of the time series, a matrix of monthly mean daily drug use was then constructed for each beneficiary (for all drugs and separately for essential and less essential drugs). The first 3 months of the time series and of coverage for newly eligible recipients were excluded to avoid artificially lower values for drug use in the first few months of available prescription information. The month immediately prior to policy implementation also was excluded because of possible prescription stockpiling, leaving 49 months for analysis.

For the prepolicy and postpolicy cohort studies, reductions in drug use were measured first by estimating an expected daily drug use for each person. The resulting expected values were then compared with observed use in the 10-month follow-up period. The expected use value was estimated as the level predicted for the last baseline month by a linear trend fit to each person's mean monthly daily drug use in the baseline year. This method conservatively assumed that expected drug use would remain constant rather than increase during follow-up. In addition, it was assumed that the impact of reductions in drug use would cumulate over time. Therefore, time-dependent measures were used to summarize differences between expected and observed use during the follow-up period. Time-dependent measures of drug use also provided a means of adjusting for unusual drug consumption patterns triggered by the features of the drug policy. For instance, the deductible and maximum ceilings instituted a pattern whereby reductions in one month may be compensated for by increases in the next when drugs were free for those persons reaching the spending ceiling. Cumulative mean monthly increases (observed > expected) and reductions (observed < expected) in drug use were calculated as the sum (from the first follow-up month) of the monthly difference in observed and expected drug use divided by the number of follow-up months. For example, an individual who had an expected value of 5 drugs per month and who filled prescriptions for 3 drugs in the first 2 months of follow-up and 8 in the third month would have a mean cumulative reduc-

showed a 9.12% (95% CI, 8.7%-9.6%) reduction in the number of essential drugs used per day (0.17 drugs; 95% CI, 0.16-0.18). Absolute and relative reductions were higher among welfare recipients (14.4%; 95% CI, 13.3%-15.6% and absolute reduction: 0.21; 95% CI, 0.19-0.23 essential drugs per day).

Relative reductions were greater in the use of less essential drugs by elderly persons and welfare recipients (15.14%; 95% CI, 14.4%-15.9% and 22.39%; 95% CI, 20.9%-23.9%, respectively) than for essential drugs (FIGURE 3). However, because fewer less essential drugs were used per day, the absolute size of the reduction was smaller for less essential drugs (elderly persons, 0.10 and welfare recipients, 0.15) than for essential drugs (elderly persons, 0.17 and welfare recipients, 0.21). Also, there was a significant decrease in the slope of less essential drug use over time in the postpolicy period (policy/time interaction) for the elderly persons ($\hat{\beta}$=−0.009; P<.001) and for the welfare recipients ($\hat{\beta}$=−0.008; P<.001).

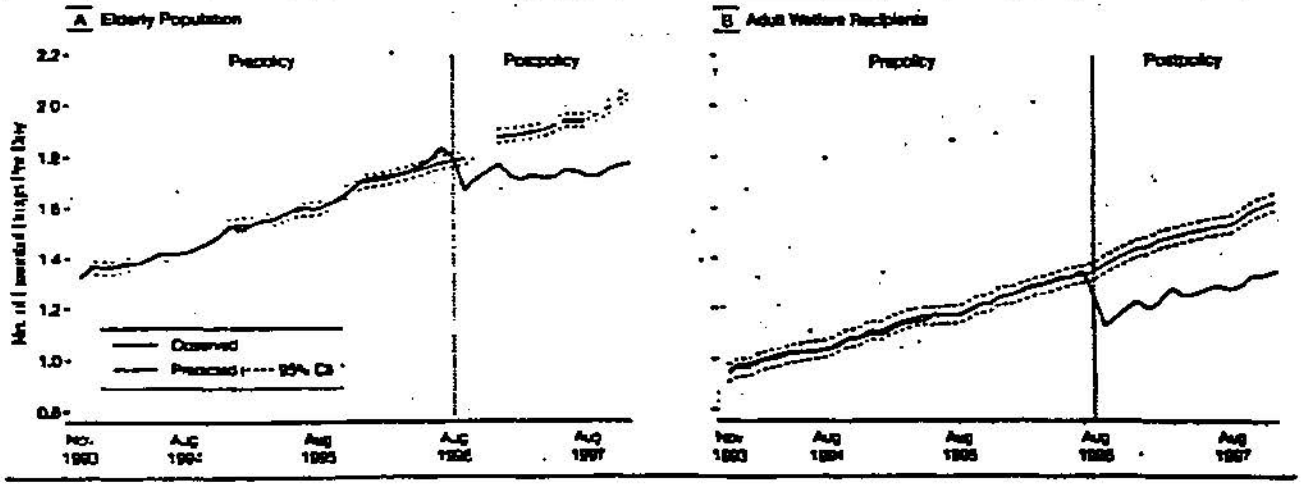
As expected, in both the prepolicy and postpolicy studies, there was a significantly higher rate of adverse events and ED visits in those individuals who reduced their use of essential drugs vs those who did not (TABLE 3). Dose-response relationships were evident between the magnitude of the reduction and the rates of both outcomes. For example, in the prepolicy control study, the rates of adverse events in those with no reduction (≤0.1 drugs/d), minor reduction (>0.1 to 0.5 drugs/d), and major reductions (≥1 drugs/d) were 256, 272, and 385 per 10000 person-months, respectively. Reduction of 1 medication would be equivalent to stopping 1 drug or rationing 2 drugs to half the expected use. Risks associated with reductions

Table 2. Characteristics of the Recipients of Essential and Less Essential Drugs in the Prepolicy Year (August 1995-July 1996)

	Elderly Persons		Adult Welfare Recipients	
	Essential Drugs	Less Essential Drugs	Essential Drugs	Less Essential Drugs
Total No. of medication recipients	93 950		55 333	
Medication recipients, No. (%)	70 801 (75.3)	38 065 (40.5)	25 820 (46.7)	14 888 (26.9)
Demographics				
Female, %	61.4	68.9	60.9	61.7
Age, mean (SD), y	73.1 (5.6)	73.4 (5.6)	43.4 (12.6)	44.7 (11.6)
Plan type for medication recipients by income-indexed ceiling, No. (%)*				
$200/y	4011 (5.7)	2387 (6.3)	25 820 (100)	14 888 (100)
$500/y	26 157 (36.9)	14 944 (39.3)	...	...
$750/y	40 633 (57.4)	20 734 (54.5)	...	...
Drugs used per day, mean (SD), No.				
Total†	3.1 (7.2)	3.4 (8.0)	2.4 (7.3)	2.6 (8.1)
Essential	1.7 (4.3)	1.5 (4.8)	1.2 (4.1)	1.0 (4.3)
Less essential	0.3 (1.6)	0.5 (1.6)	0.3 (1.8)	0.6 (1.8)
Monthly drug costs, mean (SD), $				
Total†	87 (272)	89 (292)	75 (332)	76 (339)
Essential	48 (154)	42 (163)	39 (184)	33 (173)
Less essential	3 (18)	7 (20)	4 (26)	8 (31)
Health service use, mean (SD)				
Emergency department visits/mo	0.1 (0.9)	0.1 (1.0)	0.2 (1.2)	0.2 (1.4)
Hospitalized per year, %	27.9	30.2	27.9	30.3

*Welfare recipients were subject to an annual maximum of $200.
†Also includes drugs other than those listed in Table 1 that were covered by provincial formulary.

Figure 2. Observed and Predicted Use of Essential Medication in the Prepolicy and Postpolicy Periods



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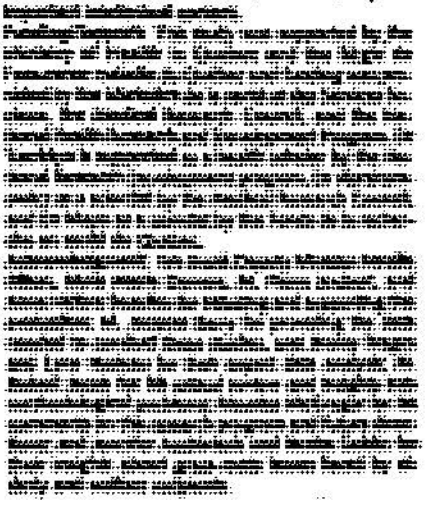
likely to be related to the cost-sharing policy. Prescription claims files do not indicate what drugs were taken, only medication purchased. Although prescription refill rates provide a reasonably accurate measure of medication compliance,[42-44] reductions in drug use could have been overestimated if individuals received free samples or purchased equivalent over-the-counter preparations (eg, aspirin) after policy implementation. However, these individuals would be falsely classified as having reduced medication use, and as a result, the risk associated with reductions in drug use in the postpolicy studies would be underestimated.

Indications for therapy were unknown. Drugs classified as less essential may have been required therapy for some individuals (eg, benzodiazepines for panic disorder), whereas some essential therapeutic drugs may have been prescribed without adequate clinical indication (eg, diuretics for transitory elevation in blood pressure). This misclassification would likely lead to an underestimation of both the potential benefits of reducing the use of less essential drugs and the risks of reducing essential drug therapy.[3,9]

Our study suggests that the primary mechanism by which cost-sharing affected the rate of adverse events was by increasing the proportion of people who made reductions in the use of essential drugs. We cannot confirm that reductions in essential drug use led to a deterioration in health status, but we believe that this is a plausible explanation for several reasons. First, there was a dose-response relationship between the magnitude of the reduction in the use of essential drugs and the risk of adverse events and ED visits. Second, reductions were associated with an increase in the risk of adverse events in the prepolicy and postpolicy period, a phenomenon that would be expected if reductions represented medication noncompliance. Finally, the risk associated with reduction was specific to essential drugs, for which there is clinical trial evidence of efficacy.

The challenge for insurers has been to craft health care policies that provide adequate access to drug therapy while simultaneously exercising fiscally responsible control over the drug budget. Consumer cost-sharing has been the principal method of fiscal control because it assumes that people will value what they pay for and as a result, they will reduce their use of unnecessary medication when they are required to contribute a portion of the payment.[4,8] While this reasoning may apply to many consumer goods, cost-sharing has been shown to have unintended effects in health care, such as increasing hospital admissions.[16,17,19,20,45-48] Consumers may not have the information needed to make wise decisions about necessary treatment. We estimate that for elderly persons alone, the drug policy reform in Quebec may result in 7000 additional adverse events per million annually. In light of the substantial impact that drug policy can have on the population's health, there is a need to redress the relative scarcity of scientific data on the outcomes of policy interventions. Our results suggest that more stringent cost-sharing pharmaceutical cost containment policies in other parts of Canada[48] and the United States[1,4] may contribute to avoidable illnesses.

Author Contributions: Dr Tamblyn participated in study concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript for important intellectual content, and provided statistical expertise, obtained funding, provided administrative, technical, or material support, and supervision.
Dr Laprise participated in study concept and design, acquisition of data, analysis and interpretation of data, critical revision of manuscript for important intellectual content, and provided statistical expertise, obtained funding, provided administrative, technical, or material support, and supervision.
Dr Hanley participated in study concept and design, analysis and interpretation of data, critical revision of manuscript for important intellectual content, provided statistical expertise, technical support, and supervised study conduct.
Dr Abrahamowitz participated in analysis and interpretation of data, drafting of manuscript, and critical revision of manuscript for important intellectual content, and provided statistical expertise.
Ms Scott participated in analysis and interpretation of data and critical revision of manuscript for important intellectual content, and provided statistical expertise.
Dr Mayo participated in study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript for important intellectual content, and provided statistical expertise and obtained funding.
Dr Hurley participated in acquisition of data and critical revision of manuscript for important intellectual content, and provided statistical expertise.
Drs Grad, Mallet, and McLeod participated in study concept and design, drafting of the manuscript, and study supervision.
Dr Latimer participated in analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and provided statistical expertise.
Dr Perreault participated in study concept and design, analysis and interpretation of data, and obtained funding.
Dr Huang participated in analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and administrative, technical, or material support.
Dr Larochelle participated in analysis and interpretation of data and critical revision of the manuscript for



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Definition of Drug-Induced Cognitive Impairment in the Elderly

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Introduction

Drug-induced cognitive impairment can generally be categorized into 2 types: delirium and dementia. Drug-induced delirium refers to the development of an acute confusional state, whereas drug-induced dementia implies a more chronic alteration in mental function.[1] Drug-induced cognitive impairment is the most common reversible cause of confusion.[2] It can be either dose related or, in some cases of delirium, it may be idiosyncratic. Cognitive impairment secondary to nonpsychoactive medications may be more likely to result from an idiosyncratic mechanism. Compared with drug-induced delirium, less is known about the prevalence of drug-induced dementia.[1]

Nearly every drug class can cause either drug-induced delirium or dementia in older persons. The elderly may be especially prone to developing drug-induced cognitive impairment due to age-related changes in drug pharmacokinetics (eg, reduced oxidative metabolism, reduced renal function) and phermacodynamics. The elderly may also be at greater risk of drug-induced confusion than younger people because of decreased functional reserve of the CNS and changes in brain perfusion. They may have alterations in neurotransmitter systems. Alzheimer's disease and vascular dementia are more common in this age group; dementia is a major predisposing risk fector for the development of drug-induced cognitive impairment. Polypharmacy, involving both prescription and over-the-counter medications, is also very common among the elderly and increases the risk of cognitive impairment. Electrolyte imbalances, which occur frequently in older persons, can predispose to cognitive changes.

Delirium

Diagnostic criteria for delirium in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), are divided into 5 categories based on the possible etiology of the syndrome, ie, whether it is thought to be attributable to: a general medical condition, substance intoxication, substance withdrawal, multiple etiologies, or not otherwise specified. For "Substance Intoxication Delirium," the criteria state that there is evidence from the history, physical examination, or leboretory findings of either disturbances in consciousness with reduced ability to focus, sustain, or shift attention OR that there is e change in cognition or the development of a perceptual disturbence that is not better accounted for by a preexisting, estebished, or evolving dementia AND that these symptoms develop during the substance intoxication AND that medication use is etiologically related to the disturbance. For "Substance Withdrawel Delirium," the symptomatology must present during or shortly after the removal of the drug. "Delirium due to Multiple Etiologies" considers the possibility that there may be more than 1 cause of the delirium, eg, drugs end the underlying medical condition. If the cause of delirium is not addressed by any of the above categories (eg, sensory deprivation), it is considered "Not Otherwise Specified."[3]

Criteria used to define drug-induced delirium in one study profocol included the following: the drug in question had central nervous system (CNS) effects; a toxic level was documented, or there was improvement with dose reduction or cessetion; and the time course of mental status change coincided with the period of drug use. This definition excluded the presence of alcohol and drug withdrawal.[4]

Other terms that have been used synonymously with delirium are transient cognitive impairment, acute brain failure, exogenous psychosis, toxic confusional state, toxic delirious reaction, toxic encephalopathy, toxic psychosis, senile delirium, acute brain syndrome, pseudosenility, clouded states, neurotoxicity, reversible dementia, intensive care unit psychosis, postsurgery psychiatric syndrome, metabolic encephalopathy, psychosis associated with organic brain syndrome, postoperative delirium, and postoperative encephalopathy.[5-9]

Delirium, which is also known as an acute confusional state, is a syndrome characterized by dieturbance in consciousness

(ie, reduced clarity of awareness of the environment), change in cognition including alteration in attention, disorganized thinking, disturbed psychomotor activity, and abnormal sleep-wake cycle.[1,6] According to DSM-IV, the essential feature of delirium is a disturbance of consciousness that is accompanied by a change in cognition that cannot be better accounted for by a preexisting or evolving dementia. This disturbance in consciousness results in altered awareness of the environment and the inability to focus, sustain, or shift attention appropriately. This change in consciousness is associated with cognitive abnormalities (which may include memory impairment, disorientation, or language disturbance such as inability to name objects or to write) or the development of perceptual disturbance (which may include misinterpretations, illusions, or hallucinations). Additional characteristic features of delirium are its development over a brief period of time and that it has a fluctuating course. Disturbances in orientation and thinking as well as bizarre psychomotor behavior are possible. These behaviors may manifest as stupor or as severe agitation with the patient trying to pull out intravenous catheters or trying to leave the facility.

Delirium is estimated to occur in 14% to 56% of hospitalized elderly patients.[10] About 15% of elderly have delirium upon admission to the hospital.[8] About 10% to 30% of hospitalized medical and surgical patients are experiencing delirium at any given time,[8,11] and 25% to 55% of elderly who are asymptomatic on admission develop confusion during their hospital course.[5] Once delirium develops, it is associated with a 10% to 75% mortality rate, although death may be related more to advanced age and severity of illness than to delirium per se. Unfortunately, 32% to 80% of delirious patients are not diagnosed properly. In the elderly, this may be an especially important problem since symptoms may falsely be attributed to dementia or senescence and because they may manifest as the hypoactive form of delirium, which is characterized by lethargy and decreased activity. Patients may also demonstrate a mixed form of delirium having elements of both the hyper- and hypoactive states. This mixed state may be the most common presentation of delirium.[10,12-14] Francis and associates[4] found that less than half of the delirious older patients in their study demonstrated disruptive behaviors, hallucinations, or delusions. Rather, somatic features such as incontinence were the problems most frequently associated with the onset of delirium.

Another problem that may occur in the elderly is the persistence of symptoms even once the underlying condition is addressed and the patient is discharged from the hospital. About one fifth of patients may have residual symptoms of the delirium present even 6 months postdischarge.[10] The risk for elderly patients of either dying or of being transferred to an institutional care setting may be especially high following the first 6 months after discharge from the hospital. Patients who succumb to these outcomes demonstrate more cognitive and functional impairment. Cognitive impairment may outlast the acute syndrome. Up to 55% of those who experience delirium may have permanent cognitive impairment, which may be a harbinger for the onset of dementia.[15] Delirium may serve as a marker of future cognitive and functional impairment.[13] The likelihood of developing delirium appears to be inversely related to a patient's physiological reserve capacity.

Delirium occurs in 25% to 40% of all patients with cancer and up to 85% of patients who are in the terminal phase of the disease. This alteration in mental status may be attributable to both the underlying condition as well as to the cancer treatment utilized. Yet, there is a paucity of data on the cognitive side effects of cancer treatments used among older adults.[5]

Surgical patients may be especially at risk for developing cognitive impairment. Postoperative delirium in the elderly occurs in 10% to 61% of those aged 65 or older. Orthopaedic patients are more likely to experience delirium than those undergoing general surgery. Delirium develops in 44% to 55% of hip surgery patients vs 10% to 14% of general surgery patients. Even patients undergoing cataract surgery are at risk. In the coronary and intensive care units, between 2% and 30% of patients experience delirium.[8,13,16]

Medications are the most common reversible cause of delirium. It is estimated that medications contribute to 22% to 39% of all cases of delirium.[10] A recent study involving older hospitalized adults found that the most likely primary cause of delirium in their study population was medication use.[17]

Dementia

According to DSM-IV, multiple cognitive deficits that occur with dementia only in the context of substance use are diagnosed as "Substance Intoxication" or "Substance Withdrawal." If the dementia results from the persisting effects of a substance (ie, a drug of abuse, a medication, or toxic exposure), "Substance-Induced Persisting Dementia" is diagnosed. Other causes of dementia (eg, "Dementia Due to a General Medical Condition") should always be considered, even in a person with substance dependence.[3]

The essential feature of dementia is the development of multiple cognitive deficits that include memory impairment and at least 1 of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning. The cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a

decline from a previously higher level of functioning.[3]

Dementia is a chronic, insidious, progressive, and often permanent form of cognitive impairment that includes impaired thinking, memory, and learning abilities and difficulties in daily functioning, problem solving, and emotional control (Table 1).[5] Dementia occurs at age 60 in about 1% of the population; however, this increases to greater than 30% by age 85.[18] Starr and Whalley[19] make the following distinction: "Drug-induced dementias reversed by withdrawal of the offending drug are probably best thought of within the spectrum of delirious states, while dementias that are drug-related and persist when the drug is withdrawn are, *de facto*, drug induced." However, as they point out, a satisfactory definition of drug-induced dementia is lacking.

Drug-induced dementia may be a cause of cognitive impairment in about 12% of patients with a suspected dementia. In the elderly, this is distinguished from age-related cognitive impairment, where the decline in mental function is considered a part of the normal aging process. The relative odds of a drug-induced dementia increase as the number of medications consumed rises. The relative odds range from 1.0 with the use of 0-1 drugs to 9.3 with the use of 4-5 medicines.[18,20] Medication side effects accounted for 5% of reversible dementias in patients aged 60 or older in one study.[21] The prevalence of drug-induced dementia in the general population is unknown.[1]

Drugs may impair cognition indirectly by metabolic effects, such as hypoglycemia, by alterations of immunologic factors within the CNS, and by actions that interfere with synaptic transmission. Classes of drugs most often associated with the development of drug-induced dementia include benzodiazepines, antihypertensives, and anticholinergic agents.[19]

DSM-IV also recognizes research criteria for "Mild Neurocognitive Disorder." This condition is defined by the presence of 2 or more of the following impairments in cognitive functioning, usually lasting for a period of at least 2 weeks: memory impairment as identified by a reduced ability to learn or recall information; disturbance in executive functioning (ie, planning, organizing, sequencing, abstracting); disturbance in attention or speed of information processing; impairment in perceptual-motor abilities; and impairment in language (ie, comprehension, word finding). However, this condition should not be considered if a patient meets the criteria for "Substance-Related Disorder," including medication-related side effects. "Substance-Related Disorders" include disorders related to the taking of drugs of abuse (including alcohol), the side effects of a medication, and a toxic exposure. Medications that cause substance-related disorders include, but are not limited to, anesthetics and analgesics, anticholinergic agents, anticonvulsants, antihistamines, antihypertensive and cardiovascular medications, antimicrobial medications, antiparkinsonian medications, chemotherapeutic agents, corticosteroids, gastrointestinal medications, muscle relaxants, nonsteroidal anti-inflammatory medications, other over-the-counter medications, antidepressant medications, and disulfiram. Within this classification is "Substance Intoxication." This diagnosis requires the development of a reversible substance-specific syndrome caused by the recent ingestion or exposure of a substance and requires that the clinically significant maladaptive behavioral or psychological changes associated with the intoxication (eg, belligerence, mood lability, cognitive impairment, impaired judgment, impaired social or occupational functioning) are attributable to the direct physiologic effects of the substance on the CNS. In "Substance-Induced Persisting Amnestic Disorder," memory disturbance must not occur exclusively during the course of a delirium or a dementia, and it must persist beyond the usual duration of substance intoxication or withdrawal.[3]

Delirium may be superimposed on dementia. Approximately 22% of ambulatory demented elderly have concomitant delirium.[22] For any patient with a diagnosis of dementia who suddenly develops a change in mental status, delirium should be ruled out. The manifestation of delirium in a patient with dementia may be atypical. Even in demented patients, cognitive function may temporarily improve if an offending agent is removed. Delirium and dementia may be 2 places along a spectrum ie, if delirium is not reversed, it may evolve into dementia. Further, depression may mimic either dementia or the early stages of delirium.

Risk Factors for Drug-Induced Cognitive Impairment

Major risk factors that have been identified as predisposing to delirium include a diagnosis of dementia or other neuropsychological disorders, advanced age, and sepsis. Other predisposing factors include hypoalbuminemia, hospitalization, postoperative status, myocardial infarction, congestive heart failure, acute blood loss, stroke involving subcortical regions, severe chronic illnesses, total knee arthroplasty, cardiac and noncardiac thoracic surgical procedures, aortic aneurysm surgery, functional impairment, high blood urea nitrogen/serum creatinine ratio (azotemia), proteinuria, lymphocytosis, HIV disease, sensory impairment, untreated pain, fluid and electrolyte imbalances, acid-base disturbances, infection, hypoxia/ hypercarbia, Parkinson's disease, depression, abnormal glucose levels, acute urinary retention, nutritional deficiencies (vitamin B_{12}, folate), collagen diseases, blood dyscrasias, constipation/diarrhea, hypo- or hyperthermia, unfamiliar environment/ isolation, sleep deprivation, malignancies, alcohol or substance abuse, psychosocial factors or acute stress, disorders caused by hypersensitivity, injury by physical agents, male gender, fracture present on admission, family history of mental illness, history of serious brain trauma, and, of course, medications (eg, anticholinergic agents, psychotropic drugs).[2,5,6,8,10,11,13,15,17,22,24,25] Often, multiple causes and risk factors for the development of cognitive impairment are

present.

It is not known what causes delirium; however, among the theories proposed are: a reduction of cerebral oxidative metabolism; CNS dopamine and endorphin hyperfunction; brain acetylcholine-dopamine-serotonin-glutamate imbalances; increased CNS cortisol activity; damaged neuronal enzyme systems; decreased synthesis and function of neurotransmitters, namely acetylcholine; increased central noradrenergic activity; dysfunction of beta-endorphinergic neurons; disturbances of the normal ionic passage through excitable membranes; gross changes in the electrolyte and water content, osmolality, and pH of the internal milieu; presence of false neurotransmitters; impaired synthesis of macromolecules needed for renewal of the structural and functional integrity of neurons; mismatch of metabolic supply and demand; involvement of cytokines; and neuronal loss.[5,7] These proposed mechanisms point to a number of ways in which drugs may be involved in inducing delirium by affecting the function, supply, or use of substrates of CNS neurotransmitters or neuropeptides. Cerebrospinal fluid (CSF) somatostatin-like immunoreactivity and CSF beta endorphin-like immunoreactivity were found to be lower in delirious vs nondelirious patients, and these changes persisted even 1 year after the initiating event.[8,24,25]

In the elderly, polypharmacy may predispose patients to developing drug-induced delirium. However, there is a lack of data on this subject, because reports citing multiple causative agents are often not published. In the late 1970s, Summers[26] tried to estimate the risk of developing drug-induced delirium based on the propensity of a drug either to have anticholinergic effects OR to be associated with the onset of altered mental status AND its daily effective dose. The relative risk of developing delirium when 3 or more medications are added during the hospital course may increase 3-fold.[27]

Drugs Associated With Cognitive Impairment

Taking a thorough drug history is one of the first steps that should be performed when assessing an older patient with changes in cognitive function. This history should include prescription drugs, over-the-counter medications, illicit substances, alcohol use, herbs, vitamins, nutraceuticals, homeopathic products, and naturopathic remedies, including the use of home remedies as well as other forms of complementary or alternative medicine. In the elderly, an increased number of medications may have a greater negative impact on orientation and memory as opposed to concentration and judgment.[28] The more complex a drug regimen, the more difficult it may be to identify the specific drug(s) that may be causing cognitive impairment. It is important to note that in the elderly, drug-induced cognitive impairment may occur even in the presence of nontoxic or therapeutic levels of a drug. Further, there may be intraclass differences in the propensity to induce cognitive impairment.

Numerous drugs have been identified in *The Medical Letter on Drugs and Therapeutics* as causing a multitude of psychiatric symptoms, including hallucinations, fearfulness, insomnia, paranoia, depression, delusions, bizarre behavior, agitation, anxiety, panic attacks, manic symptoms, hypomania, depersonalization, psychosis, schizophrenic relapse, aggressiveness, nightmares, vivid dreams, excitement, disinhibition, rage, hostility, mutism, hypersexuality, suicidality, crying, hyperactivity, euphoria, dysphoria, lethargy, seizures, Tourette-like syndrome, obsessiveness, fear of imminent death, illusions, emotional lability, sensory distortions, impulsivity, and irritability, which can impact on mental capacity. Further, there are a number of medications that may be linked to causing cognitive impairment by inducing delirium, confusion, disorientation, memory loss, amnesia, stupor, coma, or encephalopathy. Among these drugs are: acyclovir, anticholinergics and atropine, anticonvulsants, tricyclic antidepressants, asparaginase, baclofen, barbiturates, benzodiazepines, beta-blockers, buspirone, caffeine, chlorambucil, chloroquine, clonidine, clozapine, cytarabine, digitalis glycosides, disulfiram, dronabinol, ganciclovir, histamine-2 antagonists, ifosfamide, interleukin-2, ketamine, levodopa, maprotiline, mefloquine, methyldopa, methylphenidate, metrizamide, metronidazole, pergolide, phenylpropanolamine, pilocarpine, propafenone, quinidine, salicylates, selegiline, sulfonamides, trazodone, and trimethoprim-sulfamethoxazole. Often these medications produce more than 1 type of psychiatric symptom.[29]

A simple mnemonic to help remember the drugs or drug classes that are associated with acute changes in mental status in the elderly is ACUTE CHANGE IN MS (Table 2).[30]

Many of these drugs have already been recognized as being potentially inappropriate for use in the elderly. In 1991, Beers and colleagues[31] published explicit criteria for determining inappropriate medication use in nursing home residents. These criteria were derived by expert consensus using the Delphi method. The risk-benefit profile of specific agents within various drug classes, including sedative-hypnotics, antidepressants, antipsychotics, antihypertensives, nonsteroidal anti-inflammatory agents, oral hypoglycemics, analgesics, dementia treatments, platelet inhibitors, H_2-blockers, antibiotics, decongestants, iron, muscle relaxants, gastrointestinal antispasmodics, and antiemetics, were examined. Many of the drugs were cited because of potential CNS adverse effects.[31] This list was later updated in 1997 to include drug-disease combinations that may also be inappropriate for use by the elderly.[32] In 1999, the Health Care Financing Administration drafted new nursing facility survey procedures and interpretative guidelines based on these 2 articles. Under these new guidelines, which went into effect on July 1, 1999, drugs that were considered to have a high potential for severe CNS adverse outcomes were pentazocine, long-acting benzodiazepines, amitriptyline, doxepin, meprobamate, disopyramide, digoxin, methyldopa, chlorpropamide (if

hypoglycemia results), gastrointestinal antispasmodic drugs, and barbiturates (Table 3).

Other drugs that were considered to be potentially inappropriate, but were thought to produce less severe adverse outcomes, were identified. Among the medications that may produce adverse CNS effects are indomethacin, reserpine, diphenhydramine, muscle relaxants, sedating antihistamines, and trimethobenzamide (which can cause extrapyramidal effects). Lastly, drugs were identified that may exacerbate insomnia. This list of medications included decongestants, theophylline, desipramine, selective serotonin reuptake inhibitors (SSRIs), methylphenidate, monoamine oxidase inhibitors, and beta-agonists.[33]

Anesthetics

Both anesthetics and preoperative medications such as anticholinergic agents used to dry up secretions or sedative premedication (barbiturate or benzodiazepine) have been associated with the development of delirium postoperatively. Since it is thought that the residual effects of anesthetics on cognitive function may remain 48-72 hours after surgery, the choice of the anesthetic drug is important. Newer medications with shorter elimination half-lives may be preferred in the elderly.[16] The type of anesthesia (ie, general vs spinal) does not seem to affect the occurrence rate of postoperative delirium.[14]

Antibiotics/Anti-infectives

Although sepsis is one of the main risk factors for delirium, antibiotics and anti-infective agents may also produce changes in mental status. Among the agents that have been associated with delirium are aminoglycosides (eg, gentamicin, tobramycin, streptomycin), penicillins, cephalosporins, sulfonamides, and fluoroquinolones (eg, ciprofloxacin, ofloxacin).[10,34] Inhibition of GABA may be involved in fluoroquinolone- and penicillin-induced delirium. Penicillin can induce psychosis and encephalopathy. Risk factors for drug-induced delirium include renal impairment, increased permeability of the blood-brain barrier, high antibiotic dosage, intrathecal or intravenous administration of antibiotics, prior psychiatric illness, severe medical illness, slow acetylator status, and advanced age. Overall, however, this class of drugs has a low risk of inducing cognitive changes.[18] Other anti-infectives that have been associated with drug-induced cognitive impairment are erythromycin, clarithromycin, ketoconazole, amphotericin B, isoniazid, rifampin, quinacrine, chloroquine, quinine, trimethoprim/sulfamethoxazole, amantadine, acyclovir, and zidovudine.[2,30] Trimethoprim-sulfamethoxazole can cause acute psychosis and a catatonic depressive-like reaction.[30]

Anticholinergic Agents

This class includes drugs with known anticholinergic properties such as the first-generation, sedating antihistamines (eg, diphenhydramine, hydroxyzine, chlorpheniramine, meclizine), antispasmodics (eg, belladonna, diphenoxylate, clinidium, dicyclomine, hyoscyamine), oxybutynin, trazodone, ipratropium bromide, tricyclic antidepressants (which are discussed separately under antidepressants), phenothiazines (eg, thioridazine, prochlorperazine, promethazine, chlorpromazine, fluphenazine), muscle relaxants (cyclobenzaprine, orphenadrine), mydriatics (atropine, homatropine, tropicamide), diphenoxylate/atropine, antiparkinsonian agents (eg, benztropine, trihexyphenidyl), and antiarrhythmics (eg, disopyramide, quinidine, procainemide). Further, other drugs which may have possible anticholinergic effects include codeine, colchicine, warfarin, digoxin, furosemide, haloperidol, isosorbide dinitrete, meperidine, nifedipine, cimetidine, ranitidine, prednisolone, quinidine, and theophylline.[10,35-37] Many drug classes starting with the prefix "anti" have anticholinergic properties (eg, antihistamines, antidepressants, antipsychotics, antispasmodics, antiparkinsonian drugs, and some antihypertensives) and may help alert the practitioner to drugs that may be a source of confusion in their patients.[38]

Anticholinergic agents have been causally linked to the development of memory impairment in healthy subjects. Memory impairment may be associated with basal forebrain cholinergic pathways, whereas changes in consciousness seen in delirium may be attributable to alterations in pontine cholinergic pathways projecting into the frontal cortex and brain stem. Acetylcholine is also involved with attention, the sleep-wake cycle, and other aspects of cognitive functioning.[8,13]

In a study that was published in 1983, approximately 60% of nursing home residents and 23% of ambulatory patients were receiving drugs with anticholinergic properties. In some cases, patients may have received 3 or more anticholinergic medications concurrently.[39]

Tune and others[36] examined the anticholinergic effects of drugs commonly prescribed for the elderly as a potential means for assessing risk of delirium (Table 4). Using a standard concentration of 10^{-6} M of 25 compounds and an anticholinergic radioreceptor assay, they assessed these substances against an internal standard of atropine. Atropine equivalents represented in nanograms per milliliter of equivalent amounts of atropine were compared to the test drug. Of the 25 drugs tested, 14 produced detectable anticholinergic effects with 10 of these 14 medications, resulting in anticholinergic levels that have been associated with significant deficits in memory and attention in normal elderly.

Medications that were not associated with anticholinergic effects in this study included hydrochlorothiazide, propranolol, salicylic acid, nitroglycerin, insulin, methyldopa, ibuprofen, diltiazem, atenolol, metoprolol, and timolol.[36]

In an earlier paper, Tune and colleagues[40] had found that postoperative cardiac surgery patients who had experienced delirium had high serum levels of anticholinergic drugs and that impairment in cortical function was related to this elevated level. This group later examined the cumulative anticholinergic effects of drug regimens among surgical intensive care unit patients.[41] They have since expanded their work to examine the anticholinergic effects of 48 commonly prescribed medications.[42]

Flacker and colleagues[35] analyzed the association of serum anticholinergic activity with delirium in medical patients aged 75 or older. Delirium was associated with a higher serum anticholinergic activity quintile. The number of symptoms of delirium were also associated with higher serum anticholinergic activity. Mach and colleagues[43] demonstrated the resolution of delirium in an elderly population upon discontinuation of medications, which resulted in a reduction of serum anticholinergic levels. Only 5 of 17 medications discontinued were known to have in vitro anticholinergic activity. Even topically administered anticholinergic ophthalmic preparations have been associated with the development of delirium.[44,45] Other investigators have reported the presence of high serum anticholinergic levels among patients who have not received a drug that blocks acetylcholine, which raises the possibility of an endogenous source of anticholinergic activity that may possibly increase during times of stress.[35,46] Among elderly nursing home residents, serum anticholinergic activity seems to increase during illness and declines upon recovery, regardless of medication changes.[47]

In the presence of central anticholinergic toxicity, the use of physostigmine (a 1- to 2-mg test dose) may rapidly improve mental status. However, this drug has many severe side effects, including increased secretions, bronchospasm, vomiting, aspiration, and bradycardia, so its routine use cannot be advocated in the elderly.[10] The value of acetylcholinesterase inhibitors such as donepezil in this setting is unclear. Often, removing the causative agent and offering supportive care may be sufficient.

In summary, the likelihood of developing delirium following ingestion of an anticholinergic is unpredictable and may depend on other concomitant medications that exert anticholinergic effects, baseline cognitive status, pharmacokinetic or pharmacodynamic effects, specific agent used, and the total anticholinergic burden.[18]

It should also be stated that despite all of this evidence, the association between anticholinergic drugs and the development of delirium is not universally accepted. Francis and coworkers [4] and Schor and colleagues[48] failed to demonstrate causality between the use of these agents and the development of delirium in elderly medical inpatient populations. Yet others have felt that the lack of association between delirium and anticholinergic drugs in epidemiologic studies is one of misclassification of drug effects rather than the inability of the anticholinergic effects of drugs not to produce delirium.[14]

Anticonvulsants

All anticonvulsants can affect cognition, even in the presence of therapeutic drug levels. They may cause drug-induced delirium or dementia. These effects appear to be dose related. Further, repeated episodes of uncontrolled seizures can adversely affect cognition. Phenobarbital, primidone, and clonazepam have a greater negative impact on cognition than do valproic acid, carbamazepine, or phenytoin. The mental status changes of phenytoin, phenobarbital, and primidone may be attributable to interference with normal folate mechanism.[30] In the elderly, it is important to check both serum albumin and serum creatinine when dosing phenytoin, because both hypoalbuminemia and an elevated serum creatinine necessitate lowering the dose administered. Newer anticonvulsants may also have a lower risk of cognitive impairment.[1,18] The Neurotoxicity Scale has been developed to help assess the adverse effects of anticonvulsants on cognitive function. The revised version of the Neurotoxicity Scale consists of 24 questions. Among the domains tested are fatigue, slowing, memory, concentration, language, and motor coordination. Although this scale may be useful for identifying the presence or absence of an antiepileptic drug-induced side effect, it is unsuitable for determining the type or severity of this event because it produces a global or "all or none" evaluation of whether a person on an antiseizure medication is experiencing cognitive impairment. This scale is self administered by the patient. Further, it has been tested primarily in younger patients (average 34.1 years). Therefore, it may have limited utility in assessing the drug-induced cognitive impairment of an elderly person who is already confused or delirious or who may be on a complex medication regimen.[49] Use of monotherapy and maintenance of serum concentrations within the therapeutic range (for older agents with therapeutic drug monitoring available) may help to minimize cognitive changes.

Antidepressants

It is important to note that in the elderly, depression may present as pseudodementia. Therefore, cognitive impairment can be induced by the disease process itself. However, tricyclic antidepressants are notorious for producing adverse CNS side

effects such as delirium, disorientation, and memory impairment in the elderly owing to their highly anticholinergic properties. The most common and specific feature of tricyclic-induced cognitive impairment in the elderly is impaired short-term recall memory.[50] Other types of impairment include reduced reaction time, impaired retrieval from secondary memory, and impaired information processing.[1]

Confusion or agitation developed in approximately 5% of elderly depressed patients who received either amitriptyline or imipramine.[51] The former agent has been associated with impaired cognitive performance. Preskorn and Jerkovich[52] found that 6% of patients administered tricyclics experienced CNS toxicity. Tricyclic antidepressants can also induce a Creutzfeldt-Jakob-like dementia.[19]

The use of tricyclic antidepressants has fallen out of favor for use among patients in this age group because of their side-effect profile and the availability of newer, safer classes of antidepressants. However, if tricyclic antidepressants are to be used in the elderly, 2 agents have been preferred because of their more favorable risk-to-benefit ratio. These drugs are nortriptyline and desipramine. Kutcher and Shulman[53] describe the first case report of desipramine-induced delirium in an elderly woman with a subtherapeutic serum desipramine concentration. This 68-year-old woman had initially been started on 25 mg of desipramine. After 1 week her dose was increased to 50 mg. Within 3 days of the dosage increase, this woman started experiencing bouts of confusion, demonstrated inattentiveness and hypoalertness, and had disorganized speech. Her serum desipramine level, which was drawn 13 hours after her last dose, was 112 nmol/L (therapeutic range: 500-1000 nmol/L). The drug was discontinued and 3 days later, she was back at her baseline mental state.

In general, risk factors for drug-induced delirium are high tricyclic antidepressant plasma concentration, advanced age, and female gender.[18]

Trazodone, a nontricyclic antidepressant, is also associated with impaired cognition.[1] Confusion is one of the most common side effects of nefazodone, a compound structurally related to trazodone.[30]

Fortunately, newer medications that are devoid of anticholinergic properties, such as SSRIs and reversible inhibitors of monoamine oxidase (not yet available in the United States) may actually improve cognitive function as witnessed by improved vigilance, attention, memory, and psychomotor performance in some studies. This effect may be unrelated to their antidepressant properties.[50] Yet, when these drugs are combined with other medications, caution may be advised.[54] Whereas the reversible monoamine oxidase inhibitors may have less effects on cognition, older monoamine oxidase inhibitors such as tranylcypromine have been associated with adverse CNS effects.[2] Fluoxetine has been associated with the development of acute organic brain syndrome.[55] Caution is also advocated in the face of antidepressant-induced electrolyte imbalances (eg, SSRI-induced hyponatremia). In the case of SSRIs, one also needs to be concerned about the development of serotonin syndrome, which is characterized by delirium, autonomic instability, hyperreflexia, ankle clonus, tremor, diarrhea, and rigidity.[9,18] Serotonin syndrome may occur when SSRIs are combined with tramadol.[30]

Antiparkinsonian Agents

Approximately 20% to 30% of patients with Parkinson's disease have a concomitant dementia.[1] As with patients with other neuropsychiatric conditions, Parkinson's patients may be especially prone to the development of drug-induced cognitive impairment. One of the drugs that is most often associated with changes in mental status is levodopa. About 5% of patients develop delirium from the use of this drug,[56,57] although cognitive symptoms may occur in up to 60% of patients.[30] Yet, not all mental status changes are delirium; patients may experience isolated hallucinations while maintaining a clear state of consciousness, and this would not be considered delirium. Early clues to possible worsening cognitive function may include abnormal dreaming and sleep disturbances.[30] If these signs occur, lowering the dose of medication may be helpful. A relative excess of dopamine has been proposed as a possible cause of delirium.[13] Risk factors for drug-induced confusion include increasing age, dementia, and high doses of antiparkinsonian drugs.[1] As mentioned earlier, anticholinergic drugs used in Parkinson's disease can cause cognitive impairment. If dementia is present, Parkinson's patients on anticholinergic agents may be more than twice as likely to develop delirium compared with nondemented Parkinson's patients.[58] Amantadine's adverse cognitive effects may be dose dependent. The dose needs to be reduced in the elderly because of decreased renal function. High-potency dopamine agonists, such as pergolide, may be associated with higher rates of delirium than levodopa, with altered mental function occurring in 11% to 33% of patients. Bromocriptine can induce mental status changes even when used in low doses. Drug-induced delirium is also common with selegiline. Psychiatric side effects to these medications may become more common as the disease progresses. If these medications were to be ranked by their potential to cause cognitive changes, anticholinergic Parkinson's drugs would have the highest propensity, whereas bromocriptine, levodopa, and selegiline would be associated with medium degree of risk.[18] If a patient develops drug-induced cognitive impairment while on multiple antiparkinsonian agents, it may be beneficial to slowly withdraw the anticholinergics, selegiline, and amantadine before removing other agents from the regimen.[1]

Antipsychotics

As with other psychoactive medications, the risk of developing drug-induced cognitive impairment may be dose related. However, age may also be a significant risk factor for the development of this condition. Many traditional antipsychotics possess anticholinergic properties (eg, thioridazine, chlorpromazine, trifluoperazine), which may partly explain the predisposition of this class of drugs to the development of delirium and accelerated cognitive decline. One of the newer atypicals, clozapine, is also highly anticholinergic. Other atypicals that are devoid of significant anticholinergic effects, such as risperidone, appear less likely to cause drug-induced delirium. Such drugs as thioridazine and chlorpromazine may have a medium potential to induce cognitive changes, whereas risperidone has a low risk of such an event. The possibility of neuroleptic malignant syndrome should also be ruled out in patients in whom delirium develops shortly after the administration of an antipsychotic. Neuroleptic malignant syndrome is characterized by delirium, fever, autonomic dysfunction, extrapyramidal syndrome, and recent history of antipsychotic use.[9,18] One flaw in some of the studies on delirium and major tranquilizer use is that they fail to distinguish whether antipsychotics were the cause of delirium or were used to treat the delirium.

Cardiac Medications/Antihypertensives

This category includes the antiarrhythmics (eg, digoxin, amiodarone, lidocaine, disopyramide, procainamide, quinidine, flecainide, mexiletine, propafenone, tocainide), dipyridamole, and antihypertensives such as beta-blockers (eg, propranolol), methyldopa, clonidine, reserpine, calcium channel blockers, and angiotensin-converting enzyme inhibitors (ACEIs).[5,10,18] It is important to keep in mind that hypertension itself is a risk factor for vascular dementia and that aggressive lowering of blood pressure may also have a deleterious effect on cognition. Uncontrolled blood pressure and plasma lipids may lead to vascular dementia.

Among the antihypertensives that historically have been associated with significant adverse CNS effects (both delirium and dementia) is methyldopa. This drug produces cognitive impairment and decreased visual motor performance.[4] Methyldopa acts like a false neurotransmitter being converted to alpha-methyl-noradrenaline. In general, centrally acting antihypertensives such as clonidine and guanabenz are associated with more adverse cognitive effects. Reserpine irreversibly damages noradrenergic storage granules, thereby inducing altered mental function.[19] Dipyridamole has been associated with decreased Mini-Mental Status Examination scores.[59] CNS effect may be the first and only manifestation of digoxin toxicity and may be even more common than cardiac effects.[60] Both delirium and dementia can be signs of digoxin toxicity.

Cognitive changes can occur even in the presence of therapeutic digoxin levels.[61] Amiodarone's long half-life may promote prolonged confusion. Diuretics can cause fluid and/or acid-base imbalances, which can result in confusion, especially in the postoperative patient. CNS toxicity is common with lidocaine. Beta-blockers can be associated with pseudodementia. The incidence of neuropsychiatric toxicity ranges from 1% to over 20%.[30] Although controversial, less lipophilic beta-blockers may be preferred over highly hydrophilic agents as a way to reduce possible CNS adverse effects. Topical beta-blockers used for glaucoma have also been associated with the development of delirium.[2]

For drugs such as ACEIs, calcium channel blockers, and amiodarone, drug-induced delirium may represent an idiosyncratic event. The risk of cognitive impairment remains low for such drugs as diuretics and ACEIs. Other drugs, including quinidine, digoxin, methyldopa, alpha-blockers, postganglionic blockers, and beta-blockers, may have a medium risk of inducing such changes.[2,18]

Chemotherapeutic Agents

Drugs, either alone or when combined with other treatment modalities in cancer in the presence of a compromised host, can cause adverse CNS effects. For example, cognitive impairment induced by methotrexate is enhanced when this drug is administered to a patient undergoing cranial radiation. Among the chemotherapeutic agents that have been identified as causing delirium are carmustine, vincristine, vinblastine, L-asparaginase, ifosfamide, intrathecal procarbazine, high-dose cytosine arabinoside, methotrexate, 5-fluorouracil, hexamethylmelamine, etoposide, nitrogen mustard, lomustine, dacarbazine, and cytarabine.[2,5] Adjunctive agents such as antiemetics, cyclosporin, biologic response modifiers (interferon, interleukins) and corticosteroids are causally related to the production of mental status changes. Interleukins (eg, IL-2) may produce drug-induced dementia by increasing the blood-brain barrier's permeability to neurotoxins; by activating inappropriate central neuropeptidergic systems that impair attention, registration and memory; or by a direct neurotoxic effect. Cyclosporin's adverse CNS effects may be attributable to similar mechanisms, as it inhibits IL-1 and IL-2.[19] The actual propensity for each drug to cause cognitive impairment is unclear because these medications are often used in combination as part of treatment protocols.[2,5]

Corticosteroids

One of the proposed theories of what causes delirium is increased CNS cortisol levels. Exogenously administered corticosteroids may produce a similar effect. Corticosteroids can induce both delirium and chronic cognitive impairment as well as psychosis. Use of high-dose steroids (> 80 mg/day of prednisone), long duration of use, or the abrupt discontinuation of these hormonal agents can induce mental status changes. Even brief exposure to high doses of steroids can reversibly affect neuronal activity in the hippocampus, the area of the brain associated with memory; with continued use, permanent injury occurs. Overall, there is a medium risk of cognitive-induced impairment secondary to this class of drugs.[15] In addition to high dose, female gender and concomitant neuropsychiatric disease are predisposing risk factors for drug-induced mental status changes.[30]

Herbal Products

There is a misconception among consumers that because a product is natural or herbal it is without toxicity. A recent report has linked the use of St. John's Wort to the development of mania.[62] In another report, 2 patients developed encephalopathy and neuropathy following the ingestion of a Chinese herbal broth that contained podophyllin.[63] Melatonin use may be associated with the development of confusion.[64-66] Most recently, the FDA has warned of the potential neurotoxic effects of GHB or gamma-butyrolactone, a substance whose uses include sleep induction, release of growth hormone, enhancement of sexual activity and athletic performance, relief of depression, and prolongation of life.[67]

H2 Antagonists

All histamine-2 (H2) receptor antagonists have been associated with acute CNS toxicity, including delirium.[18,68] The drug that has received the most attention as being associated with medication-induced delirium is cimetidine. Cimetidine is thought to possess anticholinergic properties. Whether or not this explains it, its association with the development of delirium is unclear. However, cimetidine-induced delirium has been reversed with the use of physostigmine.[1,69] Cantu and Korek[70] found that there was no difference among the H2-blockers in their propensity to cause CNS changes. Among hospitalized patients, about 1% to 2% develop drug-induced cognitive changes compared with 15% to 80% of intensive care unit patients.[18] Advanced age and impaired renal function may be risk factors for the drug-induced CNS changes. Nonetheless, the overall risk of H2-antagonist-induced cognitive impairment is low.

Hypoglycemic Agents

Insulin and oral hypoglycemic agents may cause both reversible and irreversible brain damage secondary to hypoglycemia, which may result in cognitive loss.[71]

Lithium

Lithium may impair memory and psychomotor performance. It is also associated with the development of delirium. Lithium has a high risk of inducing cognitive impairment. It may induce a Creutzfeldt- Jakob-like dementia. Its ability to produce dementia may be related to its inhibition of protein kinase C, which results in interference of regulatory processes of neuronal growth and differentiation. Lithium's toxicity is potentiated by drugs such as thiazide diuretic and nonsteroidal anti-inflammatory agents, which interact with this drug to produce higher lithium levels.[1,2,18,72,73]

Narcotic Analgesics

It is important to recognize that untreated pain itself can cause delirium. However, narcotics can also induce this condition, especially among postoperative patients. Narcotics are among the primary causes of delirium in the postoperative patient. The risk of drug-induced delirium may be highest with meperidine. In one study, among individual narcotic agents studied, only meperidine was significantly associated with the development of delirium (odds ratio 2.7) among postoperative patients aged 50 or older.[46] Meperidine has long been recognized as a drug that should not be given to older persons because this age group undergoes an age-related decline in renal function, which allows for accumulation of normeperidine, a neurotoxic substance. The delirium induced by meperidine has been characterized by fluctuations in levels of awareness, confusion, disorientation, illusions, visual and auditory hallucinations, persecutory delusions, and seizures. Further, both meperidine and normeperidine have anticholinergic properties. This drug was originally developed as an antispasmodic alternative to atropine during the 1930s. Meperidine's toxicity may be more pronounced when this drug is combined with the enzyme inhibitor cimetidine or with other drugs possessing anticholinergic activity.[74] Francis and colleagues[4] and Schor and others[48] also found a correlation between the use of narcotics and the development of delirium. The route of administration (eg, intramuscular vs patient-controlled analgesia) may also influence the risk of developing drug-induced delirium. Epidural and

intramuscular administration may be more problematic than patient-controlled analgesia.[1] Even tramadol has been associated with drug-induced confusion.[30]

Nonsteroidal Anti-Inflammatory Agents (Including Salicylates)

Aspirin use may pose a problem in the elderly because older patients may not even consider this substance a medication. This age group is more prone to having pains and aches and is therefore more likely to use this drug. Delirium is the major manifestation of salicylate toxicity. Confusion can also occur at therapeutic doses. Acetaminophen, while safe in usual doses, may also cause cognitive impairment in an overdose situation. Drug-induced cognitive effects from nonsteroidal anti-inflammatory agents range from delirium with indomethacin (medium risk for cognitive changes) and sulindac to disturbances in memory and concentration with naproxen and ibuprofen (low risk for cognitive changes).[18] However, in light of recent data that nonsteroidal anti-inflammatory agents may be protective against the development of Alzheimer's disease, the role of these agents in inducing cognitive impairment needs to be clarified. It may be that high doses (not therapeutic doses) of nonsteroidal anti-inflammatory agents have an adverse effect on cognition.[1]

Over-the-Counter Products

The elderly consume a large amount of over-the-counter medications. These medications, which are often less expensive than prescription drugs, may be used by older adults in an attempt to save money and to help maintain their independence. However, these medications, especially cough/cold products, sleep aids, and antinausea agents, contain potent anticholinergic substances that can induce delirium in older persons. Oral decongestants such as phenylpropanolamine and pseudoephedrine can also cause delirium in the elderly. Mental status changes associated with the use of decongestants may occur with low doses and topical administration.[30]

Promotility Agents

Metoclopramide has been associated with the development of drug-induced delirium.[75] This drug crosses the blood-brain barrier and effects both dopaminergic and cholinergic systems. Cisapride, a newer promotility agent, may have fewer CNS effects; however, it is associated with very serious drug interactions, so caution is advised when using this agent.

Proton Pump Inhibitors

Omeprazole may be associated with neuropsychiatric adverse effects, especially in older patients and in patients with liver disease.[30,76]

Sedative-Hypnotics

This class of drugs includes benzodiazepines such as flurazepam and diazepam, barbiturates, meprobamate, chloral hydrate, and sedating antihistamines, which are found in over-the-counter sleep aids. Long-acting benzodiazepines, such as flurazepam, especially if used in high doses, are the most likely drugs to cause or exacerbate dementia. Shorter-acting drugs, such as diazepam or temazepam, have a medium risk of causing drug-induced cognitive impairment.[18] CNS toxicity is often dose dependent.

In one study, exposure to long-acting benzodiazepines was significantly associated with the development of delirium (odds ratio 3.0) among postoperative patients aged 50 or older.[45] Another study found that 11% of older patients admitted to a general hospital developed cognitive impairment following benzodiazepine use.[77] Benzodiazepines have been associated with impaired learning of verbal and visual information,[1] immediate and delayed memory, and psychomotor performance.[78] The psychomotor and cognitive impairment may be persistent with long-term use of benzodiazepines. Anterograde amnesia occurs more commonly with higher potency and shorter-acting benzodiazepines, thereby limiting the usefulness of these medications.[1]

Barbiturates can cause chronic cognitive impairment, which may mimic Alzheimer's disease. The sedation produced by sedative-hypnotics may lower the elderly person's threshold for developing drug-induced delirium or dementia.[18] Even newer agents such as zolpidem are associated with adverse cognitive effects similar to those seen with triazolam. Zolpidem produces memory impairment that corresponds to its peak blood concentration.[79]

Theophylline

Although theophylline may be associated with drug-induced cognitive impairment, it is unlikely to occur when this drug is used in usual doses.[1] Most adverse cognitive effects ("theophylline madness") occur in an overdose situation. If overdose occurs, one must be very watchful for seizures, which may soon develop if they are not present already.[30]

Urinary Antispasmodics

These drugs (eg, oxybutynin, flavoxate) induce delirium either via their anticholinergic effects or by causing urinary retention ("cystocerebral syndrome"). This latter condition is thought to be related to an increase in adrenergic tone, which leads to increased peripheral and CNS catecholamine levels. Risk factors for this condition include benign prostatic hypertrophy, dementia, and diabetes associated with autonomic dysfunction.[30]

Withdrawal Effects

Delirium associated with the withdrawal of centrally active psychotropics such as benzodiazepines, barbiturates, or alcohol may be attributable to understimulation of the inhibitory neurotransmitter GABA, which leads to symptoms of hyperactivity.[13] In the surgical patient, withdrawal from alcohol resulting in delirium may not manifest until 12-48 hours after surgery.[18] In the elderly, mortality associated with alcohol withdrawal-induced delirium tremens may be as high as 27%.[80] It is important to keep in mind that although the discontinuation of anticholinergic drugs is encouraged, rapid withdrawal of these agents may result in cholinergic rebound. This has been noted with clozapine, among other drugs.[81]

Strategies to Prevent Drug-Induced Cognitive Impairment in the Elderly

Perhaps the single most important step one can take to minimize the risk of drug-induced cognitive impairment is to administer the least possible number of medications to older patients, thereby avoiding the problem of polypharmacy. Proper dose adjustments based on age and renal or hepatic function are also necessary. Elderly patients should be encouraged to discuss all of their over-the-counter drug purchases with either their pharmacist or physician. Having a high index of suspicion that a drug may be likely to cause cognitive impairment is also one of the main ways to help prevent this problem in the elderly. It is important to be familiar with the known risk factors for cognitive impairment. Whenever possible, every attempt should be made to avoid high-risk medications such as sedative-hypnotics and drugs with anticholinergic effects, as well as other drugs that may readily cross the blood-brain barrier.

Pain needs to be adequately controlled. In patients experiencing mild pain symptoms, drugs such as acetaminophen or the cyclooxygenase-2 nonsteroidal anti-inflammatory agents may be tried instead of narcotics. If a patient has already been receiving a psychoactive medication for a long time and discontinuation is desired, a gradual dose reduction should be employed, because abrupt cessation may lead to withdrawal symptoms and delirium. Maintaining adequate nutritional and fluid status is also helpful. Caution is especially advised in patients with dementia whenever a new medication is prescribed. It may be helpful to obtain a baseline mental status examination in all elderly patients so that subtle changes can be identified early. Should a problem arise, ascertaining the likelihood that a drug may be associated with cognitive impairment may help determine which drug or drugs to eliminate first from the regimen.

Tables

Table 1. Differential Diagnosis of Delirium and Dementia

Feature	Delirium	Dementia
Onset	Abrupt, acute (sometimes subacute) with an identifiable date	Gradual, chronic, insidious
Course	Fluctuates during day with worsening of symptoms at night	Consistent pattern—no diurnal variation; may develop sundowning in later stages of disease
Duration	Hours to weeks/months in elderly (some permanent residual effects may remain)	Progressive, continuous
Interaction with environment	Reduced awareness Fluctuating alertness	In early stages, no problem with awareness

	Impaired attention Orientation impaired and fluctuating	In early stages, normal alertness Relatively unaffected, especially in early stages Often impaired
Memory	Immediate and recent impaired	Recent memory initially impaired; as it progresses, remote impaired
Thought process and language	Disorganized, distorted, fragmented, incoherent speech, global cognitive impairment	Perseveration and confabulation, difficulty with abstraction, thoughts impoverished, judgment impaired, agnosia, anomia
Perception	Distorted with illusions, delusions, and hallucinations (visual and auditory) and difficulty distinguishing reality from misperceptions and psychomotor disturbances (hypo- or hyperalertness or mixed state)	Early stage minimally affected; later stages may be associated with delusions and hallucinations
Sleep	Always disrupted with reversal of sleep-wake cycle	Fragmented sleep
Mental status testing	Distracted, often unable to participate in testing	Usually tries hard; often tries to hide deficiencies

Adapted from Weinrich and Sarna,[5] Lipowski,[6,11,23] Flacker and Marcantonio,[14] Espino et al,[22] Dessonville et al.[24]

Table 2. Acute Change in MS

Initial	Drug Class
A	Antiparkinsonian drugs
C	Corticosteroids
U	Urinary incontinence drugs
T	Theophylline
E	Emptying drugs
C	Cardiovascular drugs
H	H2-blockers
A	Antimicrobials
N	NSAIDs
G	Geropsychiatric drugs
E	ENT drugs
I	Insomnia drugs
N	Narcotics
M	Muscle relaxants
S	Seizure drugs

Adapted from Flaherty.[30]

Emptying drugs: a class of drugs that stimulate motility of the upper gastrointestinal tract (eg, metoclopramide)

Geropsychiatric drugs: includes any drug that works in the brain and that can cause confusion (eg, tricyclic antidepressants, SSRIs, benzodiazepines, antipsychotics, anticholinergics)

ENT drugs: ear, nose, and throat; agents taken for ailments of the respiratory and sinus passageways (eg, decongestants, antihistamines, expectoranta, antitussives)

Table 3. Drugs Identified in HCFA's Revised Nursing Home Guidelines That Have CNS Adverse Effects

Drugs	Adverse Effects
Pentazocine	Confusion, hallucinations, dizziness, lightheadedness, euphoria, and sedation
Long-acting benzodiazepines	Sedation, drowsiness, ataxia, fatigue, confusion, weakness, dizziness, vertigo, syncope, psychological changes
Amitriptyline	Anticholinergic and sedating properties, which can result in confusion, delirium, or hallucinations
Doxepin	Anticholinergic and sedating properties, which can result in confusion, delirium, or hallucinations
Meprobamate	Highly addictive and sedating, which can result in drowsiness and ataxia
Disopyramide	Strongly anticholinergic properties, which can result in confusion, delirium, and hallucinations
Digoxin	Toxic signs include headache, fatigue, malaise, drowsiness, and depression
Methyldopa	May exacerbate depression
Chlorpropamide	Hypoglycemia, which can result in altered mental state (confusion, amnesia, coma)
GI antispasmodics	Highly anticholinergic properties, which can result in confusion, delirium, or hallucinations
Barbiturates	Highly addictive and sedative, resulting in drowsiness, lethargy, depression, severe CNS depression
Indomethacin	Headache, dizziness, vertigo, somnolence, depression, fatigue
Reserpine	Depression, sedation
Diphenhydramine	Highly anticholinergic, which can result in confusion, delirium, or hallucinations
Muscle relaxants	Anticholinergic properties, which can result in sedation, weakness, confusion, delirium, or hallucinations
Antihistamines	Anticholinergic properties, which can result in confusion, delirium, or hallucinations
Trimethobenzamide	Extrapyramidal side effects

Adapted from Health Care Financing Administration.[33]

Table 4. Anticholinergic Drug Level

Medication	Anticholinergic Drug Level (ng/mL of atropine equivalents)

Captopril	0.02
Cimetidine	0.86
Codeine	0.11
Digoxin	0.25
Dipyridamole	0.11
Dyazide	0.08
Furosemide	0.22
Isosorbide dinitrate	0.15
Lanoxin	0.25
Nifedipine	0.22
Prednisolone	0.55
Ranitidine	0.22
Theophylline	0.44
Warfarin	0.12

Adapted from Tune et al.[36]

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Collaborative Practice Agreements by State

STATE	CDTM	Year	S,R,G*		STATE	CDTM	Year	S,R,G*
Alabama	No				Missouri	No		
Alaska	No				Montana	No		
Arizona	YES	2000	S		Nebraska	YES		S
Arkansas	YES		S		Nevada	YES		S
California	YES	1995	S		New Hampshire	No		
Colorado	No				New Jersey	No		
Connecticut	No				New Mexico	YES	1978	S
Delaware	No				New York	No		
DC	No				North Carolina	Yes	1999	S
Florida	YES		S		North Dakota	YES		S
Georgia	YES	2000	S		Ohio	YES	1999	S
Hawaii	YES		S		Oklahoma	No		
Idaho	YES	1998	R		Oregon	YES	1998	R
Illinois	No				Pennsylvania	No		
Indiana	YES		S		Rhode Island	No		
Iowa	YES	1996	G		South Carolina	YES	1998	S
Kansas	YES	1996	S		South Dakota	YES		S
Kentucky	YES	1982	S		Tennessee	No		
Louisiana	YES	1993	S		Texas	YES	1997	S
Maine	No				Utah	No		
Maryland	No				Vermont	YES		R
Massachusetts	No				Virginia	YES	1999	S
Michigan	YES	1994	S		Washington	YES	1991	S
Minnesota	YES	1999	S		WestVirginia	No		
Mississippi	YES		S		Wisconsin	No		
					Wyoming	YES		R

CDTM - Collaborative Drug Therapy Management (also known as Collaborative Practice)
S - Statute
R - Regulation
G - Guideline

November 2000 - ASHP

ASCP ANALYSIS OF MEDICAID PHARMACY AWP CHANGES 1/02

State	Ingredient Reimbursement	Dispensing Fee	2002 Changes	LTC Add-on
Alabama	WAC+9.2%	$5.40		No
Alaska	AWP-5%	$3.45 - $11.46		No
Arizona	Managed Care: AHCCCS Program		Discount Card Legislation	No
Arkansas	AWP-10.5%	$5.51	Proposal (AWP-14%-B; AWP-25% or FUL-G,	No
California	AWP-5%	$3.80		No
Colorado	AWP-11%	$4.08		No
Connecticut	AWP-13%	$4.10		No
Delaware	AWP-12%	$3.65		No
Florida	AWP-13.2%	$3.15 - $4.23		Yes - $.50
Georgia	AWP-10% (MFN)	$4.83	Pharm Study - Commissioner not supportive	No
Hawaii	AWP-10.5%	$4.67		No
Idaho	AWP-11%	$4.54	PA after 4 drugs	Yes - $1.00
Illinois	WAC+8%/12%	$4.17		No
Indiana	AWP-10%	$4.00	Rule-AWP-13%, disp. fee $3.00/Pharm Study	No
Iowa	AWP-10%	$4.13 - $6.42		No
Kansas	AWP-10%	$4.82		No
Kentucky	AWP-10%	$4.51	Bud. Proposal-AWP-12%,exempt from disp. fee decrease	Yes - $.02 for manu un
Louisiana	AWP-15%/16.5% (tiered)	$5.77		No
Maine	AWP-10% (MFN)	$3.35 (extra fees for compounding)		No
Maryland	WAC+10% or AWP-10% (lowest of to fit E	$4.21	Proposal AWP-13%	Yes - $1.40
Massachusetts	WAC+10% (MFN)	$3.00		No
Michigan	AWP-13.5% (5+ stores=AWP-15.1%)	$3.77	Appealing Drug Formulary Program	No
Minnesota	AWP-8%	$3.65	AWP-14%, Disp. Fee $4.15	Yes - $0.30
Mississippi	AWP-10%	$4.91	Lowest State, Bud. Proposal - $2.50	No
Missouri	WAC+10%	$4.09		Yes - $0.15
Montana	AWP-10%	$2.00 - $4.20	Minus 2.6% from Medicaid	No
Nebraska	AWP-8.71%	$2.84 - $5.05		No
Nevada	AWP-10%	$4.64		No
New Hampshire	AWP-12%	$2.50		No

MFN = Most Favored Nation
OP = Outpatient
LTC = Long-Term Care
B = Brand
G = Generic

Prepared by ASCP

ASCP ANALYSIS OF MEDICAID PHARMACY AWP CHANGES 1/02

State	Ingredient Reimbursement	Dispensing Fee	2002 Changes	LTC Add-on
New Jersey	AWP-10%(G); AWP-15%(B)	$3.73 - $4.07		Yes - Varies
New Mexico	AWP-12.5%	$4.00		No
New York	AWP-10%	B: $3.50, G: $4.50	Bud. Proposal-AWP-15%-defeated	No
North Carolina	AWP-10%	$5.60(G); $4.00(B)		No
North Dakota	AWP-10%	$4.60		No
Ohio	AWP-11.2%	$3.70		No
Oklahoma	AWP-10.5%	$4.15	PDL Legislation	No
Oregon	AWP-13%	$3.80 for unit dose/ $3.50 for all others	Budget Proposal AWP-15 to AWP-20%	Yes - refer to disp. Fee
Pennsylvania	AWP-10%	$4.00		No
Rhode Island	WAC+5%	OP: $3.40, LTC: $2.85		No
South Carolina	AWP-13%	$2.05	JR - reverse disp. fee reduction	No
South Dakota	AWP-10.5%	$4.75		Yes - $0.40 - $0.80 (dep
Tennessee	AWP-13% (MFN)	$2.50		No
Texas	AWP-15% or WAC+12%	$5.27+2% of ingredient		No
Utah	AWP-12%	$3.90(urban); $4.10 (rural)	Gov's Prop. (AWP-15%-B; AWP-20%-G) - def	No
Vermont	AWP-11.9%	$4.25		No
Virginia	AWP-9%	$4.25	Budget Proposal (AWP-11%)	Yes - .0157/tablet
Washington	AWP-11%	$3.98 - $4.92 (based on annual # of Rxs)	Budget Proposal (AWP-20%-B; AWP-65%-G	No
Washington, DC	AWP-10%	$3.75		No
West Virginia	AWP-12%	$3.90 (extra fee for compounding)		No
Wisconsin	AWP-11.25%	$4.88 (minus .50 on claims to $4.38)		Yes - $0.0015/dose (wh
Wyoming	AWP-11%	$5.00		No

MFN = Most Favored Nation
OP = Outpatient
LTC = Long-Term Care
B = Brand
G = Generic

Prepared by ASCP

A POCKET GUIDE TO

DEMENTIA AND ASSOCIATED BEHAVIORAL SYMPTOMS:

DIAGNOSIS, ASSESSMENT, AND MANAGEMENT.

FIRST EDITION

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A POCKET GUIDE TO DEMENTIA AND ASSOCIATED BEHAVIORAL SYMPTOMS:

DIAGNOSIS, ASSESSMENT, AND MANAGEMENT.

FIRST EDITION

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PURPOSE OF THIS GUIDE

The purpose of this guide is to provide an easy-to-use reference for health care professionals managing patients with dementia. This guide will provide an overview of the presentation and diagnosis of some of the different subtypes of dementia, patient assessment, and a rational approach to treatment based on the patient's associated medical conditions and behavioral manifestations.

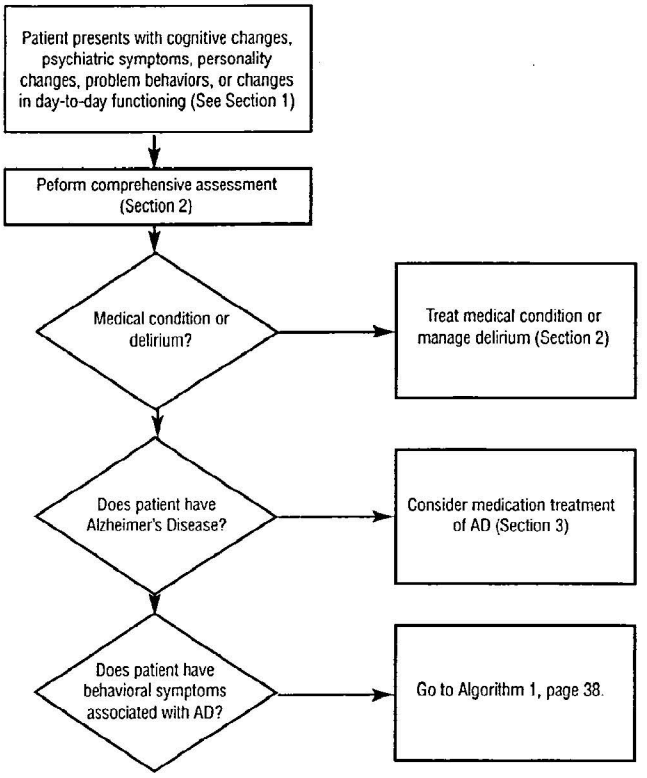
EDUCATIONAL OBJECTIVES

After reading this reference guide, you should be able to:

- Understand the basic pathophysiology of Alzheimer's disease and other dementias
- Recognize dementia and understand diagnosis and staging of Alzheimer's disease and other dementias
- Appreciate the role of non-medication interventions as first-line management for behavioral symptoms of Alzheimer's disease and other dementias
- Describe the current pharmacotherapy of Alzheimer's disease, other dementias, and behavioral symptoms associated with dementia
- Present a treatment plan for patients with newly diagnosed dementia or ongoing behavioral and cognitive symptoms of dementia

USE OF THIS GUIDE

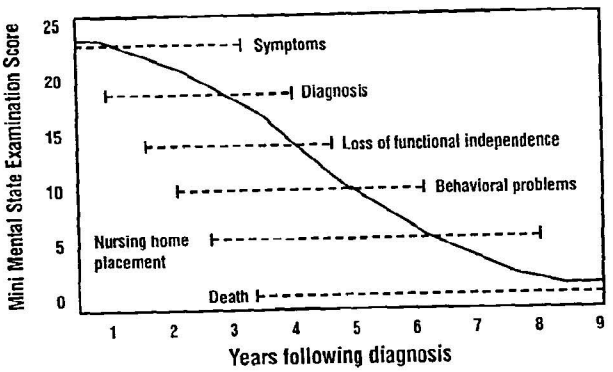
The algorithm shown below provides a roadmap to the contents of this guide.



BACKGROUND

Approximately 10% of the US population aged 65 and older suffers from dementia. Current eveidence suggests that dementia prevalence doubles every five years after age 60 (Ritchie K & Kildea D. Lancet 1995; Graves AB et al. Am J Epidemiol 1996). Defined as global cognitive deterioration sufficient to interfere significantly with social and occupational function, dementia is a growing public health threat that has adverse social, psychological, and economic consequences for affected persons and their families. (Feldman H, Gracon S, 1996.) Dementia is also a risk factor for increased home health care use, hospitalization, nursing home entry, and mortality.

Alzheimer's Disease Natural History
Typical Case



Feldman H, and Gracon S, 1996.

The prevalence of dementia in the U.S. is estimated to be between 2 and 4 million (5% and 10%) elderly (Evans DA et al., JAMA 1989; Canadian Study of Health and Aging Working Group, J Can Med Assoc 1994). The U.S. Census Bureau, in Census 2000, reported 281.4 million persons in the US, with 34.9 million 65 years of age and over. In the Framingham study, the dementia incidence rate for individuals 85 years or older was fourteen times higher than that in the 65 to 69 year age group (Bachman EL et al. Neurology 1993). It is important to note that an individuals' lifetime risk of dementia is actually lower than would be estimated from cumulative incidence rates because of the strong probability of death from other causes (Seshadri S et al. Neurology 1997).

A summary of dementia and AD prevalence and incidence studies is presented in Table 1.

The single largest subcategory of dementia is Alzheimer's disease (AD), with estimates ranging from 50% to 90% (Kukull WA et al., Neurology Clinics 2000). More recent studies support the lower number as other causes are more clinically recognized. Dementia with Lewy Bodies (DLB), and vascular dementia are other important subcategories. There is increasing evidence of the coexistence of dementia subtypes, particularly DLB, and our understanding of the prevalence of these conditions continues to improve with the evolution of diagnostic criteria and identification of new syndromes (Del Ser T et al. Alz Dis Assoc Disord 2001; Seshadri S et al. Neurology 1997)

Other important causes of dementia include alcoholism, Parkinson's disease, metabolic disorders (e.g., liver or kidney failure), endocrine disorders (e.g., hypothyroidism), nutritional disorders (e.g., vitamin B12 or folate deficiency), central nervous system infections (e.g., HIV, neurosyphilis), inflammatory disorders, frontotemporal disease (e.g., Pick's disease), and intracranial lesions. Severe depression and dilirium can also mimic dementia, and should be considered.

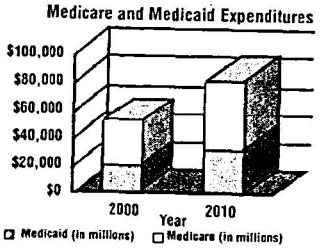
Table 1. Prevalence and Incidence Studies of Dementia in the United States.

Authors	Main Outcome Measure	Definition used for diagnosis
Evans et al, 1989	Overall prevalence of AD (>65): 10.3%	DSM-III-R, NINCDS-ADRDA
White et al, 1996	Overall prevalence of AD for study cohort: 7.6% (age-standardized)	DSM-III-R, NINCDS-ADRDA
Graves et al, 1996	Overall prevalence of AD: 6.3% (age-standardized)	DSM-III-R, NINCDS-ADRDA
Bachman et al, 1992	AD Prevalence: 2.3%	DSM-III-R, NINCDS-ADRDA
Bachman et al, 1993	Cumulative 5-year, age-specific incidence of AD: 4.3%	NINCDS-ADRDA
Kawas et al, 2000	Crude incidence rate (all dementia) 1.67% per year (≥ 55 years)	DSM-III-R, NINCDS-ADRDA

* See DSM, NINCDS-ADRDA in Appendix D. for description.

IMPACT OF DEMENTIA

Dementing illnesses have a significant impact on their victims, families, caregivers, and society. Most elderly with dementia progressively become functionally dependent on others for instrumental activities of daily living (IADLs) (e.g., driving, telephoning, shopping, cleaning, etc.) and activities of daily living (ADLs) (e.g., bathing, toileting, dressing, etc). Functional dependence is associated with diminished quality of life, increased costs, increased mortality, and significant caregiver stress. Additionally, increasing dependency on caregivers increases the risk of elder abuse or neglect (Jones JS et al. Am J Emer Med 1997; Lachs M et al. Gerontologist 1997).



Source: Alzheimer's Association, Medicare and Medicaid Costs for People with Alzheimer's Disease. April 3, 2001

The Alzheimer's Association reports that in the year 2000, Medicare and Medicaid spending for beneficiaries with AD was an estimated $31.9 billion and $18.2 billion, respectively, for a total cost of over $50 billion. (Alzheimer's Association Report, 2001). Figures for Medicaid spending are limited to nursing facilities only. By 2010, combined Medicare and Medicaid spending is expected to exceed $80 billion/year.

PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

There are different types of dementia, each distinct in how they affect the functioning of the brain. The descriptions below are for the most common subtypes of dementia.

Alzheimer's Disease (AD)

Alzheimer's disease is an irreversible, degenerative brain disorder that occurs gradually and results in cognitive deterioration. The hallmark of AD is the presence of two abnormal structures in the brain: amyloid plaques and neurofibrillary tangles. In AD, plaques develop first in areas of the brain used for memory and other cognitive functions. Neurofibrillary tangles, a consequence of abnormal tau protein metabolism, result in malfunctions in communication between nerve cells and may lead to neuronal death.

Attachment 10 to Agreed Statement of Facts
U.S. v. Abbott Laboratories

The most prominent identified risk factor for AD is age. The prevalence of dementia increases from 2-3% in the 65-74 year age group to 30% or more in those 85 years of age and older (Hendrie HC. Am J Geriatr Psychiatry 1998; Ritchie K et al. Lancet 1995; Desai A, Grossberg G. Clin Geriatr 1999). There is still controversy over what happens to prevalence of AD in those more than 90 years of age, but recent epidemiological studies suggest that prevalence continues to increase, even into very late life. Other factors associated with increased risk include family history, APO E4 genotype, Down's syndrome, female gender, and a history of psychiatric illness or depression. Other factors associated with increased risk of AD include low educational level, head injury, hypertension, diabetes, and environmental exposures. (Coffey CE & Cummings JL 2000; Desai A, Grossberg G. Clin Geriatr 1999; National Institutes of Health, 2000)

Vascular dementia (sometimes referred to as multi-infarct dementia)
Vascular dementia has been described as a nondegenerative cause of dementia and results from the effects of cerebrovascular disease. The risk factors for cerebrovascular disease leading to dementia are still not completely understood, but factors such as arterial hypertension, cardiac disease, diabetes, hyperlipidemia, and smoking increase the risk of stroke and vascular dementia (Coffey & Cummings, 2000). Factors that may increase the likelihood that dementia is due to stroke include the presence of aphasia, a major dominant stroke clinical syndrome, a history of prior cerebrovascular disease, and low educational level. (Pohjasvaara T, Stroke 1998). In many patients, it is often unclear of whether the sole cause of dementia is cerebrovascular lesions, or if the lesions significantly contribute to the clinical features of an underlying neurodegenerative disease ("mixed dementia").Dementia whose onset coincides with a stroke is often the best clue.

Lewy Body Disease (also called Dementia with Lewy Bodies or Lewy Body variant of AD (LBV))
Dementia with Lewy bodies (DLB) is a progressive, degenerative dementia. On autopsy, patients with DLB are found to have extensive neuritic plaque similar to that in patients with AD, though fewer neurofibrillary tangles. Extensive Lewy body formations are found throughout the cortical areas as well as in the substantia nigra. DLB patients have a choline acetyltransferase deficit, which is more marked in patients with prominent visual hallucinations (Coffey & Cummings, 2000.) Autopsy studies indicate that Lewy bodies are in 15% –25% of all cases of elderly demented patients (McKeith et al. Neurology 1996).

DLB should be considered when determining the diagnosis of dementia because it has important implications for appropriate treatment. Primary cognitive features include progressive, insidious cognitive decline with pronounced fluctuations in attention and arousal, well-formed and detailed visual hallucinations, and motor feature consistent with parkinsonism. Impairments in executive control and visuospatial and visuomotor skills are likely early prominent features, though memory deficits may not be apparent in the early stages. The use of neuroleptics in patients with DLB should be carefully considered, due to characteristic neuroleptic sensitivity.

It remains debated whether DLB is a distinct disease entity, a form of AD, or a form of Parkinson's disease (PD). PD dementia clinically distinguishes itself from DLB as the motor findings precede cognitive changes in PD dementia whereas in DLB the opposite finding is more likely. There is considerable disagreement about the relationship of DLB with PD and AD, since DLB can be related to both and can also exist as a separate entity. It is thought there is some relationship to ApoE genotype, but weaker than that for AD.

Frontotemporal dementia
Frontotemporal dementia (FTD), involves the prefrontal cortex and anterior temporal lobes, resulting in presentation with disturbed personality, behavior, and language. Though FTD has classically been associated with Pick's disease, FTD can exist without the presence of Pick's bodies. FTD often has an earlier age of onset than is typical for AD, and is often familial. Symptoms of FTD include impulsivity, impaired judgement, disinhibition, and apathy.

Risk factors are still generally unknown, however research is starting to indicate that ApoE genotype or the chromosome 17 are related to FTD. Autopsy studies have also reported that tau abnormalities may be an important cause of FTD.

Mixed Dementia

The term "mixed dementia" has been used to refer to the coexistence of AD and vascular dementia (Cohen et al, 1997). There is debate over the term and the use of more precise terminology based on established criteria for each distinct type of dementia is preferred.

Although AD is the leading cause of dementia, other causes of dementia and conditions coexisting with AD are becoming recognized more frequently (Morris JC. Neurologic Clinics, 2000). Disorders responsible for mixed dementia may also mimic AD even when acting indepently.

Table 2. Clinical presentation of different types of dementia.

Dementia type	Typical Presentation
Alzheimer's disease	Impaired recent memory, aphasia and impaired naming, apraxia, general intellectual decline, visuospatial processing deficits, poor memory recognition and retention
Vascular dementia	General intellectual decline over time, memory disturbance, executive dysfunction, apathy, and amotivation; associated features may include gait disturbance, visual field loss, paresis, and paralysis
Dementia with Lewy Bodies	Fluctuating cognition with pronounced variation in attention and alertness, recurrent detailed visual hallucinations, spontaneous motor features of parkinsonism; usually neuroleptic sensitivity
Parkinson's dementia	Memory relatively preserved early in illness, impaired speech marked by hypophonia and dysarthria, apathy, irritable and depressive features
Frontotemporal dementia	Changes in personality, executive function, and behavior; apathy, disinhibition, instrusiveness, explosiveness, irritability, and assaultiveness; relatively preserved memory

DIAGNOSIS OF DEMENTIA

Differential Diagnosis

The most important data sources for determining the differential diagnosis of dementia include family history, infectious exposure, degenerative processes, inflammatory processes, and trauma or injury. The charts that follow address these processes. Although many specialists no longer use cortical versus subcortical differentiation, it may be useful in distinguishing between the two, based on clinical impression, to help differentiate the diagnosis.

Table 3. Cortical Versus Subcortical Dementia

	CORTICAL (primarily AD)	SUBCORTICAL (primarily vascular dementia)
Key feature	Loss of core ability (capacity) to "do" cognition	Loss of ability to coordinate cognition
Mnemonic	The four A's	The four D's
Features	Amnesia Apraxia Agnosia Aphasia	Dysmnesia Dysexecutive Delay Depletion
Typical symptoms	Can't recall or recognize Repeats questions Can't do things Doesn't "know" things Trouble with language	Benefits from cues to remember Thinking/movement are slowed Trouble planning or executing Less flexible Less initiative

Adapted from: Rabins PV, et al Practical Dementia Care. Oxford University Press. New York. 1999. pg 9.

SECTION 1: WHEN TO SCREEN FOR DEMENTIA

Many times, patients or family members approach a trusted health care provider noting signs and symptoms. Some should trigger consideration of a dementia evaluation. These include:

Cognitive changes - new forgetfulness, more trouble understanding spoken and written communication, difficulty finding words, not knowing things the person should know, disorientation

Psychiatric symptoms - withdrawal, depression, anxiety, insomnia, fearfulness, paranoia, abnormal beliefs, hallucinations, delusions, irritability

Personality changes - inappropriate friendliness, apathy, affective lability or blunting, social withdrawal, excessive flirtatiousness, low tolerance leading to frustration, suspiciousness, disinhibition

Problem behaviors - wandering, noisiness, restlessness, being out of bed at night (sundowning), catastrophic reactions, explosive spells, recklessness, carelessness; verbally and physically aggressive, verbally and physically nonaggressive agitation

Changes in day-to-day functioning - difficulty driving, handling money, shopping; neglecting self-care, hygiene, household chores; getting lost; making mistakes at work or with bills; missing appointments

Adapted from Rabins et al. Practical dementia care and AHCPR guidelines, Early Alzheimer's identification.

SECTION 2: INITIAL CLINICAL ASSESSMENT

The assessment of patients suspected of having dementia involves a broad range of skills and should include physicians, nurses, psychologists, pharmacists, social workers, family members, and others included in care of the affected individual. These individuals should have the requisite training in diagnosis and treatment of patients with dementia. The health care team should identify who will be involved in the conduct of each of the assessments outlined below.

In addition to basic identifying data (age, gender, race, referral source) the following components should be included:

Component	Typical Questions
Chief complaint	Why referred? What answers are being sought?
Personal history	Place of birth? Formal level of education obtained? Occupational history and possible toxin exposure in job? Current hobbies and activities? Religious faith? Typical day for patient? Any changes in these in past 1-5 years? Advanced directives, durable power-of-attorney, arrangements for finances and health-in-place?
Current living environment	Place of residence? Living alone? Receive help with daily activities? Any financial or legal concerns? Use any community resources? Source of water in home (i.e., well or city)?

Component	Typical Questions
Medical history	What are current medical problems? Surgical history? Any historical medical problems (review of systems)? What are current medications (including current or leftover prescriptions, OTC, herbal, borrowed medications, other)? Are any other physicians or other health care providers involved in care? History of substance abuse? Family history of illness?
Personality	What are traits of behavior and other predispositions? What is general affect/mood? What is general level of activity? What are ways of coping with stress or loss?
Neuropsychiatric history	History of psychiatric symptoms, assessments, or treatment? History of seizures, head trauma, stroke or other neurological disease? Focal weakness, transient problems with speech, strength, brief confusion, gait, incontinence?
History of present illness	What is course of present illness (onset date, pattern, and features)?
Following the thorough history assessment, a systematic series of examinations should be conducted.	
Perform Examinations	Physical examination Neurological examination Cognitive examination Mental status examination Functional assessment
Laboratory evaluation	Biochemical tests (see page 17) Other evaluations as indicated

IS IT DELIRIUM OR DEMENTIA (OR BOTH)?

It is important to distinguish the cause of cognitive impairment. The essential clinical features of delirium are 1) relatively acute onset with fluctuating course, 2) disorganized thinking, 3) alteration in level of consciousness, and 4) inattention. Delirium can be determined by using the Confusion Assessment Method (CAM) Diagnostic Algorithm, shown on the following page. In many cases, delirium is reversible. Keep in mind that delirium and dementia often coexist, unfortunately making diagnosis more difficult.

Possible causes of delirium include: dehydration, electrolyte imbalance, hypercalcemia, hyperglycemia, hypoglycemia, thyroid disorder, liver or kidney failure, hypoxia, head trauma, vasculitis, infection, severe constipation, medications (including neuroleptics, tricyclic antidepressants, anticholinergics, lithium, steroids, etc), neurologic causes, depression, and drug or alcohol withdrawal.

Dementia is a common predisposing factor for delirium but other etiologies must not be ignored.

Confusion Assessment Method (CAM)
Diagnostic Algorithm for the Diagnosis of Delirium
The diagnosis of delirium by CAM requires features 1 and 2 with either 3 or 4.

Feature 1. Acute Onset and fluctuating Course
This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day; that is, tend to come and go, or increase and decrease in severity?

PLUS

Feature 2. Inattention
This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible or having difficulty keeping track of what was being said?

AND EITHER

Feature 3. Disorganized Thinking
This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

OR

Feature 4. Altered Level of Consciousness
This feature is shown by an answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness (alert [normal], vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])?

Source: Inouye SK et al. Ann Intern Med 1990;113:941-8.

Laboratory and Other Evaluations as Part of Initial Assessment
Conducting the following laboratory and other evaluations will help determine if the cause of the dementia (or delirium) is potentially reversible (fully or in part).

Laboratory/Other procedures Primary (all patients)	Rationale or to rule out:
Complete blood count	hematologic or infectious etiology
Serum electrolytes	metabolic or electrolyte abnormalities
Other serum chemistries	other metabolic, liver or renal function, or nutritional problems
B12 and folate	CNS symptoms; can occur without anemia
Thyroid function test	thyroid disease
Serologic test for syphilis	syphilis infection
Brain computed tomography (CT) scan or MR	CNS problems or to clarify nature of the diagnosis

Laboratory/Other procedures Secondary (selected patients)	Rationale or to rule out:
ECG	cardiac problems
Chest X-ray	cardiac/respiratory etiology
Erythrocyte sedimentation rate	inflammatory conditions
Toxicology screens	substance abuse or environmental exposure
HIV test	based on history/clinical picture
Lyme disease titer	based on history/clinical picture; region of country
Lumbar puncture	rapidly progressive dementia, delirium, infectious etiology (e.g., TB, syphilis, etc.)
EEG	seizure disorder; Creutzfeldt-Jacob disease (CJD)
Apolipoprotein E testing	based on history/clinical picture; to clarify nature of diagnosis
CSF 14-3-3 protein	CJD
Brain magnetic resonance imaging (MRI)	CNS changes (e.g., stroke, ischemia, granulomas, tumor)
Single photon emission computed tomography (SPECT) or positron emission tomography (PET)	CNS focal vascular deficits

MENTAL STATUS EXAMINATION

A general mental status examination should precede other mental status testing. Components of this examination should include:

Component	Description
Substance abuse	Is the patient using or abusing alcohol or other prescription or nonprescription drugs or substances?
Appearance	Is the patient wearing appropriate clothing? (e.g., clothing neat, unwrinkled, matching color, appropriate for weather). Is the patient neatly groomed or disheveled? Does the patient appear sleepy? Level of awareness?
Behavior	Does the patient appear relaxed/calm or stressed/anxious? Is the behavior erratic or inconsistent? Is the patient able to enter the examining area unaided? What is the general posture? Are there signs of involuntary movement? Agitation or psychomotor retardation?
Speech	Is the speech fluent? Does the patient have difficulty finding words or expressing thoughts in conversation? Does the patient appear to comprehend questions? Does the patient use any repetitive phases, sounds, or words in conversation?
Sensorium	Are any of the patient's senses impaired? What is their ability to pay attention or shift attention?
Orientation	Is the patient essentially oriented to person, place, time, and situation?
Thought content/ perceptual process	Is the patient seeing, hearing, feeling, or smelling things that seem odd or unreal? Hallucinations? Delusions? Does the patient have ideas that bother him/her or that he/she cannot get out of his/her head? Paranoia? Obsessions? Paucity of thought? Suicidal ideation? Does the patient seem disinhibited (e.g., making rude, caustic, or sexual remarks)?
Mood	What is the patient's mood? Is it appropriate for the situation? Is the mood labile changing from happiness to sadness? Does the patient cry or laugh inappropriately during the examination?
Judgment	Can the patient use logical thinking to solve problems?
Insight	Is the patient aware of personal strengths or weaknesses?
General intellect	Does the patient have average intellect? Well below average? Well above?

COGNITIVE MENTAL STATUS EXAMINATION

The Mini-Mental State Examination (MMSE) developed by Folstein is the most commonly used cognitive function test. It takes approximately 10 minutes to complete. Its scoring should be consistent, its limitations understood, and it should be completed by an experienced practitioner. Individuals with high premorbid intellectual capacity typically score better than others, despite impairment. Early in the course of dementing illness, it is not sensitive and it does not discriminate severity of illness in more advanced cases. It is nonetheless a useful tool for following the course of illness in individuals with dementia. There are some individuals who score high on the MMSE, even though there is significant impairment. This should not be the only test used to determine presence of cognitive impairment.

Median Mini-Mental State Examination Score by Age and Educational Level

Age	Education (years) 0-4	5-8	9-12	≥12
60-64	23	26	28	29
65-69	22	26	28	29
70-74	22	26	27	28
75-79	21	25	27	28
80-84	20	25	25	27
≥85	19	23	26	27
Overall mean for educational level*	22	26	28	29

** Includes all ages 18 - ≥85*
Scores represent mean MMSE score for that group.
Adapted from Crum RM et al. JAMA 1993;269:2386-91

For further information on the MMSE:

Folstein MF, Folstein, SE McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res 1975; 12: 196-8

Psychological Assessment Resources, Inc. (800) 331-8378 or www.parinc.com

Clock Drawing Test

Clock-drawing is used as a screening tool to test cognitive function in persons suspected of having cognitive impairment. Based on studies, clock drawing appears to be generally independent of education, ethnic, and socioeconomic status, since the clock face is generally familiar to most populations even though they may not be able to tell time.

Clock-drawing instructions

The patient is instructed to draw the numbers with a pre-drawn circle 3-3/8 inches in diameter to make that circle look like the face of a clock.

Scoring rules

1. Divide the circle into 4 equal quadrants by drawing one line through the center of the circle and the number 12 (or mark that best corresponds to the 12) and a second perpendicular to and bisecting the first.
2. Count the number of digits in each quadrant in the clockwise direction beginning with the digit corresponding to number 12. Each digit is counted only once. If a digit falls on one of the reference lines, it is included in the quadrant that is clockwise to the line. Any three digits in a quadrant is considered to be correct.
3. For any error in the number of digits in the first, second, or third quadrants assign a score of 1. For any error in the number of digits in the fourth quadrant assign a score of 4.
4. Normal range of score is 0-3. Abnormal (demented) score is 4-7.

Adapted from Watson YI et al. Clock completion: an objective screening test for dementia. J Am Geriatr Soc 1993;41:1235-40.

Functional Assessment

The Functional Activities Questionnaire is an informant-based measure of functional abilities. Informants provide performance ratings of the target person on 10 complex, higher-order activities.

Functional Activities Questionnaire (FAQ)

Individual Items of the FAQ

- Writing checks, paying bills, balancing checkbook
- Assembling tax records, business affairs, or papers
- Shopping alone for clothes, household necessities, or groceries
- Playing a game of skill, working on a hobby
- Heating water, making a cup of coffee, turning off stove
- Preparing a balanced meal
- Keeping track of current events
- Paying attention to, understanding, discussing TV, book, magazine
- Remembering appointments, family occasions, holidays, medications
- Traveling out of neighborhood, driving, arranging to take buses

The levels of performance assigned ranged from dependence to independence, and are rated as follows:

- Dependent = 3
- Requires assistance = 2
- Has difficulty but does by self = 1
- Normal = 0

Two other response options can also be scored:

- Never did [the activity], but could do now = 0
- Never did and would have difficulty now = 1

A total score for the FAQ is computed by simply summing the scores across the 10 items. Scores range from 0 to 30. A cutpoint of "9" (dependent in three or more activities) is recommended.

Adapted from: Pfeffer RI, Kurosaki TT, Harrah CH, et al. J Gerontology 1982.

Assessment of *Caregiver Burden*

Caregiver burden, which is the term used to describe the physical, emotional, and financial toll of providing care, must also be taken into account when considering the impact of dementing illness. High caregiver burden is associated with increased morbidity and mortality of caregivers and increased risk of long-term care placement of the dementia sufferer. (IPA, BPSD Educational Pack, 1998). Health problems suffered due to caregiving include depression, anxiety, low immune function, and perceived low health status. (Baumgarten M et al. Ann Intern Med 1994). Caregivers report 46 percent more physician visits, use 70 percent more prescription drugs, and are more likely to be hospitalized than others their age (Alzheimer's Association, 2001).

Caregiver burden should be assessed regardless of where the patient is residing. Both caregivers at home and in institutional settings are susceptible to the stress of caring for someone with dementia.

Factors (Patient Behaviors) Associated With Caregiver Burden

- screaming
- verbal and physical aggression
- personality clashes
- wandering
- depression
- resistance to help with ADLs
- suspiciousness, accusations
- not sleeping at night
- recklessness or careless behavior
- repetitive questions
- sexually inappropriate behavior

The above symptoms are reported to be the most burdensome and are also the most common reasons for psychiatric referral and premature institutionalization.

Predictors of Burden (patient characteristics)

Very important in predicting caregiver burden

- delusions, hallucinations, and depression
- disruptive behaviors (e.g., physical aggression)

Somewhat important in predicting caregiver burden

- male gender of patient
- younger age of patient

Doubtful or not important in predicting caregiver burden

- type of dementia
- severity of dementia (i.e., level of cognition)
- impairment (need for assistance)
- duration of dementia

Predictors of Burden (caregiver characteristics)

- care providers experience greater burden than care managers
- spouses > relatives
- women > men
- propinquity (caregiver in closest contact; cohabiting caregivers are under most stress)
- immature coping mechanism (e.g., easily angered or frustrated)
- low support from family and friends
- low knowledge about dementia, its effects, and management
- poor premorbid relationship with dementia person (e.g., high levels of negative expressed emotions, notably hostility and criticism)

Protective factors

- social support (e.g., caring neighbors)
- knowledge about dementia, its effects, and management
- mature coping skills (e.g., problem solving)
- support groups (e.g., Alzheimer's Association)

Source: International Psychogeriatric Association. Behavioral and Psychological Symptoms of Dementia Educational Pack, Module 4. 1998.

To assess family caregiver burden, the Zarit Burden Interview is recommended (see Appendix B). Caregiver interventions can be targeted at three broad areas: psychological support, educational activity, and development of a social support system.

Professional caregivers are also affected by behavioral symptoms, and should be evaluated in institutional and other care settings. Many of the same problems facing family caregivers affect professional caregivers. High dependence of a person with dementia, communication difficulties, lack of feedback from persons with dementia, and abuse can affect staff stress levels and cause low job satisfaction, guilt, low creativity, burnout, and poorer quality of care. Ongoing education and support of staff is an important component in preventing or reducing stress associated with providing care to these patients.

SECTION 3: TREATMENT OF ALZHEIMER'S DISEASE

Currently, there is no cure for AD or any other type of progressive dementia. However, there are a few pharmacotherapy options for treatment of the symptoms of AD. AD is a neurodegenerative disease with characteristic complex histological changes, including neurofibrillary tangles, neuritic plaques, and multiple neurochemical deficits that affect the serotonergic, noradrenergic, and cholinergic systems. Acetylcholinesterase inhibitors (AChE-Is) exert their beneficial effect on intellectual functioning by blocking acetylcholinesterase and enhancing cholinergic function.

Pharmacotherapy Options for Alzheimer's Disease

Before starting pharmacotherapy for AD, the diagnosis of AD stage must be determined. AChE-Is are approved for mild to moderate AD.

Tacrine HCl (Cognex®), the first FDA-approved AChE-I, is not recommended as it is no longer considered a first-line option based on the favorable toxicity profile and easier dosing protocols of the newer agents. For AD patients currently maintained on tacrine with a favorable response, the primary health care provider or family may choose to continue therapy.

The first step to consider when evaluating a patient for AChE-I therapy is the stage of dementia.

STAGES OF ALZHEIMER'S DISEASE

Developed by physicians at the New York University Medical Center's Aging and Dementia Research Center, the Functional Assessment Staging (FAST) Scale provides a method of staging AD for initial and ongoing assessment of change.

Functional Assessment Staging Scale (FAST)

Stage	Characteristics	Clinical Diagnosis
1	No functional decrement	Normal Adult
2	Personal awareness of some functional decline. (e.g., subjective deficit in recalling names or location of objects)	Normal-older adult
3	Noticeable deficits in demanding occupational and social settings (e.g., may get lost traveling by auto)	Early AD
4	Requires assistance in complicated daily life tasks such as handling finances, grocery shopping, and planning meals	Mild AD
5	Requires assistance in choosing proper attire, and for independent community functioning (e.g., the individual will wear incongruous clothing); some patients may forget to bathe regularly (unless reminded) and driving is severely compromised	Moderate AD
6	Requires physical assistance in dressing, bathing, and toileting. Urinary and fecal incontinence in the absence of infection or other etiologies	Moderately severe AD
7	Speech limited to about six words in the course of an average day. Progressive loss of abilities to walk, sit up, smile, and hold head up	Severe AD

Adapted from Reisberg B. Geriatrics 1986;41:31-46.

FDA-Approved Medications For Treatment Of Mild To Moderate Dementia of the Alzheimer's Type

Drug (Trade name, Manufacturer)	Starting dose	Titration	Target dose
Donepezil (Aricept®, Eisai/Pfizer)	5 mg daily, with or without food at bedtime	4-6 weeks, with possible Increase to 10 mg	10 mg/day
Galantamine* (Reminyl®, Janssen)	4 mg bid, with meals	8 mg bid after at least 4 weeks, if dose tolerated	12 mg bid (8 mg bid in patients with moderate hepatic or renal impairment)
Rivastigmine** (Exelon®, Novartis)	1.5 mg bid, taken with food	3 mg bid after two weeks, if tolerated	6 mg bid (12 mg daily)

General cautions: Anticholinergic medications should not be given concurrently with AChE-Is.

* If therapy interrupted for several days or longer, the patient should be restarted at the lowest dose and dose escalated to the previous dose.

**If adverse effects cause intolerance during treatment, patient or caregiver should be instructed to discontinue treatment for several doses, than restart at the same or next lower dose level. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose and titrated as described previously.

Keep in mind that the disease continues to progress despite treatment and typical effect is modest. Ongoing assessment of cognition, behavior, and functioning should be part of the patient's ongoing care plan.

Side Effects Associated with Acetylcholinesterase Inhibitors

Agent	Significant side effects
Donepezil	Gastrointestinal effects (i.e., anorexia, nausea, diarrhea, vomiting), insomnia, dizziness, fatigue, muscle cramps, headache
Rivastigmine	Gastrointestinal toxicity (i.e., nausea, vomiting, diarrhea, abdominal pain, anorexia) Attempt slow titration to minimize
Galantamine	Gastrointestinal effects (i.e., nausea, vomiting, abdominal pain, dyspepsia, anorexia), psychiatric disorders (i.e., depression, insomnia), somnolence, urinary tract infection, dizziness, headache, fatigue, bradycardia

The AChE-Is are being examined for efficacy in other types of dementia, but are currently not approved for other uses.

Other compounds that have been used in an attempt to prevent or slow decline of AD and other dementias include:

- selegiline
- vitamin E (alpha-tocopherol)
- gingko biloba
- anti-inflammatory drugs
- estrogen

Currently there are no adequately controlled positive trials supporting the use of any of these agents. However, the American Academy of Neurology suggests that Vitamin E 1000 IU PO BID should be considered in an attempt to slow the progression of AD (Doody RS et. al. Neurol 2001; 56: 1154-66).

Drug Interactions Associated with Acetylcholinesterase Inhibitors

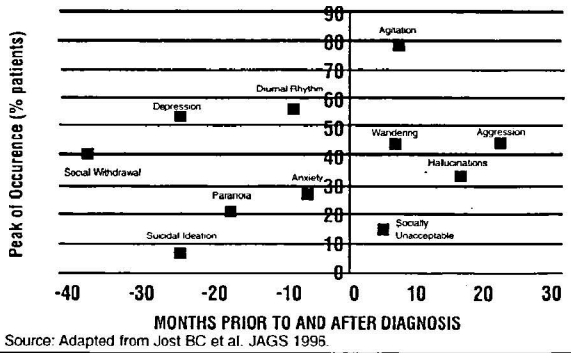
Medication	Interacts with	Effect
Donepezil	anticholinergic agents	donepezil may interfere with anticholinergic agent activity
	NSAIDs	Donepezil may increase gastric acid secretion. Monitor for symptoms of gastrointestinal bleeding (especially in patients with history of GI ulcers)
Rivastigmine	anticholinergic agents	rivastigmine may interfere with anticholinergic agent activity
	neuromuscular blocking agents	inhibits cholinesterase and may prolong or exaggerate muscle relaxation
	NSAIDs	Rivastigmine may increase gastric acid secretion. Monitor for symptoms of gastrointestinal bleeding (especially in patients with history of GI ulcers)
Galantamine	anticholinergic agents	galantamine may interfere with anticholinergic agent activity
	cimetidine, paroxetine	may increase galantamine bioavailability
	ketoconazole, erythromycin	may increase galantamine AUC

SECTION 4: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

Behavioral symptoms are commonly associated with the progression of dementia. Behavioral and psychological symptoms of dementia (BPSD) is a term that has been adopted by the International Psychogeriatric Association (IPA) for referring to the symptoms of disturbed perception, thought content, mood, or behavior that frequently occur in patients with dementia. In this book, the term "agitation" will be used to represent the BPSD for nonpharmacologic and pharmacologic management sections.

Agitation as defined by Cohen-Mansfield is any verbal, vocal, or motor activity which is not judged by an outside observer to result directly from the needs or confusion of the agitated individual. Agitation has been reported to be one of the most frequent and difficult to treat behaviors in residents with dementia. Agitation may be mild or severe. Mild agitation, which is non-aggressive, may be disruptive to others but poses little risk of danger to the resident or others. Severe agitation, however, may endanger the resident or caregivers.

Peak Frequency of Behavioral Symptoms with Alzheimer's Disease Progression



Source: Adapted from Jost BC et al. JAGS 1996.

For assessment purposes, it is very important to describe agitation on a resident-by-resident basis by descriptors of specific behaviors such as hitting, biting, hiding things, making strange noises, refusing to eat, using hostile language, etc.

Apathy, which is another common symptom in patients with dementia, is oftentimes as distressing to caregivers as agitation. (Kaufer DI et al. JAGS 1998) Apathy is a state of reduced motivation. Patients may be indifferent, with limited or absent emotional interests and engagement. This symptom should not be confused with dysphoria, or true sadness. Apathy can exist even the in the absence of depression. (Marin RS Psychiatric Annals 1997.)

TYPES OF AGITATED BEHAVIORS IN DEMENTIA

Agitation in the individual with dementia may mimic syndromes of other psychiatric conditions. When evaluating an agitated individual, the ability to identify which syndrome type the individual most closely resembles is critical to identify the most appropriate medication treatment.

Syndrome Type	Examples of Agitated Behaviors
Physically aggressive	Pushing, biting, hitting, scratching, grabbing, throwing objects, spitting, kicking
Physically nonaggressive	Wandering, pacing, elopement, intruding on others' rooms, constant searching, inappropriate disrobing, inappropriate voiding, repetitious mannerisms, handling things inappropriately
Verbally aggressive	Screaming, yelling, cursing, swearing, making strange noises, temper outbursts
Verbally nonaggressive	Constant requests for attention, complaining, whining, negativism, repetitive questioning, repetitively calling out, rambling disjointed sentences

Adapted from: Cohen-Mansfield J et al. J Am Geriatr Soc 1986.

The IPA groups BPSD in terms of behavioral symptoms, usually identified on the basis of observation of the patient (e.g., physical aggression, screaming, restlessness, wandering, etc) or psychological symptoms, usually and mainly assessed on the basis of interviews with patients and relatives (e.g., anxiety, depressive mood, hallucinations, and delusions). All of these symptoms can result in suffering, premature institutionalization, increased costs of care, significant loss of quality-of-life for patients and caregivers, and excess disability. (Steele et al, Am J Psychiatry 1990; Cohen-Mansfield J. Geriatr Psychiatry Neurol 1995; Finkel et al, Int Psychogeriatr 1996).

INFORMATION TO COLLECT ABOUT AGITATED BEHAVIOR

Information on the characteristics and the consequences of behaviors should be collected. This information will be critical to determining if the treatment is successful, after a strategy is chosen.

Behavioral Symptom Profile

Characteristics	Consequences
• Onset and predominant pattern • Frequency, timing, and length of agitated episodes • Factors that appear to precipitate the behavior including time of day, specific activity, specific symptom • Change in the person's routine, environment, diet, etc • Change in primary caregiver • Conflict with caregiver, family, or others • Feelings of restlessness, tension, loss, insecurity, anxiety, delusions, or hallucinations • Recent changes in cognitive status • Recent changes in medication • Previous management attempts and results • Recent changes in physical condition	• Specific interference with activities of daily living • Specific interference with caregiving • Falls and injuries • Aggravation to resident or other residents • Insomnia, disturbed sleep • Placement jeopardized

Traditional behavior monitoring forms are very useful in tracking the frequency and timing of the behavior. Proper characterization of the behavior will aid in assessing the response to interventions. See Appendix A. for a list of behavioral descriptors that may help in accurately characterizing behaviors.

A team of caregivers can be recruited to seek out the necessary information. This team may include:

- patient spouse and children
- other interested family members
- physician assistants
- nurse practitioners
- nurses, CNAs
- pharmacists
- physicians
- social workers
- physical therapists
- housekeeping staff
- others

Not only can a team approach provide valuable insight into the patient's behavior, but may also help address the feelings of helplessness and frustration that are oftentimes felt by caregivers and others in dealing with a dementia victim. Being part of a team can give members the feeling they are "doing something" to help improve the quality of life for the patient and the individuals that interact with the patient.

SECTION 5: NON-MEDICATION TREATMENT OF AGITATION

Treatment of underlying medical conditions should always be one of the first treatment strategies, when possible. For those conditions or circumstances when an agitated behavior has the potential for personal injury, impact on delivery of care, or psychosocial consequences, non-medication treatment can be effective.

Types and examples of non-medication treatment include:

Non-Medication Treatment Category and Strategies		
Sensory	*Environmental*	*Behavioral*
Music, aroma, or pet therapy, massage, light therapy, food or snacks, physical touch (with caution in some), eliminating physical discomfort	Increase in personal space, reduction in disruptive stimuli, increased or decreased lighting, availability of personal effects/ mementos	Reinforcement of alternative behaviors, positive reinforcement, validation therapy, redirection, psychotherapy (with mild dementia)

Communication	*Family support and education*
Awareness of caregiver's nonverbal, verbal, and written communication skills, keep communication simple, supportive, and positive, foreshadowing (e.g., tell patient bath time will be in 10 minutes, remind again in 5 minutes, remind again on the way to shower, etc.)	Offer caregiving classes or lectures, provide written materials, refer families and caregivers to local support groups

NON-MEDICATION MANAGEMENT STRATEGIES

The resident's underlying medical conditions should always be managed prior to or concurrently with nonmedication behavioral treatment strategies.

Management strategies may vary based on the type of behavior. Examples of behavior types, potential causes, and management strategies are presented on the following pages.

Behavior and Potential Causes or Antecedents	Possible Management Strategies
Wandering	
Stress: noise, clutter, crowding	Reduce excess stimulation, remove resident from stressful situation
Restless, bored	Provide personally meaningful activity, according to patient's abilities
Environmental stimuli	Remove or camouflage environmental stimuli
Exit signs, people leaving	ID or alarm bracelets
Resisting help with bathing, dressing, or grooming	
Task too difficult or over-whelming	Break task into small steps, don't give many choices
Caregiver impatience, rushed	Be patient, allow ample time or try again later
Can't understand or follow instructions	Simplify request; give instructions and allow performance one step at a time
Resident modesty causes embarrassment	Respect resident request for privacy
Fear of task, doesn't understand need for task	Reassure, comfort, distract with music or conversation
Agitation (e.g., catastrophic reactions)	
Fatigue	Schedule adequate rest, monitor activity schedule (too much, too little?)
Mirroring of caregiver affect	Control affect with resident, model calm with lower tone and slow rate
Too much noise, clutter, crowding	Reduce excessive stimulation, remove resident from stressful situation
Resident being thwarted from desired activity	Redirect energy to similar activity, ask person to "help" with personally meaningful activity
Unfamiliar people or environment, fear	Be consistent, avoid changes or surprises, make changes gradually; reassurance
Restlessness/ boredom	Calming music, massage, or personally meaningful activity, assign tasks that provide exercise

Behavior and Potential Causes or Antecedents	Possible Management Strategies
Incontinence	
Difficulty in finding a toilet	Place appropriate signs, picture on door, ensure adequate lighting
Lack of privacy	Provide privacy
Dependency created by socialized reinforcement	Provide increased attention for continence rather than incontinence; allow independence whenever possible, even if time-consuming
Can't express need or forgets	Schedule toileting
Inappropriate or impulsive sexual behavior	
Misinterpreting caregiver's interaction	Do not give mixed sexual message, even in jest, avoid nonverbal messages, distract while performing personal care or bathing; explain in simple words
Decreased judgment and lack of social awareness	Do not overreact or confront, respond calmly and firmly, distract and redirect
Uncomfortable – too warm, clothing too tight, need to void, genital irritation	Check temperature, assist with weather appropriate clothing, ensure elimination needs are met, examine for groin rash, perineal skin problems
Need for attention, affection, intimacy	Increase or meet basic need for touch and warmth, model appropriate touch, offer soothing objects (dolls, stuffed animals)
Self stimulating, reacting to what feels good	Offer privacy, remove from inappropriate place
Suspiciousness or paranoia	
Forgot where objects were placed	Offer to help find, have more than one of same object, learn favorite hiding places
Misinterpreting actions or words	Do not argue or try to reason with resident, distract and do not take personally
Misinterpreting who people are, suspicious of their actions	Introduce self and role routinely, draw on old memory, connections; do not argue or quiz
Misinterpreting environment	Assess vision, hearing; modify environment, provide simple explanation, distract

Adapted from Carlson DL, et al. Management of dementia-related behavioral distur-bances: A nonpharmacologic approach. Mayo Clinic Proceedings 1995;70:1108-15.

SECTION 6: MEDICATION TREATMENT OF AGITATION

Most patients with dementia will exhibit agitation at some point during their illness, and may present in many different ways. Research and practice experience has shown that a number of different presentation categories help with describing the agitation syndrome and directing the caregiver to the most appropriate medication treatment.

Agitation may be due to medical conditions as described earlier. This is always an initial assessment which must be performed prior to starting any medication. Before deciding whether to treat behavioral symptoms with medication, ask the following questions:

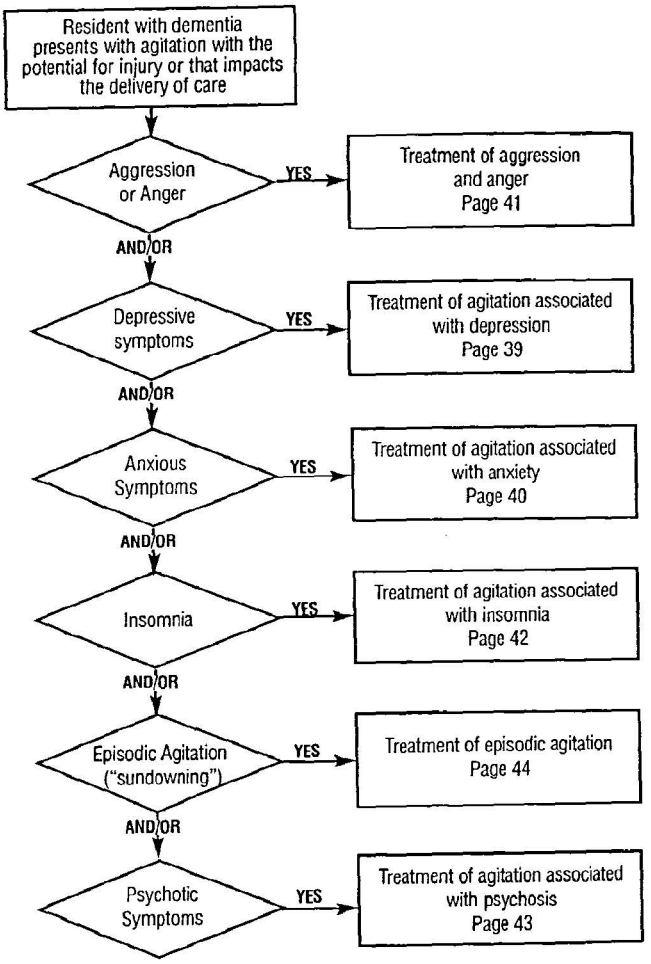
1) Does the particular symptom warrant drug treatment, and why?
2) Is this symptom drug responsive?
3) Which category of medications is most suitable for this symptom?
4) What are the predictable and potential side effects of a particular drug treatment?
5) For how long should the treatment be continued?
6) Does the severity and complexity of the behavior require a psychiatric consultation?

After these issues have been addressed, further delineation of the agitation syndrome is appropriate. Typical psychiatric diagnostic criteria are followed by a typical presentation of the agitation syndrome in the elderly resident with dementia.

In nursing facility residents, consider the HCFA Guidance to Surveyors - Long-Term-Care Facilities, Tags F329, F330, and F331 when prescribing antipsychotics, benzodiazepines, and sedative/hypnotics.

Medication recommendations made in the following sections are based on selected peer-reviewed literature, editorial advisors' opinions, and the report, "The Expert Consensus Guideline Series: Treatment of Agitation in Older Persons With Dementia" published by Postgraduate Medicine in 1998. This publication can be obtained free-of-charge from the website www.psychguides.com.

Algorithm 1. Identifying Agitation Syndromes for Appropriate Treatment



APPROPRIATE MEDICATION CHOICE

Depression and Agitation

Patients may present with tearfulness, feelings of hopelessness, helplessness, apathy, irritability, anorexia, and/or guilt and these symptoms may be with or without delusions.

Agitation associated with:	Medication	Starting dose
Depression Without Psychosis		
First-line*	Paroxetine	5-10 mg/day
	Sertraline	25-50 mg/day
	Citalopram	10-20 mg/day
	Fluoxetine	5-10 mg/day
	Nefazodone	50 mg bid
	Mirtazapine	7.5-15 mg/day
Alternative	Nortriptyline	10-25 mg/day
	Venlafaxine	25-50 mg/day
	Desipramine	10-25 mg/day
Severe depression With Psychosis		
First line	First line agent plus Risperidone	0.25-0.5 mg/day
Alternative	First line agent plus Haloperidol	0.25-0.5 mg 1-3 times/day

* Consider adding psychotherapy to antidepressant therapy for mildly demented patients. ECT may be considered for severe depression as an alternative when resident does not respond to medication.

* The Expert Consensus Guidelines only list paroxetine and sertraline as first line choices.

Anxiety and Agitation

Patients may present with physical or verbal signs of worry, nervousness, restlessness, irritability, or fear, or physical signs such as nausea and diarrhea.

Agitation associated with anxiety	Medication	Starting dose
Acute Treatment		
First-line*	Trazodone	25 mg/hs
	Lorazepam	0.25-0.5 mg/day
	SSRIs	See page 50
Alternative	Buspirone	5 mg bid
	Oxazepam	7.5-10 mg/day
Long-term Treatment		
First-line*	Trazodone	25 mg/hs
	Buspirone	5 mg bid
Alternative	Fluoxetine	5-10 mg/day
	Paroxetine	5-10 mg/day
	Sertraline	25-50 mg/day

*Note: consider communication treatment strategies (Page 34).

*The Expert Consensus Guidelines only list lorazepam as first line for acute treatment and buspirone as first-line for long-term treatment. Exercise caution when prescribing benzodiazepines in older adults and monitor for disinhibition or exacerbation of agitation/anxiety and other side effects (e.g., postural instability, increased confusion).

Anger and Agitation

Patient may present with general anger associated with activities, aggression directed at caregiver, other residents, family or self such as slapping, pushing, hitting, biting, or verbal outbursts such as accusations, name-calling, obscenities, and threats.

Agitation associated with mild anger, without aggression	Medication	Starting dose
Acute Treatment		
First-line	Trazodone	25 mg hs
Alternative	Lorazepam	0.25-0.5 mg/day
	Oxazepam	7.5-10 mg/day
Long-term Treatment		
First-line	Divalproex	125 mg bid
	Buspirone	5 mg bid
	Fluoxetine	5-10 mg/day
	Paroxetine	5-10 mg/day
	Sertraline	25-50 mg/day
Alternative	Gabapentin	100 mg qd or bid
	Carbamazepine	50 mg qd or bid
	Risperidone	0.25-0.5 mg/day

*Note: Consider all non-medication treatment strategies (page 34).

Agitation associated with severe anger, with aggression	Medication	Starting dose
Acute Treatment		
First-line	Risperidone	0.25-0.5 mg/day
Alternative	Olanzapine	2.5-5 mg/day
	Quetiapine	25 mg bid
	Haloperidol	0.25-0.5 mg 1-3 qd to tid
Long-term Treatment		
First-line	Divalproex	125 mg bid
	Risperidone	0.25-0.5 mg/day
Alternative	Carbamazepine	50-100 mg/day
	Olanzapine	2.5-5 mg/day
	Gabapentin	100 mg qd or bid

*Note: Consider all non-medication treatment strategies (page 34).

Insomnia and Agitation

Patients may present with symptoms that are physical or verbal in nature, such as wandering, frequent use of call bell, morning headaches, frequent daytime naps, and early awakenings.

Agitation associated with insomnia	Medication	Starting dose
Acute Treatment		
First-Line	Nefazodone Trazodone	50 mg bid 25 mg/hs
Alternative	Lorazepam Oxazepam Temazepam Zolpidem Zaleplon	0.25-0.5 mg/hs 7.5-10 mg/hs 7.5 mg/hs 2.5-5 mg/hs 5 mg/hs
Long-term Treatment		
First-Line	Nefazodone Trazodone	50 mg bid 25 mg hs
Alternative	Risperidone Olanzapine Quetiapine	0.25-0.5 mg/day 2.5-5 mg/day 25 mg bid
Note: consider environmental treatment strategies (Page 34).		

The agents are best used after optimizing sleep hygiene in this population. Examples of good sleep hygiene include appropriate lighting, clothing, temperature, minimal caffeine, alcohol, nicotine, or fluids use before bedtime, set bedtime every night, etc. For some residents who do not respond, setting up nighttime activities can help alleviate some of the distress associated with insomnia.

Psychosis and Agitation

Patient may present with impaired memory, visual or auditory hallucinations, delusions, disorganized speech and thought, repetitive activity.

Agitation associated with psychosis	Medication	Starting dose
Acute Treatment		
First-line	Oral: Risperidone Parenteral: Haloperidol	0.25-0.5 mg/day 0.25-0.5 mg 1-3 times/day
Alternative	Oral : Olanzapine or Quetiapine	2.5-5 mg/day 25 mg bid
Long-term Treatment		
First-line	Risperidone Olanzapine Quetiapine	0.25-0.5 mg/day 2.5-5 mg/day 25 mg bid
Alternative	Divalproex Trazodone	125 mg bid 25 mg/hs
*Note: Consider all non-medication treatment strategies (page 34).		

Episodic Agitation (also referred to as "Sundowning")
Patient may present with an increase in wandering, confusion, disorientation that starts in the late afternoon and/or becomes especially severe at night ("sundowning"). These symptoms may result from fatigue, loss of visual cues in the dark, and instability in circadian rhythm.

Medications for Episodic Agitation	Medication	Starting dose
Acute Treatment		
First Line	Divalproex	125 mg bid
	Nefazodone	50 mg bid
	Trazodone	25 mg/day
Alternative	Olanzapine	2.5-5 mg/day
	Quetiapine	25 mg bid
	Risperidone	0.25-5 mg/day
Long -Term Treatment		
First Line	Divalproex	125 mg bid
	Trazodone	25 mg/hs
Alternative	Risperidone	0.25-0.5 mg/day
*Note: Consider environmental treatment strategies (Page 34).		

Agitation due to a Medical Condition
Treatment usually limited to a few days unless a condition is identified justifying long-term treatment. Dosage titration may be required to achieve desired response.

Delirium or agitation due to medical condition	Medication	Starting dose
Acute Treatment		
First-line	Oral: Risperidone	0.25-0.5 mg/day
	Parenteral: Haloperidol	0.25-0.5 mg qd to tid
Alternative	Oral: Olanzapine or	2.5-5 mg/day
	Quetiapine	25 mg bid

Pain and Agitation
Patients with pain may present with grimacing, moaning, crying, calling out, rocking, guarding, sleep changes, and irritability. If pain is suspected, the patient should be assessed for cause, duration, and intensity, and treated with the most appropriate therapy for pain.

Agitation associated with Pain	Medication	Starting dose
Acute and Long-term Treatment		
First-line	Desipramine *†	10-25 mg/day
	Nortriptyline *†	10-25 mg/day
	Trazodone*	25 mg/hs
Alternative	Nefazodone*	50 mg bid
	Fluoxetine	5-10 mg/day
	Paroxetine	5-10 mg/day
	Sertraline	25-50 mg/day
	Citalopram	10-20 mg/day

* May cause additive sedation in residents receiving other sedating medications (e.g., opiate analgesics).
† In residents with a diagnosis of cardiac arrhythmia, these medications are considered to have a high potential for severe adverse outcomes (i.e., may induce arrhythmias).

For more information on managing pain in older persons, see the American Geriatrics Society Clinical Practice Guideline entitled, "The Management of Chronic Pain in Older Persons" available at www.americangeriatrics.org/products/chronic-pain.pdf.

Please see page 48 for determining response to therapy and changes in therapy based on response. Dosing guidelines for elderly residents with dementia are on page 50.

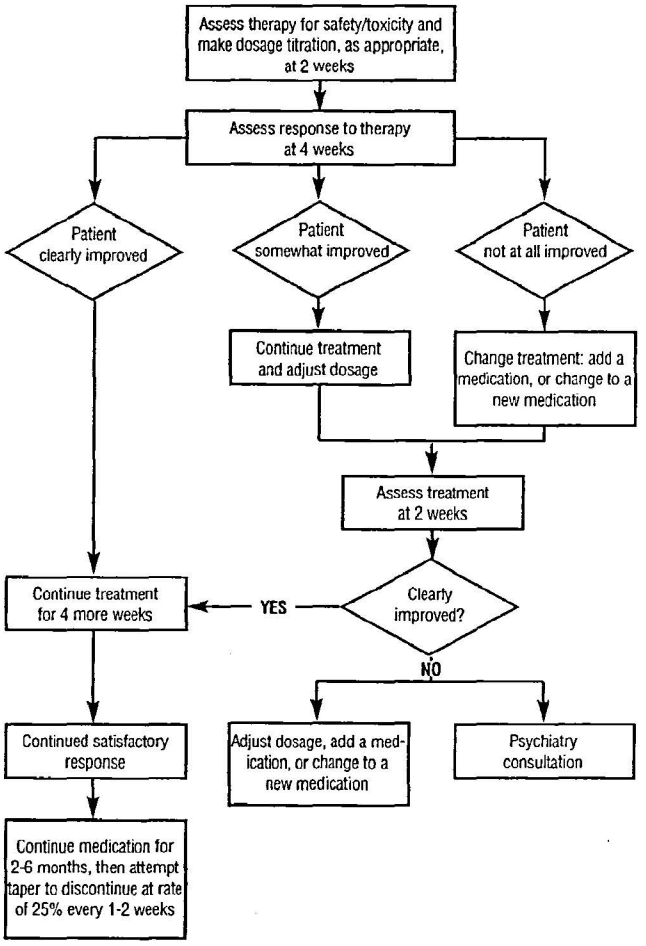
MONITORING RESPONSE TO MEDICATION TREATMENT

In order to determine the response to medication treatment, several issues need to be addressed:

1. Is the appropriate medication being taken and in the appropriate dose? (see page 50) Has the treatment been given for a long enough period to determine response? (see page 48)
2. Have any new environmental issues arisen that may have altered the response to treatment?
3. Have possible medical or medication causes of agitation been evaluated and addressed? (see page 15)
4. Has the appropriate syndrome of agitation been identified? (see page 37 and 38)
5. Have target behaviors been identified and monitored for frequency and intensity to allow you to make an assessment of response to treatment?

After these issues have been addressed, it is time to assess whether the resident has improved on the current medication regimen. A method for determining the appropriate course of action is presented in Algorithm 2 (page 47). A change in dose may be the appropriate response for some residents. Others may require the addition of a medication or a change to different medication. The dosage ranges for the medications included in the syndrome descriptions are noted in "Dosing Guidelines" (page 50). As always when dosing medications in the elderly, the "go slow" plan is suggested. Keep in mind, however, that patients are often started and left on a low dose, or inadvertently titrated to a dose that is too high, and do not receive the maximum benefit. Follow-up is critical and further titration or tapering may be required.

Algorithm 2. Monitoring Response to Therapy



ADJUNCTIVE THERAPY (May also be referred to as "augmentation")

As noted in algorithms 3 and 4, adding a drug may be an appropriate strategy for some residents, especially if a partial response is seen at the maximum titrated dose of first-line therapy.

If Initial Treatment Is		Consider Adding
Conventional antipsychotic	→	Divalproex, trazodone, SSRI
Atypical antipsychotic	→	Divalproex, trazodone, SSRI
Benzodiazepine	→	Atypical antipsychotic, conventional antipsychotic, divalproex, SSRI

As stated previously, exercise caution when prescribing benzodiazepines in older adults. Monitor for disinhibition or exacerbation of agitation/anxiety and side effects. Reconsider the need for a benzodiazepine, especially if the response is not as anticipated.

CHANGING THERAPY BASED ON RESPONSE

If the resident is clearly not improved based on the current medication or combination of medications, as explained in Algorithm 3 (page 47), then a change in therapy and a reassessment of initial diagnosis is indicated. In those who have no response to the initial treatment, a change to another medication is the appropriate strategy. As noted in algorithm 3, the initial treatment dictates which medications are appropriate for subsequent therapy.

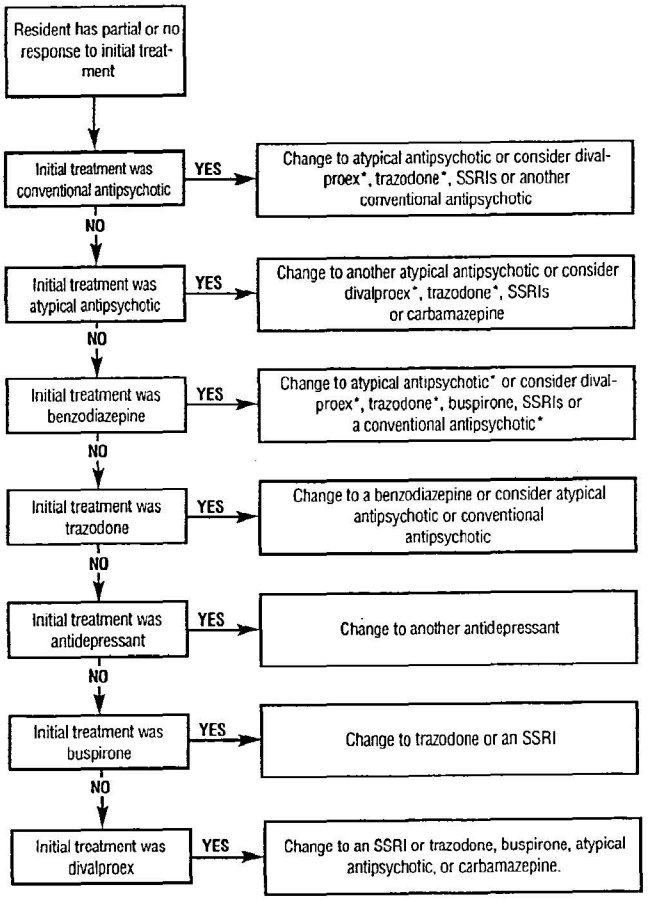
Time to Determine Response to Therapy*

The time periods listed below are guidelines for determining response to medication when used for the treatment of agitation.

Medication/Class	Acute Treatment	Long-term Treatment
Antipsychotic	2-8 days	2-4 weeks
Benzodiazepine	1-6 days	1-3 weeks
Trazodone	7-10 days	3-4 weeks
Buspirone	–	4-6 weeks
Divalproex	–	3-6 weeks
SSRI antidepressant	–	4-6 weeks
Tricyclic antidepressant	–	4-6 weeks

*Assumes an appropriate series of dosage titrations to maximize potential for response and measured from the last dose change.

Algorithm 3. Changing Therapy Based on Response



*May also be considered as adjunctive therapy to initial treatment

DOSING GUIDELINES

Medication	Initial Dose (titration)	Suggested Maximum Dose for the Elderly with dementia
Antidepressants		
Citalopram	10-20 mg/day (10 mg/day)	40 mg/day
Desipramine	10-25 mg/day (10-25 mg/day)	75 mg/day
Fluoxetine	5-10 mg/day (5-10 mg/day)	20-40 mg/day
Mirtazapine	7.5-15 mg daily (7.5 mg daily)	45 mg/day
Nefazodone	50 mg bid (50 mg/day)	200-400 mg/day
Nortriptyline	10-25 mg/day (10-25 mg/day)	75 mg/day
Paroxetine	5-10 mg/day (5-10 mg/day)	20 mg/day
Sertraline	25-50 mg/day (25-50 mg/day)	100-150 mg/day
Trazodone	25 mg/day (25 mg/day in 1-3 doses)	200-300 mg/day
Venlafaxine	25-50 mg/day in 1-2 doses (25 mg/day)	75 mg/day
Mood-stabilizing Agents		
Divalproex	125 mg bid (125 mg bid every 3-5 days)	750-2000 mg/day
Carbamazepine	50-100 mg/day (50-100 mg/day in 1-2 doses)	500-800 mg/day
Gabapentin	100 mg qd or bid	600 mg/day
Antianxiety Agents		
Buspirone	5 mg bid (10 mg/day)	60 mg/day
Lorazepam	0.25-0.5 mg/day (0.5 mg day in 1-2 doses)	2-4 mg/day
Oxazepam	7.5 - 10 mg/day (7.5-10 mg/day)	45-60 mg/day
Antipsychotics		
Loxapine	2.5 mg bid (2.5 mg bid)	10 mg/day
Olanzapine	2.5-5 mg/day (2.5 mg/day)	10 mg/day
Quetiapine	25 mg bid (25 mg/day)	200 mg/day
Risperidone	0.25-0.5 mg/day (0.25-0.5 mg/day)	2 mg/day
Ziprasidone*	20 mg bid (20 mg bid)	40-160 mg/day

**Limited experience in the elderly.*

SIDE EFFECT PROFILES

Antidepressants

	Side Effects					
			CNS	Cardiovascular		
Medication	Antichol -inergic*	Drowsiness	Insomnia/ agitation	Orthostatic hypotension	Arrhyth- mia	Gastro- intestinal
Citalopram	Low	Low	Low	Low	Low	Mod
Desipramine	Low	Low	Low	Mod	Mod	Low
Fluoxetine	Low	Low	Mod	Low	Low	Mod
Mirtazapine	Mod	Mod	Low	Low	Low	Low
Nefazodone	Low	Mod	Low	Low	Low	Low
Nortriptyline	Low	Low	Low	Mod	Mod	Low
Paroxetine	Low	Low	Mod	Low	Low	Mod
Sertraline	Low	Low	Mod	Low	Low	Mod
Trazodone	Low	High	Low	Mod	Low	Low
Venlafaxine	Low	Low	Low	Low	Low	Mod

**Dry mouth, confusion, blurred vision, urinary hesitancy, and constipation.*

Medication	Side Effects
Antianxiety Medications	
Buspirone	dizziness, lightheadedness, drowsiness, loss of consciousness, stomach upset, nausea, vomiting, unusually small pupils
Lorazepam, Oxazepam	sedation, dizziness, weakness, unsteadiness, disorientation, sleep disturbance, agitation
Mood Stabilizers	
Divalproex sodium	Somnolence, nausea, dyspepsia, diarrhea, vomiting, abdominal pain, increased appetite, asthenia, ataxia, dizziness, tremor, weight gain, back pain, alopecia, thrombocytopenia, hepatotoxicity, pancreatitis
Carbamazepine	Leukopenia, drowsiness, aplastic anemia, thrombocytopenia, rash, hepatotoxicity, ataxia, cardiac and thyroid effects
Gabapentin	Sedation, ataxia, confusion

Antipsychotics

Medication	Side Effect: Anticholinergic*	Side Effect: Extrapyramidal	Side Effect: Sedation	Orthostatic hypotension
Haloperidol	Low	High	Low	Low
Thioridazine¶	High	Low	High	High
Risperidone	Low	Low-Mod†	Mod	Mod
Olanzapine	Mod	Low	Mod	Low
Quetiapine	Mod	Low	Mod-High	Mod
Ziprasidone¶	Low	Low-Mod	Mod	Low

*Dry mouth, blurred vision, urinary hesitancy, constipation.
† Dose related - low at doses of less than 1 mg/day.
¶ Should not be used with other drugs that prolong the QT interval. The potential exists for any antipsychotic to affect cardiac conduction.

AVAILABLE DOSAGE FORMS

Medication	Available Forms	Usual T1/2
Mood Stabilizing Agents		
Carbamazepine (Tegretol®, Tegretol XR®)	oral suspension: 100 mg/5 ml tablets:100 mg (chewable), 200 mg (Tegretol®) extended release tablets: 100, 200, 400 mg (Tegretol XR®)	25-65 hrs chronic dose: 8-29 hrs (average 12-17 hrs)
Divalproex (Depakote®, Depakote Sprinkle®, Depakote ER®)	sprinkle capsules: 125 mg (Depakote sprinkle®) delayed release tablets: 125 mg, 250, 500 mg (Depakote®) extended release tablets: 500 mg once daily dosing (Depakote ER®)	variable, from 6 to 16 hrs; may be considerably longer in residents with hepatic function impairment, in the elderly. May be considerably shortened in residents receiving hepatic enzyme inducing anticonvulsants
Gabapentin (Neurontin®)	Capsules: 100, 300, 400 mg tablets: 600, 800 mg oral solution: 250 mg/5 ml	5-7 hours with normal renal function; CrCl, <30: 52 hrs

Available Dosage Forms (continued)

Medication	Available forms	Usual T1/2
Selective Serotonin Reuptake Inhibitor (SSRI) Antidepressants		
Citalopram (Celexa®)	tablets: 20, 40 mg oral solution: 10 mg/5 ml	mean about 35 hrs
Fluoxetine (Prozac®) (Prozac® Weekly™)	capsules: 10, 20, 40 mg tablet: 10 mg oral solution: 20 mg/5 ml capsule: 90 mg (Prozac® Weekly™)	4-6 days with long term administration
Mirtazapine (Remeron®) (Remeron® Soltab™)	tablets: 15, 30, 45 mg orally disintegrating tablets: 15, 30, 45 mg (Remeron® Soltab™)	About 20 to 40 hours; significantly longer in males than females
Nefazodone (Serzone®)	tablets: 50, 100, 150, 200, 250 mg	2-4 hrs
Paroxetine (Paxil®)	tablets: 10, 20, 30, 40 mg oral suspension: 10 mg/5 ml	about 24 hrs (range, 3-65 hrs)
Sertraline (Zoloft®)	tablets: 25, 50, 100 mg oral concentrate: 20 mg/ml	24-26 hrs
Venlafaxine (Effexor®, Effexor XR®)	tablets: 25, 37.5, 50, 75, 100 mg (Effexor®) extended release capsules: 37.5, 75, 150 mg (Effexor XR®)	5-11 hrs
Other Antidepressants		
Desipramine (Norpramin®)	tablets: 10, 25, 50, 75, 100, 150 mg	12-24 hrs
Nortriptyline (Pamelor®)	capsules: 10, 25, 50, 75 mg oral solution: 10 mg/5 ml	18-44 hrs
Trazodone (Desyrel®)	tablets: 50, 100, 150, 300 mg	3-9 hrs
Antianxiety Agents (Benzodiazepines and Others)		
Buspirone (Buspar®)	tablets: 5, 10, 15, 30 mg	about 2.5 hrs
Lorazepam (Ativan®)	oral concentrate: 2 mg/ml tablets: 0.5, 1, 2 mg injection: 2 mg/ml, 4 mg/ml	10-20 hrs
Oxazepam (Serax®)	capsules: 10, 15, 30 mg tablets: 15 mg	5-20 hrs

Attachment 10 to Agreed Statement of Facts
U.S. v. Abbott Laboratories

Available Dosage Forms (continued)

Medication	Available forms	Usual T1/2
Atypical Antipsychotics		
Olanzapine (Zyprexa®, Zyprexa® Zydis®)	tablets: 2.5, 5, 7.5, 10, 15, 20 mg (Zyprexa®) orally disintegrating tablets: 5, 10 mg (Zyprexa® Zydis®)	mean 30 hrs range: 21 to 54 hrs
Quetiapine (Seroquel®)	tablets: 25, 100, 200, 300 mg	mean, about 6 hrs
Risperidone (Risperdal®)	oral solution: 1 mg/ml tablets: 0.25, 0.5, 1, 2, 3 , 4 mg	20 to 24 hrs; in residents with renal function impairment, increased elimination half-lives have been reported
Ziprasidone (Geodon™)	capsules: 20, 40, 60, 80 mg	mean, about 7 hours
Conventional Antipsychotics		
Haloperidol (Haldol®)	oral solution: 2 mg/ml tablets: 0.5, 1, 2, 5, 10, 20 mg injection: 5 mg/ml IM or IV (5 mg/min) depot injection: 50 mg/ml, 100 mg/ml	12-36 hrs (21 days for depot inj.)
Loxapine (Loxitane®)	capsules: 5, 10, 25, 50 mg tablets: 5, 10, 25, 50 mg	
Medications for the Treatment of Alzheimer's Disease		
Donepezil (Aricept®)	tablets: 5, 10 mg	70 hours
Galantamine (Reminyl®)	tablets: 4, 8, 12 mg	7 hours
Rivastigmine (Exelon®)	capsules: 1.5, 3, 4.5, 6 mg	1.5 hours

GENERIC/BRAND NAMES OF PSYCHOTHERAPEUTIC MEDICATIONS

Generic	Brand	Manufacturer (phone number; web site)
Mood-stabilizing Agents		
Carbamazepine	Tegretol® Tegretol XR®	Novartis (800-742-2422 www.novartis.com)
Divalproex	Depakote® Depakote Sprinkle® Depakote ER®	Abbott Laboratories (800-633-9110; www.depakote.com)
Gabapentin	Neurontin®	Parke-Davis (800-223-0432; www.pfizer.com)
Antidepressants		
Citalopram	Celexa®	Forest (800-678-1605; www.celexa.com)
Desipramine	Norpramin®	Aventis (800-552-3656; www.aventispharma-us.com)
Fluoxetine	Prozac® Prozac® Weekly™	Eli Lilly and Company (800-545-5979; www.prozac.com)
Mirtazapine	Remeron® Remeron® Soltab™	Organon (800-241-8812; www.remeron.com)
Nefazodone	Serzone®	Bristol-Myers Squibb (800-321-1335; www.serzone.com)
Nortriptyline	Pamelor®	Novartis (800-742-2422 www.novartis.com)
Paroxetine	Paxil®	GlaxoSmithKline (800-366-8900; www.paxil.com)
Sertraline	Zoloft®	Pfizer (888-879-3477; www.zoloft.com)
Trazodone	Desyrel®	Mead Johnson Pharmaceuticals (800-321-1335; www.bms.com)
Venlafaxine	Effexor® Effexor XR®	Wyeth-Ayerst (800-934-5556; www.effexor.com)

GENERIC/BRAND NAMES OF PSYCHOTHERAPEUTIC MEDICATIONS

Generic	Brand	Manufacturer (phone number; web site)
Antianxiety Agents		
Buspirone	Buspar®	Bristol-Myers Squibb (800-321-1335; www.buspar.com)
Lorazepam	Ativan®	Wyeth-Ayerst (800-934-5556; www.wyeth.com)
Oxazepam	Serax®	Wyeth-Ayerst (800-934-5556; www.wyeth.com)
Atypical Antipsychotics		
Olanzapine	Zyprexa® Zyprexa® Zydis®	Eli Lilly (800-545-5979; www.zyprexa.com)
Quetiapine	Seroquel®	AstraZeneca (800-456-3669; ww.seroquel.com)
Risperidone	Risperdal®	Janssen (800-JANSSEN; ww.risperdal.com)
Ziprasidone	Geodon™	Pfizer (888-879-3477; www.pfizer.com)
Typical Antipsychotics		
Haloperidol	Haldol®	Ortho-McNeil (800-682-6532; www.ortho-mcneil.com)
Loxapine	Loxitane®	Watson Pharmaceuticals (www.watsonpharm.com)
Nonbenzodiazepine (pyrazolopyrimidine) Agents		
Zaleplon	Sonata®	Wyeth-Ayerst (800-934-5556; www.sonatatonight.com)

COMMON MEDICATION INTERACTIONS (NOT ALL INCLUSIVE)

Medication	Interacts With	Effect
Paroxetine	barbiturates	paroxetine levels may be decreased
	cimetidine	paroxetine levels may be increased
	phenytoin	levels of either drug may be decreased
	theophylline	theophylline levels may be increased
	tricyclic antidepressants (TCA)	TCA levels may be increased
	monoamine oxidase inhibitors	concurrent use contraindicated
	warfarin	risk for bleeding may be increased
Sertraline	cimetidine	sertraline levels may be increased
	monoamine oxidase inhibitors	concurrent use contraindicated
	TCA	TCA levels may be increased
	warfarin	risk for bleeding may be increased
Venlafaxine	monoamine oxidase inhibitors	concurrent use contraindicated
	cimetidine	venlafaxine levels may be increased
	haloperidol	haloperidol levels may be increased
Citalopram	monoamine oxidase inhibitors	concurrent use contraindicated
Nefazodone	cisapride, monoamine oxidase inhibitors	concurrent use contraindicated

Medication	Interacts With	Effect
Divalproex	warfarin, heparin	risk for bleeding may be increased
	barbiturates	barbiturate levels may be increased
	carbamazepine	divalproex (expressed as valproic acid) levels may be decreased
	felbamate	divalproex (expressed as valproic acid) levels may be increased
	phenytoin	divalproex (expressed as valproic acid) levels may be decreased, phenytoin levels may be increased or decreased
Carbamazepine	warfarin	warfarin effectiveness may be reduced
	phenytoin, divalproex	phenytoin and valproic acid levels may be decreased
	cimetidine, clarithromycin, erythromycin, verapamil, diltiazem, itraconazole, ketoconazole, isoniazid	carbamazepine levels may be increased
	felbamate	carbamazepine levels may be decreased
	Tricyclic antidepressants, typical antipsychotics	CNS depressant effects may be enhanced, may lower seizure threshold, anticholinergic effects may be potentiated
	lamotrigine	lamotrigine levels may be decreased
Buspirone	erythromycin, itraconazole	Cmax and AUC of buspirone increased
	monoamine oxidase inhibitors	elevation in blood pressure

APPENDIX A. GLOSSARY

Activities of daily living (ADLs) - personal care activities necessary for everyday living (e.g., eating, bathing, hygiene, and oral care; dressing and grooming; toileting; and moving between bed and chair)

Advance directives - written legal documents, completed and signed when a person is competent to make necessary decisions about the instructive statements contained in the document. They state the person's choices for future medical care decisions

Agnosia - loss or diminution of the ability to recognize familiar people, objects, or stimuli

Antecedents - the circumstances or conditions that exists before an incident; knowing what happened before a behavioral incident may help in determining what precipitates or triggers the behavior

Aphasia - loss or impairment of the power to use or comprehend words; can affect ability to follow instructions, participate in conversations, or express needs

Apraxia - loss or impairment of the ability to execute complex coordinated movements without impairment of the muscles or senses

Autonomy - making independent choices; for persons with dementia, autonomy relates to respect for rights and dignity of a person, even when his or her abilities to make choices are limited or lost

BPSD - Behavioral and Psychological Symptoms of Dementia; acronym used by the International Psychogeriatric Association (IPA) when discussing behavioral disturbances; symptoms of disturbed perception, thought content, mood, or behavior that frequently occur in patients with dementia

Catastrophic reaction - inability to cope when faced with physical or cognitive deficits and expressed with anxiety, tears, aggressive behavior, swearing, refusal, etc.

Caregiver burden - the physical, emotional, and financial toll of providing care

CMAI - Cohen-Mansfield Agitation Inventory; a list of descriptors of agitated behaviors in 4 catagories.

Cognition - an individual's meaningful thought, knowledge, and intelligence; the ability to know, understand, and make sense of the world

Cognitive abilities - brain functions associated with thinking, knowing and understanding; includes memory, intelligence, learning, skills, problem solving, judgment, comprehension, attention, orientation to time, place, and to one's own self

Cognitive impairment - decreased capacity in one or more cognitive ability

Competence - person's ability to make informed choices as determined by a court of law; a person may be legally incompetent, but may still have capacity to make decisions about things in his or her daily life

Delirium - an acute confusional state, distinct from dementia

Delusion - a false idea, sometimes originating in misinterpretation, but firmly believed and strongly maintained in spite of obvious proof or evidence to the contrary

Dementia - a syndrome of progressive decline in multiple areas (domains) of cognitive function eventually leading to a significant inability to maintain occupational and social performance

Executive function - goal formulation, planning, and execution of plans

Focal neurological signs and symptoms - include extensor plantar response, pseudobulbar palsy, gait abnormalities, exaggeration of deep tendon reflexes, or weakness of an extremity

Frontotemporal dementia - type of dementia less common than AD, vascular dementia, or DLB; typical neuropsychologic features include deficits on frontal system tasks, including verbal fluency, abstraction, and executive function; difficult to distinguish from AD

Hallucination - a sensory experience where a person sees, hears, or feels something or someone that is not audible or visible to anyone else

HCFA Guidelines - Health Care Financing Administration Nursing Home Survey Procedures and Interpretive Guidelines (HCFA name changed to Center for Medicare and Medicaid Services in 2001)

IADLs - instrumental activities of daily living; includes more complex skills required for independent living: shopping, cooking, housekeeping, laundry, using the phone, using transportation, managing money, managing medications

IPA - International Psychogeriatric Association; whose goal is to provide physicians, healthcare professionals, and scientists with information about behavioral and biological aspects of mental health in the elderly, through publications, meetings, and special educational projects

Lewy bodies - abnormal structures that remain after nerve cells in the substantia nigra have died; long recognized in brain stem nuclei of patients with Parkinson's disease

Dementia with Lewy Bodies (DLB) - common cause of dementia; presence of Lewy bodies; defined clinically by the presence of dementia, gait/balance disorder, prominent hallucinations and delusions, sensitivity to traditional antipsychotics, fluctuations in alertness, prominent deficits in attention, profound deficits in visuo-contructional skills, and relative sparing of memory

Limbic system - a group of subcortical structures (e.g., the hypothalamus, the hippocampus, and the amygdala) of the brain that are concerned especially with emotion and motivation

MDS - Minimum data set; OBRA 87 required that HCFA designate a resident assessment instrument (RAI) that includes a minimum data set. HCFA's RAI consists of the MDS, triggers, and 18 Resident Assessment Protocols (RAPs). See www.hcfa.gov/medicaid/mds20 for more information.

NINCDS-ADRDA - Neurological and Communication Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations

Praxis - the doing or performance of an action, movement, or series of movements.

Sundowning – increase in wandering, confusion, disorientation that starts in the late afternoon and/or becomes especially severe at night.

Tag F329 - HCFA interpretive guidelines section entitled "Unnecessary Drugs"

Tag F330 - HCFA interpretive guidelines section entitled "Antipsychotic Drug Dosage Levels"

APPENDIX B. - THE ZARIT BURDEN INTERVIEW

Score:	Do you feel:
	1. Your relative asks for more help than he/she needs?
	2. Because of the time you spend with your relative that you don't have enough time for yourself?
	3. Stressed between caring for your relative and trying to meet other responsibilities for your family or work?
	4. Embarrassed over your relative's behavior?
	5. Angry when you are around your relative?
	6. Your relative currently affects your relationships with other family members or friends in a negative way?
	7. Afraid of what the future holds for your relative?
	8. Your relative is dependent on you?
	9. Strained when you are around your relative?
	10. Your health has suffered because of your involvement with your relative?
	11. You don't have as much privacy as you would like because of your relative?
	12. Your social life has suffered because you are caring for your relative?
	13. Uncomfortable about having friends over because of your relative?
	14. That your relative seems to expect you to take care of him/her as if you were the only one he/she could depend on?
	15. That you don't have enough money to care for your relative in addition to the rest of your expenses?
	16. That you will be unable to take care of your relative much longer?
	17. You have lost control of your life since your relative's illness?
	18. You wish you could just leave the care of your relative to someone else?
	19. Uncertain about what to do about your relative?
	20. You should be doing something more for your relative?
	21. You could be doing a better job in caring for your relative?
	Overall, how burdened do you feel in caring for your relative (not at all, a little, moderately, quite a bit, extremely)?

Source: Zarit & Zarit, 1983

Score items 1-21 as follows: 0=never, 1=rarely, 2=sometimes, 3=quite frequently, 4=nearly always. Add the scores for the questions.
Score categories are as follows:
0-20: little or no burden
21-40: mild to moderate burden
41-60: moderate to severe burden

Catastrophic reaction - inability to cope when faced with physical or cognitive deficits and expressed with anxiety, tears, aggressive behavior, swearing, refusal, etc.

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	Overall, how burdened do you feel in caring for your relative (not at all, a little, moderately, quite a bit, extremely)?

Source: Zarit & Zarit, 1983

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41-60: moderate to severe burden

APPENDIX C. BEHAVIORAL DESCRIPTORS

Cohen-Mansfield Agitation Inventory (CMAI)

- Biting
- Complaining
- Constant unwarranted requests for attention or help
- Cursing or verbal aggression
- Eating/drinking inappropriate substances
- General restlessness
- Grabbing onto people
- Handling things inappropriately
- Hiding things
- Hitting (including self)
- Hoarding things
- Hurting self or others
- Inappropriate dress or disrobing
- Intentional falling
- Kicking
- Making faces
- Making physical sexual advances
- Making verbal sexual advances
- Negativism
- Pacing, aimless wandering
- Performing repetitious mannerisms
- Pushing
- Repetitive sentences or questions
- Scratching
- Screaming
- Spitting (including at meals)
- Strange movements
- Strange noises (weird laughter or crying)
- Tearing things or destroying property
- Throwing things
- Trying to get to a different place

Source: Cohen-Mansfield J. Instruction Manual for the Cohen-Mansfield Agitation Inventory (CMAI). Rockville, MD: The Research Institute of the Hebrew Home of Greater Washington. (c) 1986, Jiska Cohen-Mansfield.

Note that each behavior is actually a group of related behaviors. If the person to be rated manifests an inappropriate behavior which is close to a behavior on the CMAI but not spelled out exactly, add it to the category.

The agitated behavior the resident is experiencing can be selected from the CMAI, the Disruptive Behavior Scale (following page), or other appropriate characterization, and recorded on a behavior monitoring form. The frequency should be charted, preferably daily, by nursing staff, or a caregiver, in order to determine the pattern of the behavior, possible antecedents, and the effectiveness of treatment strategies.

Disruptive Behavior Scale Descriptions

- Ambulates inappropriately
- Bangs objects non-destructively
- Bears a weapon
- Bites
- Damages objects in the environment
- Displays inappropriate sexual behavior
- Disrobes/exposes self
- Does not follow directions
- Dresses unsuitably for environment/activity
- Eats others' food
- Elbows
- Excessive motor activity
- Hits others
- Injures self
- Isolates self from others (physically)
- Kicks
- Loses track of one's own objects
- Makes insulting non-obscene gestures
- Makes obscene gestures
- Makes repetitious noises
- Makes sexual advances
- Makes threat implying physical harm to self
- Makes threats implying physical harm to others
- Paces
- Physically takes objects from another
- Pinches/squeezes
- Places inappropriate substances in mouth
- Pushes/shoves
- Refuses to eat/drink
- Repeats phrase(s)/words
- Scratches others
- Screams/yells
- Spits
- Spits medication
- Spits on others
- Strikes a person with an object
- Tackles
- Takes objects belonging to others
- Talks constantly
- Throws objects/food
- Unkempt personal appearance
- Urinates/defecates inappropriately
- Uses a weapon
- Uses hostile/accusatory language toward others
- Uses obscene or profane language

Source: Beck C, Heithoff K, Baldwin B, Cuffel B, O'Sullivan M, Chumbler N. Aging & Mental Health 1997;1:71-79.

Distinguishing between aggression that is offensive or assaultive in nature, and aggression that is defensive or resistive is very important when attempting to reduce or eliminate the behavior.

APPENDIX D. CRITERIA FOR DELIRIUM AND DEMENTIA

Criteria for Delirium, Dementia, and Amnestic and Other Cognitive Disorders Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV Criteria)

Delirium

The disorders in the "Delirium" section share a common symptom presentation of a disturbance in consciousness and cognition, but are differentiated based on etiology: Delirium due to a general medical condition, substance-induced delirium (including medication side effects), and delirium due to multiple etiologies. Delirium not Otherwise Specified is included for presentations in which the clinician is unable to determine a specific etiology for the delirium.

Diagnostic Criteria for 293.0 Delirium due to ... [Indicate the general medical condition]

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

Dementia

The disorders in the "Dementia" section are characterized by the development of multiple cognitive deficits (including memory impairment) that are due to the direct physiological effects of a general medical condition, to the persisting effects of a substance, or to multiple etiologies (e.g., the combined effects of cerebrovascular disease and Alzheimer's disease). The diagnostic features listed in the next section pertain to Dementia of the Alzheimer's Type, Vascular Dementia, Dementia Due to HIV Disease, Dementia Due to Head Trauma, Dementia Due to Parkinson's Disease, Dementia Due to Huntington's Disease, Dementia Due to Pick's Disease, Dementia Due to Creutzfeldt-Jakob Disease, Dementia Due to Other General Medical Conditions, Substance-induced Persisting Dementia, and Dementia Due to Multiple Etiologies. Dementia not otherwise specified is included for presentations in which the clinician is unable to determine a specific etiology for the multiple cognitive deficits.

Diagnostic Criteria for Dementia of the Alzheimer's Type

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information).
   (2) one (or more) or the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. The course is characterized by gradual onset and continuing cognitive decline.
D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

(1) other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
(2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
(3) substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium.
F. The disturbance is not better accounted for by another Axis I disorder (e.g., major depressive disorder, schizophrenia).

Diagnostic Criteria for 290.4x Vascular Dementia (formerly Multi-infarct Dementia)

A. The development of multiple cognitive deficits manifested by both
(1) memory impairment (impaired ability to learn new information or to recall previously learned information)
(2) one (or more) or the following cognitive disturbances:
(a) aphasia (language disturbance)
(b) apraxia (impaired ability to carry out motor activities despite intact motor function)
(c) agnosia (failure to recognize or identify objects despite intact sensory function)
(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance.*
D. The deficits do not occur exclusively during the course of delirium.

* These criteria subsequently shown to be too liberal. Should be temporal decline within 3 months of stroke and/or major CNS infarctions (not just one or two lacunal)

Diagnostic Criteria for Dementia Due to Other General Medical Condition

A. The development of multiple cognitive deficits manifested by both
(1) memory impairment (impaired ability to learn new information or to recall previously learned information).
(2) one (or more) or the following cognitive disturbances:
(a) aphasia (language disturbance)
(b) apraxia (impaired ability to carry out motor activities despite intact motor function)
(c) agnosia (failure to recognize or identify objects despite intact sensory function)
(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of one of the general medical conditions listed below:
HIV, Head trauma, Parkinson's disease[1] Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease
Other general medical condition not listed above: for example normal-pressure hydrocephalus, hypothyroidism, brain tumor, intracranial radiation.

[1] Subsequent authors have described Lewy body dementia not covered in DSM-IV.

Diagnostic Criteria for 297.1 Delusional Disorder

A. Nonbizarre delusions (i.e., involving situations that occur in real life such as being followed, poisoned, infected, loved at a distance, or deceived by spouse or lover, or having a disease) of at least 1 month's duration.
B. Criterion A for Schizophrenia has never been met. Note: Tactile and olfactory hallucinations may be present in delusional disorder if they are related to the delusional theme.
C. Apart from the impact of the delusions(s) or its ramifications, functioning is not markedly impaired and behavior is not obviously odd or bizarre.

D. If mood episodes have occurred concurrently with delusions, their total duration has been brief relative to the duration of the delusional periods.
E. The disturbance is not due to the direct physiological effects of a substance or general medical condition.

Criteria for Major Depressive Episode

A. Five (or more) or the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
   (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
   (2) Markedly diminished interest or pleasure in all, or almost all, activities nearly every day (as indicated by either subjective account or observation made by others).
   (3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month) or a decrease or increase in appetite, nearly every day.
   (4) Insomnia or hypersomnia nearly every day.
   (5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
   (6) Fatigue or loss of energy nearly every day.
   (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
   (8) Diminished ability to think or concentrate or indecisiveness nearly every day (either by subjective account or as observed by others)
   (9) Recurrent thoughts of death (not just fear of dying) recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B. The symptoms do no meet criteria for a Mixed Episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism)
E. The symptoms are not better accounted for by bereavement (i.e., after the loss of a loved one, the symptoms persist for long than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation).

Criteria for Manic Episode

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least one week (or any duration if hospitalization is necessary).
B. During the period of mood disturbance, three (or more) of the following symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree:
   1) inflated self-esteem or grandiosity
   2) decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
   3) more talkative than usual or pressure to keep talking
   4) flight of ideas or subjective experience that thoughts are racing
   5) distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
   6) increase in goal-directed activity (either socially or sexually) or psychomotor agitation
   7) excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
C. The symptoms do not meet criteria for a mixed episode.
D. The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
E. The symptoms are not due to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment) or a general medical condition. (e.g., hyperthyroidism).

Diagnostic Criteria for 300.02 Generalized Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B. The person finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms present for more days than not for the past 6 months).
   1) Restlessness or feeling keyed up or on edge
   2) Being easily fatigued
   3) Difficulty concentrating or mind going blank
   4) Irritability
   5) Muscle tension
   6) Sleep disturbance (difficulty falling/staying asleep, or unsatisfying sleep)
D. The focus of the anxiety and worry is not confined to an Axis I disorder, e.g., the anxiety or worry is not about having a Panic Attack, being embarrassed in public, being contaminated, being away from home or close relatives, gaining weight, having multiple physical complaints, or having a serious illness, and the anxiety and worry do not occur exclusively during Posttraumatic Stress Disorder.
E. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
F. The disturbance is not due to the direct physiologic effects of a substance, or general medical condition and does not occur exclusively during a Mood Disorder, Psychotic Disorder, or a Pervasive Developmental Disorder.

Diagnostic Criteria for 307.42 Insomnia Related to ...[indicate the Axis I or Axis II Disorder]

A. The predominant complaint is difficulty initiating or maintaining sleep or non-restorative sleep, for at least 1 month that is associated with daytime fatigue or impaired daytime functioning.
B. The sleep disturbance (or daytime sequelae) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The insomnia is judged to be related to another Axis I or Axis II disorder (e.g., Major Depressive Disorder, Generalized Anxiety Disorder, Adjustment Disorder with Anxiety), but is sufficiently severe to warrant independent clinical attention.
D. The disturbance is not better accounted for by another Sleep disorder (e.g., Narcolepsy, Breathing-Related Sleep Disorder, a Parasomnia).
E. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

DSM-IIIR criteria for dementia states, "The essential feature of Dementia is impairment in short- and long- term memory, associated with impairment in abstract thinking, impaired judgment, other disturbances of higher cortical function, or personality change. The disturbance is severe enough to interfere significantly with work or usual social activities or relationships with others. The diagnosis of Dementia is not made if these symptoms occur... in Delirium..."

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According to the recent practice parameter by the American Academy of Neurology, the DSM-IIIR definition and the DSM-IV definition are identical, and should be used routinely. (Knopman DS et al. Neurology 2001;56:1142-53).

Criteria for Diagnosis of Probable Alzheimer's Disease From The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations (NINCDS & ADRDA)

- Dementia established by clinical examination, and documented by a standard test of cognitive function (e.g., Mini-Mental State Examination, Blessed Dementia Scale, etc.), and confirmed by neuropsychological tests
- Significant deficiencies in two or more areas of cognition, for example, word comprehension and task-completion ability
- Progressive deterioration of memory and other cognitive functions.

- No loss of consciousness
- Onset from age 40 to 90, typically after 65
- No other diseases or disorders that could account for the loss of memory and cognition

A Diagnosis of Probable Alzheimer's Disease is Supported By:

- Progressive deterioration of specific cognitive functions: language (aphasia), motor skills (apraxia), and perception (agnosia)
- Impaired activities of daily living and altered patterns of behavior
- A family history of similar problems, particularly if confirmed by neurological testing
- The following laboratory results: Normal cerebrospinal fluid (lumbar puncture test), normal electroencephalogram (EEG) test of brain activity, evidence of cerebral atrophy in a series of CT scans.

Other Features Consistent With Alzheimer's Disease

- Plateaus in the course of illness progression
- CT findings normal for the person's age
- Associated symptoms, including: depression, insomnia, incontinence, delusions, hallucinations, weight loss, sex problems, and significant verbal, emotional, and physical outbursts
- Other neurological abnormalities, especially in advanced disease including: increased muscle tone and a shuffling gait

Features That Decrease the Likelihood of Alzheimer's Disease:

- Sudden onset
- Such early symptoms as: seizures, gait problems, and loss of vision and coordination

Adapted from McKhann, G. et al. "Clinical Diagnosis of Alzheimer's Disease: Report of the NINCDS/ADRDA Work Group, Dept. of HHS Task Force on Alzheimer's Disease," Neurology 1984; 34:939.

APPENDIX E.
NURSING HOME SURVEYOR GUIDELINES

Section F330

(i) Residents who have not used antipsychotic drugs are not given these drugs unless antipsychotic drug therapy is necessary to treat a specific condition as diagnosed and documented in the clinical record; and

Antipsychotic drugs should not be used unless the clinical record documents that the resident has one or more of the following "specific conditions."

1. Schizophrenia
2. Schizo-affective disorder
3. Delusional disorder
4. Psychotic mood disorders (including mania and depression with psychotic features)
5. Acute psychotic episodes
6. Brief reactive psychosis
7. Schizophreniform disorders
8. Atypical psychosis
9. Tourette's disorder
10. Huntington's disease
11. Organic mental syndrome (now called delirium, dementia, and amnestic and other cognitive disorders by DSM-IV) with associated psychotic and/or agitated behaviors
    a. Which have been quantitatively and objectively documented. This documentation is necessary to assist in: (1) assessing whether the resident's behavioral symptoms are in need of some form of intervention, (2) determining whether the behavioral symptom is transitory or permanent, (3) relating the behavioral symptom to other events in the resident's life in order to learn about potential causes (e.g., death in the family, not adhering to the resident's customary daily routine, (4) ruling out environmental causes such as excessive heat, noise, overcrowding, (5) ruling out medical causes such as pain,

constipation, fever, infection. For a more complete description of behavioral monitoring charts and how they can assist in the differential diagnosis of behavioral symptoms see the RAP on behavior problems (soon to be known as behavioral symptoms); and

b. Which are persistent, and
c. Which are not caused by preventable reasons; and
d. Which are causing the residents to:
   (1) Present a danger to himself/herself or to others,
   (2) Continuously scream, yell, or pace if these specific behaviors cause impairment in functional capacity (to evaluate functional capacity, see S483.25. a) through k) and MDS sections B through P; MDS 2.0 sections B through P), or
   (3) Experience psychotic symptoms (hallucinations, paranoia, delusions) not exhibited as dangerous behaviors or as screaming, yelling, or pacing but which cause the resident distress or impairment in functional capacity; or

12. Short-term (7 days) symptomatic treatment of hiccups, nausea, vomiting, or pruritus. Residents with nausea and vomiting secondary to cancer or cancer chemotherapy can be treated for longer periods of time.

Antipsychotics should not be used if one or more of the following is/are the only indication;

- Wandering
- Poor self care
- Restlessness
- Impaired memory
- Anxiety
- Depression (without psychotic features)
- Insomnia
- Unsociability
- Indifference to surroundings
- Fidgeting
- Nervousness
- Uncooperativeness
- Agitated behaviors which do not represent danger to the resident or to others

Guidelines: S483.25(1)(2)(ii)

Residents must, unless clinically contraindicated, have gradual dose reductions of the antipsychotic drug. The gradual dose reduction should be under close supervision. If the gradual dose reduction is causing an adverse effect on the resident and the gradual dose reduction is discontinued, documentation of this decision and the reasons for it should be included in the clinical record. Gradual dose reductions consist of tapering the resident's daily dose to determine if the resident's symptoms can be controlled by a lower dose or to determine if the dose can be eliminated together.

Section F331

(ii) Residents who use antipsychotic drugs receive gradual dose reductions, and behavioral interventions, unless clinically contraindicated, in an effort to discontinue these drugs.

"Behavioral intervention" means modification of the resident's behavior or the resident's environment, including staff approaches to care, to the largest degree possible to accommodate the resident's behavioral symptoms.

"Clinically contraindicated" means that a resident NEED NOT UNDERGO a "gradual dose reduction" or "behavioral intervention" IF:

1. The resident has a "specific condition" (as listed under one through ten on page P-185 and has a history of recurrence of psychotic symptoms (e.g., delusions, hallucinations), which have been stabilized with a maintenance dose of an antipsychotic drug without incurring significant side effects);

2. The resident has organic mental syndrome (now called "Delirium, Dementia, and Amnestic and other Cognitive Disorders" by DSM-IV) and has had a gradual dose reduction attempted twice in one year and that attempt resulted in the return of symptoms for which the

drug was prescribed to a degree that a cessation in the gradual dose reduction, or a return to previous dose reduction was necessary; or

3. The resident's physician provides a justification why the continued use of the drug and the dose of the drug is clinically appropriate. This justification should include: (a) a diagnosis, but not simply a diagnostic label or code, but the description of symptoms; (b) a discussion of the differential psychiatric and medical diagnosis (e.g., why the resident's behavioral symptom is thought to be a result of a dementia with associated psychosis and/or agitated behaviors, and not the result of an unrecognized painful medical condition of a psychosocial or environmental stressor); (c) a description of the justification for the choice of a particular treatment, or treatments; and (d) a discussion of why the present dose is necessary to manage the symptoms of the resident. This information need not necessarily be in the physician's progress notes, but must be a part of the resident's clinical record.

Procedures: §483.25(1)(2)(i) and (ii)

In determining whether an antipsychotic drug is without a specific condition or that gradual dose reduction and behavioral interventions have not been performed, allow the facility an opportunity to justify why using the drug outside of the guidelines is in the best interest of the resident.

The facility can refer to a prescriber's (or appropriately trained health professional's) justification as a valid justification for the use of a drug. It may not justify the use of a drug, its dose, its duration, solely on the basis that "it was ordered" without supportive information.

If the survey team determines that there is a deficiency in the use of antipsychotics, cite the facility under either the unnecessary drug regulation or the antipsychotic drug regulation, but not both quality care tags.

APPENDIX F. GERIATRIC DEPRESSION SCALE

GERIATRIC DEPRESSION SCALE – SHORT FORM

1.	Are you basically satisfied with your life?	❍ Yes ❍ No*
2.	Have you dropped many of your activities and interests?	❍ Yes* ❍ No
3.	Do you feel that your life is empty?	❍ Yes* ❍ No
4.	Do you often get bored?	❍ Yes* ❍ No
5.	Are you in good spirits most of the time?	❍ Yes ❍ No*
6.	Are you afraid that something bad is going to happen to you?	❍ Yes* ❍ No
7.	Do you feel happy most of the time?	❍ Yes ❍ No*
8.	Do you often feel helpless?	❍ Yes* ❍ No
9.	Do you prefer to stay at home rather than going out and doing new things?	❍ Yes* ❍ No
10.	Do you feel you have more problems with memory than most people?	❍ Yes* ❍ No
11.	Do you think it is wonderful to be alive now?	❍ Yes ❍ No*
12.	Do you feel pretty worthless the way you are now?	❍ Yes* ❍ No
13.	Do you feel full of energy?	❍ Yes ❍ No*
14.	Do you feel that your situation is helpless?	❍ Yes* ❍ No
15.	Do you think that most people are better off than you are?	❍ Yes* ❍ No

* Each starred answer counts 1 point.
Scores of more than 5 points is suggestive of depression and warrant follow-up.

Source: Sheikh JI, Yesavage JA. Int Psychogeriatrics 1991; 3: 23-28.

APPENDIX G. RESOURCES

Administration on Aging
Public Affairs Office
Department of Health and Human Services
330 Independence Ave. SW.
Washington, DC 20201
(202) 401-4543
www.aoa.dhhs.gov

Family Caregiver Alliance
690 Market Street, Ste. 600
San Francisco, CA 94104
(415) 434-3388
www.caregiver.org

The National Institute of Neurological Disorders and Stroke
31 Center Drive, MSC 2540
Bldg. 31, Room 8A-06
National Institutes of Health
Bethesda, MD 20892-2540
(301) 496-5751; (800) 352-9424 (recording)
www.ninds.nih.gov/index.htm

Alzheimer's Disease Education and Referral (ADEAR) Center,
National Institute on Aging
P.O. Box 8250
Silver Spring, MD 20907-8250
(301) 495-3311; (800) 438-4380
www.alzheimers.org

National Family Caregivers Association
(800) 896-3650
www.nfcacares.org

Alzheimer's Association
919 Michigan Avenue, Ste. 1100
Chicago, IL 60611-1676
(800) 272-3900
www.alz.org

National Eldercare Locator
(800) 677-1116
www.aoa.dhhs.gov/elderpage/locator.html

National Center on Elder Abuse (NCEA)
1225 I Street, N.W., Ste. 725
Washington, DC20005
202-898-2586
www.elderabusecenter.org

American Association of Retired Persons (AARP)
601 E St., NW
Washington, DC 20049
800-424-3410
www.aarp.org

National Association of State Units on Aging (NASUA)
1225 I Street NW, Suite 725
Washington, DC 20005
(202) 898-2578
www.nasua.org

International Psychogeriatric Association (IPA)
550 Frontage Road, Ste 2820
Northfield, IL 60093
(847) 784-1701
www.ipa-online.org

American Geriatrics Society
The Empire State Building
350 Fifth Ave., Ste. 801
New York, NY 10118
(212) 308-1414
www.americangeriatrics.org

APPENDIX H. READING LIST

Epidemiology

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Chui HC, Mack W, Jackson E et al. Clinical criteria for the diagnosis of vascular dementia. A multicenter study of comparability and interrater reliability. Arch Neurol 2000;57:191-6.

Small GW, Rabins PV, Barry PP et al. Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. JAMA 1997;278:1363-71.

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Behavioral and psychological symptoms of dementia

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Available at http://www.ipa-online.net/ipaonline/

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General

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POST-TEST REVIEW

To receive 2.0 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association, please review this monograph carefully and answer the questions that follow. Answer ALL the questions. Complete the enrollment form and mail to ACCESS Medical Group, Department of Continuing Medical Education 3395 North Arlington Heights Road, Arlington Heights, Illinois 60004. Your corrected test, a copy of the answers, and a certificate of credit will be returned to you. Should you have any questions, call 847-392-2227.

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After completing the CME quiz and adding your personal information, please photocopy the answer sheet and evaluation form, and return it to Medical Outcomes Management, Inc, 132 Central Street, Suite 106, Foxborough, MA 02035. Credit can be awarded for submissions received through April 30, 2001. Thank you for participating in this program.

CME Post-Test

1. Which of the following accounts for the most cases of irreversible dementia in North America?
   a. Alzheimer's dementia
   b. Vascular dementia
   c. Lewy body dementia
   d. Parkinson's disease

2. Risk factors for dementia include:
   a. APOE4 gene
   b. Down's syndrome
   c. increasing age
   d. head trauma
   e. all of the above

3. Delirium differs from dementia in all of the following characteristics except:
   a. acute onset
   b. fluctuating course
   c. disorganized thinking
   d. altered consciousness
   e. none of the above

4. Worsening cognition and behavior are found in nursing facility residents with dementia when they experience a superimposed delirium. Which of the following are possible causes of delirium?
   a. infection
   b. hypoxia
   c. dehydration
   d. antipsychotic medications
   e. all of the above

5. Many of the problems faced by family caregivers in caring for individuals with dementia affect professional caregivers as well.
   a. true
   b. false

6. Which of the following behaviors are commonly observed in residents with dementia?
   a. verbal aggression
   b. physical aggression
   c. sexually inappropriate behavior
   d. all of the above
   e. none of the above
   f. a and b only

7. Underlying medical conditions should always be managed prior to initiating long-term medication therapy for dementia-related behavioral symptoms.
   a. true
   b. false

8. Which of the following statements is true regarding behavioral symptoms related to dementia?
   a. nonmedication methods of management should always be tried and can be very effective in minimizing behavioral symptoms.
   b. medication should always be tried first, as this will many times alleviate the symptoms.
   c. a combination of nonmedication approaches and medication is usually not very helpful.
   d. the living environment has little impact on the behavior of persons with dementia.

9. Which of the following non-medication interventions have been found to be useful in residents with dementia and behavioral symptoms?
   a. exercise program
   b. reduce excess stimulation
   c. eliminate caffeine and alcohol
   d. toileting schedule
   e. all of the above

10. When evaluating an agitated individual, it is critical to thoroughly describe the behavioral symptoms, so that appropriate treatment can be chosen.
   a. true
   b. false

11. The cholinesterase inhibitors are approved by the FDA for:
   a. vascular dementia
   b. mild to moderate dementia
   c. only severe dementia
   d. delirium associated with medical conditions
   e. All dementia

12. The atypical antipsychotics risperidone, quetiapine, and olanzapine, have what advantages over traditional antipsychotics?:
   a. lower sedation
   b. no extrapyramidal effects
   c. more effective in treating psychotic disorders
   d. all of the above
   e. none of the above

13. Possible side effects of benzodiazepines that may limit use in treating aggressive behavior include:
   a. confusion
   b. ataxia
   c. sedation
   d. memory disturbance
   e. all of the above

14. The class of antidepressants considered the safest for use in the elderly is:
   a. selective serotonin reuptake inhibitors
   b. tricyclic antidepressants
   c. monamine oxidase inhibitors
   d. heterocyclic antidepressants

15. For depressed residents with agitation but without psychotic symptoms, which of the following is an appropriate medication option for treatment (in addition to nonmedication interventions):
   a. SSRIs
   b. haloperidol
   c. lorazepam
   d. olanzapine

16. For a resident presenting with symptoms of mild anger, aggression aimed at other residents, and verbal aggression, possible long-term medication management may include:
   a. IM haloperidol
   b. divalproex
   c. buspirone
   d. sertraline
   e. b, c, or d
   f. none of the above

17. When encountering a resident with aggressive behavior and psychosis not adequately responsive to an atypical antipsychotic, adding another medication may be an appropriate strategy.
    a. true
    b. false

18. For some medications and some residents, determining response to therapy:
    a. is not needed. All patients respond to medication.
    b. may take up to 6 weeks to show full response.
    c. should be assessed at 1 week because response will be clear for all residents by then
    d. none of the above

19. The suggested upper limit for risperidone in the elderly is:
    a. 2 mg/day
    b. 0.5 mg/day
    c. 4 mg/day
    d. None of the above

20. The interaction between carbamazepine with clarithromycin may result in an increase in carbamazepine serum concentration.
    a. true
    b. false

21. Based on the HCFA long term care guidelines, antipsychotics should not be used if one or more of the following is/are the only indication:
    a. wandering
    b. anxiety
    c. insomnia
    d. agitated behaviors which do not represent danger to the resident or others.
    e. all of the above

22. Important resources for family members regarding care of a person with dementia include:
    a. the Alzheimer's Association
    b. the Administration on Aging
    c. the National Institute on Aging
    d. the Federal Bureau of Investigation
    e. a, b, and c

23. Aphasia, the loss or impairment of the power to use or comprehend words, may affect an individual's ability to:
    a. follow instructions
    b. participate in conversations
    c. express needs
    d. all of the above

24. A delusion is a false idea, sometimes originating in misinterpretation, but firmly believed and strongly maintained in spite of obvious proof or evidence to the contrary. To differentiate, a hallucination is a sensory experience where a person sees, hears, or feels something or someone that is not audible or visible to anyone else.
    a. true
    b. false

25. According to the HCFA Long Term Care Guidelines, antipsychotic drugs should not be used unless the clinical record documents that the resident has one or more specific conditions. All of the following conditions are included except:
    a. schizophrenia
    b. delusional disorder
    c. Tourette's disorder
    d. depression
    e. Huntington's disease



Release date: May 1, 2001
Expiration date: April 30, 2004

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Circle the correct answer for each question

Question							Question						
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2	a	b	c	d	e		15	a	b	c	d		
3	a	b	c	d	e		16	a	b	c	d	e	f
4	a	b	c	d	e		17	a	b				
5	a	b					18	a	b	c	d		
6	a	b	c	d	e	f	19	a	b	c	d		
7	a	b					20	a	b				
8	a	b	c	d			21	a	b	c	d	e	
9	a	b	c	d	e		22	a	b	c	d	e	
10	a	b					23	a	b	c	d		
11	a	b	c	d	e		24	a	b				
12	a	b	c	d	e		25	a	b	c	d	e	
13	a	b	c	d	e								

EVALUATION FORM
After reviewing this monograph and completing the post-test, to what degree are you able to do the following?
Scale: 1=Low, 5=High

1 2 3 4 5 Understand the basic pathophysiology of Alzheimer's disease and other dementias

1 2 3 4 5 Recognize dementia and understand diagnosis and staging of Alzheimer's disease and other dementias

1 2 3 4 5 Review the role of non-medication interventions as first-line management for behavioral symptoms of Alzheimer's disease and other dementias

1 2 3 4 5 Discuss the current pharmacotherapy of Alzheimer's disease, other dementias, and behavioral symptoms associated with dementia

1 2 3 4 5 Present a treatment plan for patients with newly diagnosed dementia or on-going behavioral and cognitive symptoms of dementia

Commercial Bias
Was the monograph free of commercial bias? ○ Yes ○ No
If no, indicate specific examples _____

Were brand names of drugs used in monograph? ○ Yes ○ No
If yes, indicate specific examples: _____

Other than acknowledgements, were pharmaceutical companies cited in monograph?
○ Yes ○ No
If yes, indicate specific examples: _____

What topics would you like to see in future programs? _____

How can we improve this monograph? _____

_____

_____

Would you recommend this monograph to a colleague? ○ Yes ○ No

How will the information from this monograph change your perspective in using these agents?

_____

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General comments on this monograph. _____

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RAPID REFERENCE

Purpose of This Guide
Background
Section 1: When To Screen For Dementia
Section 2: Initial Clinical Assessment
Section 3: Treatment of Alzheimer's Disease
Section 4: Behavioral Symptoms Associated With Dementia
Section 5: Non-Medication Treatment Of BPSD
Section 6: Medication Treatment Of Agitation
Monitoring Response to Medication Treatment
Changing Therapy Based on Response
Dosing Guidelines
Side Effect Profiles
Available Dosage Forms
Generic/Brand Names of Psychotherapeutic Medications
Common Medication Interactions
Appendix A. Glossary
Appendix B. The Zarit Burden Interview
Appendix C. Behavioral Descriptors
Appendix D. Criteria For Delirium And Dementia
Appendix E. Nursing Home Surveyor Guidelines
Appendix F. Geriatric Depression Scale
Appendix G. Resources
Appendix H. Reading List

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Subject:CME Dissemination Pieces Top Line & Quizzes

LTC District Managers:

Over the next several weeks we will be shipping several CME Pieces to your representatives that have been approved for dissemination. Per our conference call, April 17, I am attaching the Top Line and Quiz for the Larry Tune Video and The Pocket Reference Guide. I am requesting that each of you redirect this e-mail and attachments on to each of your district members for receipt no latter than Friday, May 3, 2002. Per our discussion, I am requesting that each of your representatives review the Tune Video, the accompanying Reference Guide, the Pocket Reference Guide and the attached Top Line Review and complete the two quizzes no latter than Friday, May 10, 2002. I would like your representatives to complete the two quizzes and e-mail me the answers only by close of business Friday, May 10, 2002. Given that these quizzes are essentially an open book quiz, the expectations should be that the representatives should score very well. These quizzes will be in addition to the formal 50 question test, on the six selected proof sources, that will be given at the RM/DM and District Meetings. If any of your representatives will be unable to receive e-mail or will be out of their territories please notify me via e-mail and please make alternate arrangements for those representatives. If you should have any questions, please feel free to contact me.

Thanks,

REDACTED
RTS Long-Term Care

Top Line Review
Reviewed by: REDACTED

Title: A Pocket Guide To Dementia and Associated Behavioral Symptoms: Diagnosis, Assessment, And Management. First Edition

Editors: Steffan Gravenstein, MD, MPH, John Franklin, H. Edward Davidson, PharmD, MPH

Publication: Insight Therapeutics, LLC

Funding: This program is sponsored by an unrestricted educational grant from Abbott Laboratories.

CME: ACCESS Medical Group Department of Continuing Education, Arlington Heights, Illinois. 2.0 credits of category 1 of the Physician's Recognition Award of the AMA. Medical Outcomes Management has provided 0.2 CEU's (2.0 contact hours) for pharmacists.

Target Audience: An easy-to-use reference for health care professionals managing patients with dementia.

Educational Objectives: Understand the basic pathophysiology of Alzheimer's disease and other dementias. Understand the diagnosis and classifications of AD, the role of non-medication interventions and the role of pharmacotherapy for AD, dementia and behavioral disturbances associated with dementia.

Context: Autopsy studies indicate that Lewy bodies are in 15%-25% of all cases or elderly demented patients. The use of neuroleptics in patients with DLB should be carefully considered due to characteristic neuroleptic sensitivity. (Pg. 9) A component of the (MMSE) is mood. (Pg. 18) Divalproex is recommended first line (long-term treatment) for agitation associated with mild anger, without aggression. Divalproex is recommended first-line (long-term treatment) for agitation associated with severe anger with aggression. (Pg. 41) Divalproex is recommended alternative treatment (long-term treatment) for agitation associated with psychosis. (Pg. 43) Divalproex is recommended first line treatment (Acute & Long-term treatment) for "Sundowning". (Pg. 44) Divalproex is considered adjunctive therapy for antipsychotics, conventional or atypical and benzodiazapines. (Pg.48) Also, it is recommended that 3-6 weeks be a reasonable period of time to assess the efficacy or Divalproex. (Pg. 48) In addition, the algorithm on page 49 illustrates this same information. The dosing guidelines recommends Divalproex starting at 125mg bid every 3-5 days to a maximum dose of 750-2000 mg/day. (Pg. 50) Side effect profile of Divalproex and other medications can be reviewed. (Pg. 51-52) Available dosage forms are listed for Divalproex and can be reviewed. (Pg. 52-53) Divalproex and the common drug interactions are listed for

review. (Pg. 58) Also, there is a good glossary of terms and explanation of currently used behavioral rating scales listed in the back of the guide. (Pg. 59-79)

Discussion: This is an excellent resource that can be used to provide credit for physicians and pharmacists who are looking for additional continuing education credits. Also, there is some useful information that can offer guidance for clinicians on their use of pharmacotherapy to treat agitation and aggression in dementia.

QUIZ

A Pocket Guide To Dementia And Associated Behavioral Symptoms: Diagnosis Assessment And Management. First Edition

1. T or F This Pocket Guide offers continuing education to nurses.

2. T or F Alzheimer's disease is the major cause of dementia

3. The use of neuroleptics should be used (especially) careful with which type of dementia

    a. Lewy Body
    b. Alzheimer' disease
    c. Vascular dementia
    d. None of the above

4. T or F a Clock drawing tests can be used to determine the level of cognitive impairment in dementia patients

5. T or F during stage 5 of AD a patient is thought to be in a moderate stage of Alzheimer's disease

6. Divalproex is recommended for all of the following except.

    a. Alternative therapy (Long Term) for agitation associated with psychosis
    b. First line (Long Term) for insomnia and agitation
    c. First line (Acute) for "Sundowning"
    d. All of the above

7. Divalproex is recommended for a trial of how long to measure response to medication
    a. 1-2 weeks
    b. 2-4 weeks
    c. 3 months
    d. None of the above

8. Dosing ranges for Divalproex is recommended at
    a. 500-1500 mg/day
    b. 600-1725 mg/day
    c. 125-500 mg/day
    d. None of the above

9. T or F weight gain is not listed as a side effect of Divalproex

10. Valproic Acid levels may be increased when administered with which of the following drugs
    a. Phenytoin
    b. Heparin
    c. Barbiturates
    d. None of the above

11. A false idea, sometimes originating in misinterpretation, but firmly believed and strongly maintained in spite of obvious proof or evidence to the contrary is know as
    a. Delusion
    b. Dementia
    c. Delirium
    d. None of the above

12. HCFA interpretive guidelines section entitled "Antipsychotic Drug Dosage Levels" is known as
    a. Tag 329
    b. Tag b52
    c. Tag F330
    d. None of the above

13. Antipsychotics should not be used if the patient (only) exhibits which of the following symptoms
    a. Uncooperativeness
    b. Restlessness
    c. Depression (without psychosis)
    d. All of the above

14. T or F Gabapentin is recommended as Alternative therapy (Long Term) for agitation associated with mild anger, without aggression.

15. T or F MMSE Mini-Mental Status Exams are given to determine the patients cognitive function

Top Line Review
Reviewed by: REDACTED

Title: The Role of Mood Stabilizers in Treating Agitation: A Continuing Education Activity for Physician's, Pharmacists and Registered Nurses. A Case Study Video And Reference Guide

Authors: Larry Tune, MD, Lori Daiello, PharmD, Kay Lloyd, RNC, BSN, Andrew Weinberg, MD, CMD, FACP

Publication: ABCOMM Inc., Champaign, Illinois

Funding: Supported by an unrestricted educational grant from Abbott Laboratories.

CME: 2 hours of category 1 credit towards the AMA Physician's Recognition Award. 2 Contact hours (0.2 CEU's) for pharmacists and 1.3 contact hours for nursing.

Target Audience: Physician's, pharmacists and nurses who would like more information and continuing education of the role of mood stabilizers in treating agitation.

Purpose and Objectives: To describe the symptomology and evaluation of agitated and aggressive behaviors in dementia. Also, discuss non-pharmacological interventions as well as the role of mood stabilizers in for the treatment of agitation and aggression in dementia.

Context: The case studies in the accompanying video demonstrate that memory and judgment become increasingly impaired as individuals transition from mild to moderate and severe dementia, and thus exhibit more behavioral and psychiatric symptoms, specifically agitation and aggression. (Pg. 5) Table 1 on page 7 gives a nice illustration of a clinical assessment of agitation while Table 3 on page 9 gets more specific about defining behavioral management. It is helpful to classify behavioral and psychiatric symptoms associated with dementia (psychosis, mania/mood features, anxiety) (Pg. 10) Anticonvulsants are an option for "nonspecific" agitation and agitation presenting with affective features. (Pg. 10) Further, it is important to remember than disorders such as depression and psychosis may coexist, warranting combination therapy. (Pg. 10) There is also an in depth technical analysis of the neuropotective effects of mood stabilizers such as divalproex. (Pg. 10) The use of antipsychotic drugs to treat anxiety, restlessness, or even agitation, in the absence of psychotic features, is no longer considered appropriate, (Pg. 11) Currently, the OBRA guidelines do not mandate dosage guidelines or dose reductions for mood stabilizers in the treatment dementia-related behavior symptoms. (Pg. 11) Table 4 on page 12 and 13 shows where mood stabilizers are

recommended. Table 5 on page 14 and 15 discusses the dosage, formulation, and adverse effects of divalproex as-well-as other medications used to treat behavior. In the case of divalproex, federal nursing home guidelines do not require serum drug level monitoring. However, obtaining a serum valproate level may be helpful if a significant change in a resident's behavior or if clinical symptoms, such as excessive bruising, are observed. (Pg. 16) Table 6 on page 17 discusses the potential drug interactions of divalproex and other medications used to treat behavior. (Pg. 17)

Discussion: The reference guide to the video would be an excellent tool for selling an in-service or viewing for participants wanting additional information or continuing education of the role of mood stabilizers in treating dementia. However, I think viewing the video, in part or in totality, offers a much better educational benefit. Furthermore, Dr. Tune, Dr. Weinberg and Lori Daiello all share their clinical experience using divalproex sodium to treat behavioral problems in dementia patients. Also, it is beneficial to see the case studies and listen to the dialogue that goes on between the clinicians.

QUIZ

The Role of Mood Stabilizers in Treating Agitation: A Continuing Education Activity for Physician's, Pharmacists and Registered Nurses. A Case Study Video And Reference Guide.

1. Each year the treatment costs for dementia in the U.S. alone are?
   a. $100 billion
   b. $100 million
   c. $500 million
   d. None of the above

2. T or F This program is designed to assess behavioral and psychological symptoms in patients with dementia and discuss treatment of agitation and aggression in the long-term care setting.

3. Which of the following is a part of the healthcare team

   a. Physicians
   b. Pharmacists
   c. Family
   d. All of the above

4. T or F Sleep assessment is part of the clinical assessment of agitation.

5. T or F Cholinesterase inhibitors may be effective in treating behavioral and psychiatric symptoms

6. T or F. OBRA guidelines mandate the dosage and titration of mood stabilizers

7. T or F Lori Daiello suggests that you would probably not see LFT values change in dementia patients.

8. T or F Lori Daiello recommends that a base line LFT test be taken

9. What is the dosage range for divalproex recommended by the reference guide

   a. 250-500 mg/day
   b. 750-2000 mg/day
   c. 1000-1500 mg/day
   d. None of the above

10. Valproate levels may be increased by which of the following medications
    a. Aspirin
    b. Felbamate
    c. None of the above
    d. All of the above

REDACTED - Long Term Care Pharmacy Provider "LTCPP"

February 9, 2004

REDACTED - Abbott's Long Term Care - National Account Manager "LTC-NAM"

Abbott Laboratories, Inc.
REDACTED - LTC-NAM
National Account Manager
REDACTED

Dear REDACTED - LTC-NAM

As we continue to partner together for the benefit of our nation's elderly, we find the need to request the support of our stronger partners in order to offer high quality educational programs to our colleagues, patients, and customers.

REDACTED - LTCPP's second quarter focus will be on behavior management in long-term care. Therefore the purpose of this letter is to request funding for a restricted medical education grant in the amount of $16,250. This grant will be used to fund a targeted national educational mailer to the top 4000 prescribers of atypical antipsychotic and the top 1000 prescribers of benzodiazepine medications in long-term care. The value of this mailer will be to educate physicians on the benefits of using alternative methods to control difficult behaviors. The budget of this program includes:

- Data query and manipulation $1562.50
- Sequential addressing and materials sorting $625.00
- Labor; Copying; Material duplication and assembly $5625.00
- US Postage, logo envelopes $6250.00
- Oversight & Planning $2187.50

I'm sure that Abbott Laboratories will find significant value and merit in supporting these efforts.

We thank you for this opportunity to partner with Abbott Laboratories.

Sincerely,

REDACTED - LTCPP's National Director of Clinical Program Development "LTCPP-NDCPD"

National Director of Clinical Program Development
REDACTED - LTCPP
REDACTED ext. REDACTED
REDACTED - LTCPP-NDCPD @REDACTED - LTCPP.com
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Abbott Grant Req mailer 2-04

REDACTED - LTCPP

EDUCATIONAL GRANT ORIGINATION SHEET

DATE ON CHECK: 3-5-04

PHARMA OR COMPANY SPONSOR: Abbott Labs

TARGETED DISEASE OR TOPIC: Mailing - ~~#~~ Antipsychotic/Benzo

EXPECTED CLOSE DATE:* 3-5-05
*Default will be 12 months from opening

GRANT NUMBER: _____

GL ACCOUNT: REDACTED

ORIGINAL GRANT AMOUNT: $ 16,250

ORIGINATING PHARMACY OR DEPARTMENT: Clinical

CONTACT PERSON/ PHONE #: REDACTED - LTCPP-NDCPD

MANAGING DEPARTMENT: (Circle One)

AMBULATORY (CLINICAL) CONSULTING HOSPITALS IV / HCP

* Authorized Signer below must match with the Department

APPROVAL: REDACTED - LTCPP-NDCPD

Last Updated: 1/10/02 by LPF

ANS'D MAR 19 2004

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REDACTED - LTCPP

January 2004

Dear Health Care Professional:

As you are aware, REDACTED - LTCPP has developed a geriatric-specific drug formulary. We would like to share some important information about our Select Formulary with you. Our preferred pharmaceutical products are selected through a three-tier evaluation process that begins with review by an expert external national Pharmacy and Therapeutics (P&T) Committee. Based on the P&T Committee's evaluation and further analysis of pharmacoeconomic and cost data, REDACTED - LTCPP selects the most appropriate products for elderly residents to include within the Select Formulary.

Depakote and its derivatives have FDA approval for a variety of indications including bipolar disorder, seizure disorders, and migraine headache prophylaxis. In addition to these uses, Depakote and Depakote-ER are being used with increasing frequency to treat/manage agitation, anger, and hostility associated with dementia in the elderly. For elderly residents requiring therapy for a dementia related behavior disorder, **Depakote ER®** has been granted preferred status on the REDACTED - LTCPP's formulary. Depakote ER® is a logical cost-effective choice for treating elderly patients with these challenging behavioral symptoms.

Depakote ER® should be considered for patients with dementia related behaviors including:

- Initial therapy for patients with agitation anger, and hostility symptoms
- Adjunctive therapy for patients partially responsive to an atypical antipsychotic (antipsychotic can be tapered to a lower dose or eliminated after stabilization of behaviors)
- Replacement therapy for patients receiving benzodiazepines

- **Depakote ER®** can be dosed once daily and has improved side effects profiles vs the original Depakote DR (delayed release) with significant decreases in sedation and gastrointestinal complaints.

- **Depakote ER®** 500mg costs less than equivalent doses of the original Depakote DR (delayed release) with additional pharmacoeconomic savings in decreased med-asses and increased quality of life.

- Use of **Depakote ER®** instead of atypical antipsychotics and benzodiazepines can also positively impact the nursing facilities Quality Indicator Report.

Physician prescribing in compliance with the formulary can maintain or improve resident outcomes while containing costs. This also will minimize the number of calls and interventions from nursing and pharmacy to change prescriptions to formulary-preferred drugs. We appreciate your support of these formulary preferences for our long-term care patients.
Enclosed you will find complete prescribing information that will be helpful.

If you have any questions, please contact the REDACTED - LTCPP consultant pharmacist in the facility where you practice.

Sincerely,

REDACTED - LTCPP-NDCPD

National Director of Clinical Program Development
Chair, P&T Liaison Committee

Disclaimer: Information contained in this letter is for general guidelines only. Prescribing and dosing should be based on individual patient conditions. Portions of the accompanying literature have been supported by an unrestricted educational grant from Abbott Laboratories.

REDACTED - LTCPP

Divalproex Sodium Extended-Release (Depakote® ER, Abbott)

Preferred Extended-Release Divalproex

WHY DEPAKOTE® ER IS OUR PREFERRED DIVALPROEX OF CHOICE:

Depakote® ER (extended-release divalproex sodium) is a new formulation of divalproex sodium which is dosed once daily. At therapeutic doses, it has been shown to have significantly less somnolence and fewer adverse G.I. effects than all other valproate formulations while delivering more stable blood levels. Tolerability of Depakote ER is superior to the older products (refer to full prescribing information for specifics – available upon request).

Current indications of Depakote ER are as follows[1]:

Monotherapy and adjunctive therapy in complex partial seizures in adults
Monotherapy and adjunctive therapy in simple and complex absence seizures in adults
Migraine prophylaxis

Non-FDA-approved indications of valproic acid and divalproex sodium include agitation and aggression of dementia[2-5]. Depakote delayed-release carries the indication for mania and bipolar disorder. Current studies to evaluate the effectiveness of Depakote ER for such indications are ongoing.[6]

GERIATRIC USE:

- The most common use for Depakote ER and Depakote in the elderly is to manage agitation and aggression secondary to dementia. Consideration should be given to the effects of reduced protein binding in the elderly. This can result in an increase in the free fraction in plasma.
- Dosing for behaviors in dementia is different from that used for acute manic episodes or seizures. For behaviors, the best approach is to start low and go slow. As with all valproate formulations, Depakote ER dose should be individualized based on patient response.
- Extended release tablets should be swallowed whole and not crushed, cut or split. For nursing home residents who cannot swallow well or who use a PEG tube, consideration can be given to using Depakote Sprinkle caps.

EQUIVALENT ORAL DOSING GUIDELINES: The average bioavailability of Depakote ER given once-daily (fasting or before meals) was 81-89% relative to original Depakote delayed-release tabs given BID on a mg for mg basis. Dosing adjustments may be required when switching patients from original Depakote delayed-release tablets to Depakote ER. Such conversions are handled differently for patients with behaviors of dementia vs. control of seizures, mania, bipolar, or migraine prophylaxis. Dosing for behaviors is generally based on patient response rather than blood level, making a mg for mg conversion less important than providing a dose which improves the resident's functional status.

	DOSE CONVERSION	
INDICATION	**Prescribed Drug: Depakote®**	**Depakote Extended-Release (Depakote ER) given once daily**
Agitation and Aggression 2nd to Dementia	250 mg	**250 mg**
	375	**500**
	500	**500**
	625	**750**
	750	**750**
	875	**1000**

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REDACTED - LTCPP

Divalproex Sodium Extended-Release (Depakote® ER, Abbott)

Preferred Extended-Release Divalproex

CONVERSION WHEN USED FOR SEIZURE DISORDERS:
Depakote ER carries an indication for monotherapy and adjunctive therapy in complex partial seizures in adults and monotherapy and adjunctive therapy in simple and complex absence seizures in adults.

In clinical practice, some epilepsy patients will be converted from Depakote DR to Depakote ER. REDACTED - LTCPP supports this conversion provided that stable patients (i.e. those without seizure for 6 months) are evaluated first for stable plasma valproic acid levels. Then with that baseline level, a corresponding dose of Depakote ER can be selected, with a repeat plasma level in one to two weeks and adjusting the Depakote-ER regimen based on the follow-up lab data.

	DOSE CONVERSION	
INDICATION	Prescribed Drug: Depakote®	→ Depakote Extended-Release (Depakote ER) given once daily
Seizure Disorders[1,7] (monotherapy or adjunctive)	1000 mg	1250 mg
	1250-1375	1500
	1500-1625	1750
	1750	2000
	1875-2000	2250
	2125-2250	2500
	2375	2750
	2500-2750	3000
	2875	3250
	3000-3125	3500
Migraine Prophylaxis	250mg BID, titrate as needed up to 500mg BID	250 - 500mg once daily x 1 week minimum, thereafter titrating to 1000mg once daily if needed.

DOSAGE FORMS
Depakote ER is available in 250mg and 500mg tablets.

Supporting References:
1. Depakote ER P.I. Abbot Laboratories. North Chicago, IL. Rev 06.2002.
2. Clinical Pharmacology 2000 v.2.0.6. Electronic version. Accessed 01.2003
3. Lackner TE. Strategies for Optimizing Antiepileptic Drug Therapy in Elderly People. Pharmacotherapy. 2002;22(3):329-364.
4. Gardner ME, Ditmanson LF, Garrett RW, Slack M. Effectiveness of Divalproex Sodium in Severe Dementia-Related Aggression. *The Consultant Pharmacist.* 2001;16(9):839-843.
5. Alexopoulos GS et al (eds.) The Expert Consensus Guideline Series: Agitation in Older Persons with Dementia. A Postgraduate Medicine Special Report. April 1998. McGraw-Hill.
6. Centorrino F, Kelleher JP, Berry JM, et al. A Pilot Study of Extended Release Divalproex Sodium Switch from Standard Formulation of Divalproex Sodium in Maintenance Treatment of Bipolar Disorder and Schizoaffective Disorder, Bipolar Type. Paper presented at 42nd Annual New Clinical Drug Evaluation Unit (NCDEU) Meeting. Boca Raton, FL: 2002 June 10-13.
7. Uthman BM, Biton V, Dutta S, et al. Comparison of the Bioavailability of a Depakote Extended-Release Formulation Relative to the Depakote Delayed-Release Tablet Formulation in Adult Patients with Epilepsy on the Depakote Delayed-Release Tablet Formulation and an Enzyme-Inducing Antiepileptic Drug. Information on file at Abbott Laboratories.

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REDACTED - LTCPP

Divalproex Sodium Extended-Release (Depakote® ER, Abbott)

Preferred Extended-Release Divalproex

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Divalproex Sodium Use in the Elderly: A New Formulation Offers New Opportunities

The use of anticonvulsant medications for a variety of indications is commonplace in nursing facilities. Divalproex sodium is used for migraine headaches, bipolar disease, and behavioral disorders associated with head trauma, mental retardation, and dementia. It also is used for the management of seizures. The new formulation of divalproex (Depakote ER) may offer some new opportunities for use in nursing facility residents.

The average long-term care facility resident (patient) of today is often sicker, receives more medication, and is more prone to manifesting medication side effects and interactions. Comorbidities such as Parkinson's disease, seizure disorders, and variant forms of dementia such as Lewy body dementia are common. These comorbidities affect on drug selection and increase the risk of serious side effects from commonly prescribed medications for behavioral symptoms: Side effects may include worsening of motor function, increased seizure rate, and falls.

Antipsychotics remain the preferred agents for the treatment of the symptoms of psychosis including hallucinations, harmful delusions, and paranoia. However, antipsychotics do not appear to offer significant advantages over divalproex sodium when treating mood disorders, including those associated with abnormal aggression and idiopathic agitation. The case series by Goldberg reported a 54% "much or more improved" Global Rating Scale, with an additional 18% "minimal improved" level of behavior in 22 elderly demented residents who failed to respond to eight weeks of 2 mg to 4 mg of risperidone.[1] The divalproex sodium dose was typical for such studies and ranged between 375 mg to 1,500 mg per day, with a mean serum level of 67.2 g/mL. The author also noted the subsequent reduction of other prescribed psychoactive medications, including trazodone, anticonvulsants, benzodiazepines, and antipsychotics. Although the results are observational, the results may have implications for addressing the issue of polypharmacy and for reducing the time for nurses to administer medication.

Although antipsychotics remain effective medications for the treatment of psychotic and possibly other symptoms of dementia, there are growing concerns over potential adverse effects. Concerns exist over the impact of antipsychotics on movement disorders, sedation, orthostatic hypotension, and control of blood glucose. Recently, preliminary analyses suggest the potential of atypical antipsychotics to increase the incidence of cerebrovascular adverse events (i.e., transient ischemic attacks and strokes). It is important to note that the clinical significance of these observations is hotly debated. These concerns have increased interest in alternative drug therapies with different safety profiles for treating behavioral and psychological symptoms of dementia.

One such class of medications is the mood stabilizers (e.g., carbamazepine, divalproex, gabapentin). Although mood stabilizers such as divalproex sodium have significant side effect profiles, clinicians have had time to develop effective dosing and monitoring strategies to minimize their occurrence and clinical impact. A recent double-blind, randomized, multicenter study reported the experience of divalproex sodium as an adjuvant with risperidone and olanzapine in the treatment of schizophrenic patients.[2] These results suggest a possible additional benefit in the elderly demented resident who does not optimally respond to antipsychotics alone. The improvement in symptom control may also provide an opportunity to reduce antipsychotic dosages.

Valproic acid, as an immediate-release, short-acting compound has seen limited use because its frequent dosage administration schedule and frequently occurring side effects of nausea, somnolence, and weight gain. These troublesome side effects appear to be associated with the more frequent peaks in the serum levels inherent in the shorter-duration valproic acid. Sedation in the elderly may increase the risk of falls and interfere with the normal activities of daily living (ADLs). Gastrointestinal upset, nausea, and vomiting may lead to the use of additional gastrointestional medications for symptomatic relief. Although not life-threatening, these side effects can lead to reduced compliance, diminished efficacy, and/or reduced quality of life for the patient.

Because of wide variation in serum level peaks and valleys with valproic acid, interpretation and timing of serum level samples is more difficult. In this respect, once-a-day Depakote ER, with its steady, flat serum level curve, has an advantage over valproic acid and the 12-hour Depakote or Depakote Sprinkle, with their two peaks per day. Side effects such as som-

Attachment 12 to Agreed Statement of Facts
Case 1:12-cr-00026-SGW Document 5-14 Filed 05/07/12 Page 9 of 24 Pageid#: 432

nolence, nausea, vomiting, and weight gain are associated with the peaks of the serum levels and is significantly lessened when using Depakote ER.

Valproic acid's frequent dosing also increases the time needed for nurses to administer the drug and the opportunities for medication errors. Divalpoex sodium was developed in part to reduce the number of daily doses, thus improving compliance and reducing side effects and medication administration time. By comparing the package insert data, this sustained-release formulation resulted in about a 50% reduction in GI and central nervous system side effects. The tablet offers twice-a-day or every 12-hour dosing. Depakote also is available as Depakote Sprinkles, a sustained release product for twice-a-day or every 12-hour dosing. The Sprinkle capsule can be opened for use by residents who cannot swallow or have feeding tubes.

Depakote ER 500 mg was originally released with an indication for treatment of migraine headaches. The low incidence of side effects plus once-a-day dosing of 500 mg to 1,000 mg proved effective and well tolerated by migraine headache sufferers.[1] Recent-ly, Depakote ER was released in 250 mg strength, with an additional indication for use in seizure disorders. When only the 500-mg strength was available, the recommended gradual titration used in the elderly with behavioral disorders had to be carried out with Depakote tablets or Sprinkle, followed by a subsequent conversion to Depakote ER. Gradual titration is important in the elderly to limit the incidence of somnolence and other side effects.

The complexity with later conversion, especially in seizure patients, is compounded by the lack of bioequivalence between the two products. The bioequivalence issue results from an 11% to 19% lower serum level of valproic acid associated with Depakote ER than with Depakote. Although this difference is likely to be clinically insignificant when Depakote ER is used to control mood or behavior, it should be taken into account when converting from Depakote tablets to Depakote ER in a seizure patient. A dosing conversion table is shown in Table 1.

The degree of difference in serum levels is related to administration of Depakote ER with food. Depakote ER, under fasting and non-fasting conditions, given once daily produced an average bioavailability of 85% relative to an equal total daily dose of Depakote tablets given bid.[3]

The introduction of a lower strength of Depakote ER (250 mg) permitted the more gradual dosage titration recommended in the elderly with seizures or mood/behavior disturbances. Based on clinical experience, the maintenance dose for control of behaviors in most elderly residents will be between 500 mg and 1500 mg Depakote ER at bedtime. For the frail elderly, Depakote ER 250 mg administered at bedtime is the recommended starting dose, with an increase of 250 mg every five to seven days, based on response and presence of side effects. In less-frail elderly patients, a starting dose of 500 mg at bedtime may be appropriate, increasing the dose every five to seven days by 250 mg at bedtime.

TABLE 1. DOSE CONVERSION FROM DEPAKOTE TO DEPAKOTE ER

Depakote Total Daily Dose (mg)	Depakote ER (mg)
500 – 625	750
750 – 875	1000
1000 – 1125	1250
1250 – 1375	1500
1500 -1625	1750
1750	2000
1875 – 2000	2250
2125 – 2250	2500
2375	2750
2500 – 2750	3000
2875	3250
3000 – 3125	3500

Adapted from reference 3.

There is no information from well-designed clinical trials to suggest a target serum concentration range for divalproex in the treatment of behavioral symptoms in patients with dementia. The valproic acid level associated with control of behavior, however, is thought to be less than that required for seizure management. Seizure therapeutic ranges on laboratory reports may actually be misinterpreted as those required for behavior control by clinicians and state surveyors alike. Serum levels are useful to rule out high levels as a cause of toxicity and to help investigate reasons for

lack of benefit with normal dosage schedules. In the latter case, serum levels may detect noncompliance, drug interactions, and other causes of unexpected outcomes. For patients with dementia, the American Psychiatric Association recommends gradual dose increases based on behavioral response and side effects or until blood levels reach 50 mcg/mL to 60 mcg/ml for valproate[4].

Divalproex sodium and valproic acid carry additional side effect risks including thrombocytopenia. Although the risk for significant thrombocytopenia (<90,000/mm³) is small and often transient, a baseline complete blood count with a repeat count in four weeks to eight weeks is recommended when initiating therapy. Small decreases in platelet counts need to be assessed for the possibility of a dilutional effect. The risk of hepatotoxicity is seen most commonly in children less than two years of age with mental retardation and receiving multiple anticonvulsants. In older adults, the risk of hepatotoxicity is 1 per 118,000.[5] A baseline liver function panel, with a repeat in four weeks, is recommended. Subsequent liver function studies are ordered based on these preliminary findings or at six-month intervals. A suggested approach is to follow alanine aminotransferase (ALT) and intensify monitoring if the ALT rises more than three times the baseline. Ammonia levels are typically not obtained since false positives are common and liver function studies would need to be obtained to verify the clinical importance of an elevated ammonia level.

Divalproex sodium-induced tremors are associated with higher doses than commonly used to treat behavioral disturbances. Tremors, in my experience, if they occur, can usually be controlled with a beta-blocker, such as propranolol. Hemorrhagic pancreatitis was identified as a rare, but potentially serious, side effect at the time of the original submission to the Food and Drug Administration in 1985. Two cases occurred in the study population of 2,416 for an incidence rate of <1%. The side effect can occur up to two years into therapy and can be life threatening. The unpredictability and rarity of the side effect makes random amylase levels cost-ineffective. Amylase levels should be obtained when pancreatitis is suspected or when the gastrointestinal symptoms of pancreatitis, which are quite severe, are observed.

Divalproex sodium also has been widely accepted for treating a broad range of seizure disorders. Although the recommendation to convert seizure residents with newly diagnosed behavioral symptoms from their existing anticonvulsant therapy (i.e., phenytoin, carbamazepine, etc.) to Depakote ER would seem justified, in practice it is often challenging. Resistance is more common if the seizure disorder is under control. The consultant pharmacist may find greater acceptance to a conversion or consolidation of therapy if the seizure control is not adequate or if the treatment of seizures is just being initiated. The consultant pharmacist may need to work with the consultant neurologist, if one is involved in the resident's care. In these situations, the consultant pharmacist needs to carefully plan for gradual conversion and titration of medication as recommended in the package inserts. The pharmacist also should thoroughly screen for drug interactions, anticipating and explaining their significance to the prescriber. Often the interactions will affect the results and interpretation of the anticonvulsant serum levels.

In closing, Depakote ER offers an alternative medication for the control of behaviors commonly associated with dementia in the elderly. Mood-stabilizing agents have been included as alternatives to other psychoactive medications for the management of behavioral and psychological symptoms of dementia in several published guidelines. These include the International Psychogeriatric Associations Educational Pack on behavioral and psychological symptoms of dementia and in the American Family Physicians Guidelines for the management of dementia (see Table 2). Its lack of negative effects on dopamine and seizure threshold provides a unique opportunity for the drug's use in treating behavioral or mood disorders associated with Parkinson's disease, Lewy body dementia, and in behavioral-problem patients with seizure disorders. The once-a-day convenience of the dosage form combined with the improved safety profile makes Depakote ER a useful agent for first-line treatment as well as complimenting existing therapy for non-psychotic symptoms in dementia such as aggression, mania, idiopathic agitation, mood disorders, and bipolar-disease disease. Its value in the co-administration with atypical antipsychotics in schizophrenic patients suggests a benefit in treating

TABLE 2. MOOD-STABILIZING (ANTI-AGITATION) DRUGS IN ALZHEIMER'S DISEASE

Recommended uses: control of problematic delusions, hallucinations, severe psychomotor agitation, and combativeness; useful alternatives to antipsychotic agents for control of severe agitated, repetitive, and combative behaviors

General cautions: See comments about specific agents.

Trazodone (Desyrel)	*Initial dosage*: 25 mg per day; Maximum: 200 mg to 400 mg per day in divided doses	*Comments*: Use with caution in patients with premature ventricular contractions.
Carbamazepine (Tegretol)	*Initial dosage*: 100 mg twice daily; titrate to therapeutic blood level (4 mcg to 8 mcg per mL)	*Comments*: Monitor complete blood cell count and liver enzyme levels regularly; carbamazepine has problematic side effects and drug interactions.
Divalproex sodium (Depakote)	*Initial dosage*: 125 mg twice daily or Depakote ER 250 mg at bedtime; titrate to therapeutic blood level (40 mcg per mL to 90 mcg per mL)	*Comments*: Generally better tolerated than other mood stabilizers; monitor liver enzyme levels; monitor platelets, prothrombin time, and partial thromboplastin time as indicated.

Adapted from Reference 6.

of those only partially responding to antipsychotics or experiencing dose-related side effects. Opportunities to consolidate therapy of co-existing disorders with once-a-day therapy offers occasion to address the issues of polypharmacy and long medication pass times while simplifying the drug regimen with a relatively low cost, well-understood medication.

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President TCS Pharmacy Consultants
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Package insert

(Nos. 3826 and 7126)
03-5235-R4-Rev. January, 2003

DEPAKOTE® ER

DIVALPROEX SODIUM EXTENDED-RELEASE TABLETS

℞ only

IN PATIENTS RECEIVING
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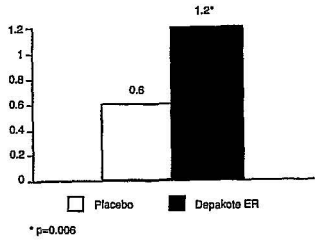
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Figure 1
Mean Reduction In 4-Week
Migraine Headache Rates



* p=0.006

Epilepsy

The efficacy of DEPAKOTE in reducing the incidence of complex partial seizures (CPS) that occur in isolation or in association with other seizure types was established in two controlled trials using DEPAKOTE (divalproex sodium delayed-release tablets).

In one, multiclinic, placebo controlled study employing an add-on design, (adjunctive therapy) using DEPAKOTE, 144 patients who continued to suffer eight or more CPS per 8 weeks during an 8 week period of monotherapy with doses of either carbamazepine or phenytoin sufficient to assure plasma concentrations within the "therapeutic range" were randomized to receive, in addition to their original antiepilepsy drug (AED), either DEPAKOTE or placebo. Randomized patients were to be followed for a total of 16 weeks. The following table presents the findings.

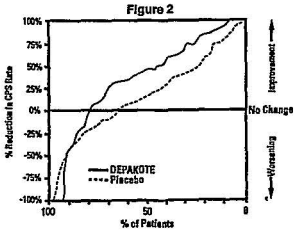
Adjunctive Therapy Study
Median Incidence of CPS per 8 Weeks

Add-on Treatment	Number of Patients	Baseline Incidence	Experimental Incidence
DEPAKOTE	75	16.0	8.9*
Placebo	69	14.5	11.5

* Reduction from baseline statistically significantly greater for DEPAKOTE than placebo at p ≤0.05 level.

Figure 2 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the adjunctive therapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for an effective treatment is shifted to the left of the curve for placebo. This figure shows that the proportion of patients achieving any particular level of improvement was consistently higher for DEPAKOTE than for placebo. For example, 45% of patients treated with DEPAKOTE had a ≥50% reduction in complex partial seizure rate compared to 23% of patients treated with placebo.

Figure 2



The second study assessed the capacity of DEPAKOTE to reduce the incidence of CPS when administered as the sole AED. The study compared the incidence of CPS among patients randomized to either a high or low dose treatment arm. Patients qualified for entry into the randomized comparison phase of this study only if 1) they continued to experience 2 or more CPS per 4 weeks during an 8 to 12 week long period of monotherapy with adequate doses of an AED (i.e., phenytoin, carbamazepine, phenobarbital, or primidone) and 2) they made a successful transition over a two week interval to DEPAKOTE. Patients entering the randomized phase were then brought to their assigned target dose, gradually tapered off their concomitant AED and followed for an interval as long as 22 weeks. Less than 50% of the patients randomized, however, completed the study. In patients converted to DEPAKOTE monotherapy, the mean total valproate concentrations during monotherapy were 71 and 123 µg/mL in the low dose and high dose groups, respectively.

The following table presents the findings for all patients randomized who had at least one post-randomization assessment.

Monotherapy Study
Median Incidence of CPS per 8 Weeks

Treatment	Number of Patients	Baseline Incidence	Randomized Phase Incidence
High dose DEPAKOTE	131	13.2	10.7*
Low dose DEPAKOTE	134	14.2	13.8

* Reduction from baseline statistically significantly greater for high dose than low dose at p ≤0.05 level.

Figure 3 presents the proportion of patients (X axis) whose percentage reduction from baseline in complex partial seizure rates was at least as great as that indicated on the Y axis in the monotherapy study. A positive percent reduction indicates an improvement (i.e., a decrease in seizure frequency), while a negative percent reduction indicates worsening. Thus, in a display of this type, the curve for a more effective treatment is shifted to the left of the curve for a less effective treatment. This figure shows that the proportion of patients achieving any particular level of reduction was consistently higher for high dose DEPAKOTE than for low dose DEPAKOTE. For example, when switching from carbamazepine, phenytoin, phenobarbital or primidone monotherapy to high dose DEPAKOTE monotherapy, 63% of patients experienced no change or a reduction in complex partial seizure rates

THE DATA DESCRIBED BELOW WERE GAINED ALMOST EXCLUSIVELY FROM WOMEN WHO RECEIVED VALPROATE TO TREAT EPILEPSY. THERE ARE MULTIPLE REPORTS IN THE CLINICAL LITERATURE WHICH INDICATE THAT THE USE OF ANTIEPILEPTIC DRUGS DURING PREGNANCY RESULTS IN AN INCREASED INCIDENCE OF BIRTH DEFECTS IN THE OFFSPRING. ALTHOUGH DATA ARE MORE EXTENSIVE WITH RESPECT TO TRIMETHADIONE, PARAMETHADIONE, PHENYTOIN, AND PHENOBARBITAL, REPORTS INDICATE A POSSIBLE SIMILAR ASSOCIATION WITH THE USE OF OTHER ANTIEPILEPTIC DRUGS. THEREFORE, ANTIEPILEPSY DRUGS SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING POTENTIAL ONLY IF THEY ARE CLEARLY SHOWN TO BE ESSENTIAL IN THE MANAGEMENT OF THEIR SEIZURES.

THE INCIDENCE OF NEURAL TUBE DEFECTS IN THE FETUS MAY BE INCREASED IN MOTHERS RECEIVING VALPROATE DURING THE FIRST TRIMESTER OF PREGNANCY. THE CENTERS FOR DISEASE CONTROL (CDC) HAS ESTIMATED THE RISK OF VALPROIC ACID EXPOSED WOMEN HAVING CHILDREN WITH SPINA BIFIDA TO BE APPROXIMATELY 1 TO 2%.

OTHER CONGENITAL ANOMALIES (EG, CRANIOFACIAL DEFECTS, CARDIOVASCULAR MALFORMATIONS AND ANOMALIES INVOLVING VARIOUS BODY SYSTEMS), COMPATIBLE AND INCOMPATIBLE WITH LIFE, HAVE BEEN REPORTED. SUFFICIENT DATA TO DETERMINE THE INCIDENCE OF THESE CONGENITAL ANOMALIES IS NOT AVAILABLE.

THE HIGHER INCIDENCE OF CONGENITAL ANOMALIES IN ANTIEPILEPTIC DRUG-TREATED WOMEN WITH SEIZURE DISORDERS CANNOT BE REGARDED AS A CAUSE AND EFFECT RELATIONSHIP. THERE ARE INTRINSIC METHODOLOGIC PROBLEMS IN OBTAINING ADEQUATE DATA ON DRUG TERATOGENICITY IN HUMANS; GENETIC FACTORS OR THE EPILEPTIC CONDITION ITSELF, MAY BE MORE IMPORTANT THAN DRUG THERAPY IN CONTRIBUTING TO CONGENITAL ANOMALIES.

PATIENTS TAKING VALPROATE MAY DEVELOP CLOTTING ABNORMALITIES. A PATIENT WHO HAD LOW FIBRINOGEN WHEN TAKING MULTIPLE ANTICONVULSANTS INCLUDING VALPROATE GAVE BIRTH TO AN INFANT WITH AFIBRINOGENEMIA WHO SUBSEQUENTLY DIED OF HEMORRHAGE. IF VALPROATE IS USED IN PREGNANCY, THE CLOTTING PARAMETERS SHOULD BE MONITORED CAREFULLY.

HEPATIC FAILURE, RESULTING IN THE DEATH OF A NEWBORN AND OF AN INFANT, HAVE BEEN REPORTED FOLLOWING THE USE OF VALPROATE DURING PREGNANCY.

Animal studies have demonstrated valproate-induced teratogenicity. Increased frequencies of malformations, as well as intrauterine growth retardation and death, have been observed in mice, rats, rabbits, and monkeys following prenatal exposure to valproate. Malformations of the skeletal system are the most common structural abnormalities produced in experimental animals, but neural tube closure defects have been seen in mice exposed to maternal plasma valproate concentrations exceeding approximately 230 µg/mL (2.3 times the upper limit of the human therapeutic range for epilepsy) during susceptible periods of embryonic development. Administration of an oral dose of 200 mg/kg/day or greater (50% of the maximum human daily dose or greater on a mg/m^2 basis) to pregnant rats during organogenesis produced malformations (skeletal, cardiac, and urogenital) and growth retardation in the offspring. These doses resulted in peak maternal plasma valproate levels of approximately 340 µg/mL or greater (3.4 times the upper limit of the human therapeutic range for epilepsy or greater). Behavioral deficits have been reported in the offspring of rats given a dose of 200 mg/kg/day throughout most of pregnancy. An oral dose of 350 mg/kg/day (approximately 2 times the maximum human daily dose on a mg/m^2 basis) produced skeletal and visceral malformations in rabbits exposed during organogenesis. Skeletal malformations, growth retardation, and death were observed in rhesus monkeys following administration of an oral dose of 200 mg/kg/day (equal to the maximum human daily dose on a mg/m^2 basis) during organogenesis. This dose resulted in peak maternal plasma valproate levels of approximately 280 µg/mL (2.8 times the upper limit of the human therapeutic range for epilepsy).

The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Tests to detect neural tube and other defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving valproate.

PRECAUTIONS

Hepatic Dysfunction

See **BOXED WARNING, CONTRAINDICATIONS** and **WARNINGS.**

Pancreatitis

See **BOXED WARNING** and **WARNINGS.**

Hyperammonemia

Hyperammonemia has been reported in association with valproate therapy and may be present despite normal liver function tests. In patients who develop unexplained lethargy and vomiting or changes in mental status, hyperammonemic encephalopathy should be considered and an ammonia level should be measured. If ammonia is increased, valproate therapy should be discontinued. Appropriate interventions for treatment of hyperammonemia should be initiated, and such patients should undergo investigation for underlying urea cycle disorders (see **CONTRAINDICATIONS** and **WARNINGS – Urea Cycle Disorders**).

Asymptomatic elevations of ammonia are more common and when present, require close monitoring of plasma ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered.

General

Because of reports of thrombocytopenia (see **WARNINGS**), inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters, (e.g., low fibrinogen), platelet counts and coagulation tests are recommended before initiating therapy and at periodic intervals. It is recommended that patients receiving DEPAKOTE be monitored for platelet count and coagulation parameters prior to planned surgery. In a clinical trial of DEPAKOTE as monotherapy in patients with epilepsy, 34/126 patients (27%) receiving approximately 50 mg/kg/day on average, had at least one value of platelets ≤ 75 x 10^9/L. Approximately half of these patients had treatment discontinued, with return of platelet counts to normal. In the remaining patients, platelet counts normalized with continued treatment. In this study, the probability of thrombocytopenia appeared to increase significantly at total valproate concentrations of ≥ 110 µg/mL (females) or ≥ 135 µg/mL (males). Evidence of hemorrhage, bruising, or a disorder of hemostasis/coagulation is an indication for reduction of the dosage or withdrawal of therapy.

Since DEPAKOTE may interact with concurrently administered drugs which are capable of enzyme induction, periodic plasma concentration determinations of valproate and concomitant drugs are recommended during the early course of therapy where clinically appropriate (see **PRECAUTIONS – Drug Interactions**).

Infection	15%	14%

[1]The following adverse events occurred in greater than 5% of DEPAKOTE ER-treated patients and at a greater incidence for placebo than for DEPAKOTE ER: asthenia and flu syndrome.

The following additional adverse events were reported by greater than 1% but not more than 5% of DEPAKOTE ER-treated patients and with a greater incidence than placebo in the placebo-controlled clinical trial for migraine prophylaxis:

Body as a Whole: Accidental injury, viral infection.
Digestive System: Increased appetite, tooth disorder.
Metabolic and Nutritional Disorders: Edema, weight gain.
Nervous System: Abnormal gait, dizziness, hypertonia, insomnia, nervousness, tremor, vertigo.
Respiratory System: Pharyngitis, rhinitis.
Skin and Appendages: Rash.
Special Senses: Tinnitus.

Table 2 includes those adverse events reported for patients in the placebo-controlled trials where the incidence rate in the DEPAKOTE-treated group was greater than 5% and was greater than that for placebo patients.

Table 2
Adverse Events Reported by >5% of DEPAKOTE-Treated Patients During Migraine Placebo-Controlled Trials with a Greater Incidence than Patients Taking Placebo[1]

Body System Event	Depakote (N=202)	Placebo (N=81)
Gastrointestinal System		
Nausea	31%	10%
Dyspepsia	13%	9%
Diarrhea	12%	7%
Vomiting	11%	1%
Abdominal Pain	9%	4%
Increased Appetite	6%	4%
Nervous System		
Asthenia	20%	9%
Somnolence	17%	5%
Dizziness	12%	6%
Tremor	9%	0%
Other		
Weight Gain	8%	2%
Back Pain	8%	6%
Alopecia	7%	1%

[1]The following adverse events occurred in greater than 5% of DEPAKOTE -treated patients and at a greater incidence for placebo than for DEPAKOTE: flu syndrome and pharyngitis.

The following additional adverse events not referred to above were reported by greater than 1% but not more than 5% of DEPAKOTE-treated patients and with a greater incidence than placebo in the placebo-controlled clinical trials:

Body as a Whole: Chest pain.
Cardiovascular System: Vasodilatation.
Digestive System: Constipation, dry mouth, flatulence, stomatitis.
Hemic and Lymphatic System: Ecchymosis.
Metabolic and Nutritional Disorders: Peripheral edema.
Musculoskeletal System: Leg cramps.
Nervous System: Abnormal dreams, confusion, paresthesia, speech disorder, thinking abnormalities.
Respiratory System: Dyspnea, sinusitis.
Skin and Appendages: Pruritus.
Urogenital System: Metrorrhagia.

Epilepsy

Based on a placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures, DEPAKOTE was generally well tolerated with most adverse events rated as mild to moderate in severity. Intolerance was the primary reason for discontinuation in the DEPAKOTE-treated patients (6%), compared to 1% of placebo-treated patients.

Table 3 lists treatment-emergent adverse events which were reported by ≥5% of DEPAKOTE-treated patients and for which the incidence was greater than in the placebo group, in the placebo-controlled trial of adjunctive therapy for treatment of complex partial seizures. Since patients were also treated with other antiepilepsy drugs, it is not possible, in most cases, to determine whether the following adverse events can be ascribed to DEPAKOTE alone, or the combination of DEPAKOTE and other antiepilepsy drugs.

Table 3
Adverse Events Reported by ≥ 5% of Patients Treated with DEPAKOTE During Placebo-Controlled Trial of Adjunctive Therapy for Complex Partial Seizures

Body System/Event	Depakote (%) (n = 77)	Placebo (%) (n = 70)
Body as a Whole		
Headache	31	21
Asthenia	27	7
Fever	6	4
Gastrointestinal System		
Nausea	48	14
Vomiting	27	7
Abdominal Pain	23	6
Diarrhea	13	6
Anorexia	12	0
Dyspepsia	8	4
Constipation	5	1
Nervous System		
Somnolence	27	11
Tremor	25	6
Dizziness	25	13
Diplopia	16	9
Amblyopia/Blurred Vision	12	9

(including ileostomy or colostomy), gastrointestinal disorders with shortened GI transit times, there have been post-marketing reports of DEPAKOTE ER tablets in the stool.

CNS Effects: Sedative effects have occurred in patients receiving valproate alone but occur most often in patients receiving combination therapy. Sedation usually abates upon reduction of other antiepileptic medication. Tremor (may be dose-related), hallucinations, ataxia, headache, nystagmus, diplopia, asterixis, "spots before eyes", dysarthria, dizziness, confusion, hypesthesia, vertigo, incoordination, and parkinsonism have been reported with the use of valproate. Rare cases of coma have occurred in patients receiving valproate alone or in conjunction with phenobarbital. In rare instances encephalopathy with or without fever has developed shortly after the introduction of valproate monotherapy without evidence of hepatic dysfunction or inappropriately high plasma valproate levels. Although recovery has been described following drug withdrawal, there have been fatalities in patients with hyperammonemic encephalopathy, particularly in patients with underlying urea cycle disorers (see **WARNINGS -- Urea Cycle Disorders** and **PRECAUTIONS**).

Several reports have noted reversible cerebral atrophy and dementia in association with valproate therapy.

Dermatologic: Transient hair loss, skin rash, photosensitivity, generalized pruritus, erythema multiforme, and Stevens-Johnson syndrome. Rare cases of toxic epidermal necrolysis have been reported including a fatal case in a 6 month old infant taking valproate and several other concomitant medications. An additional case of toxic epidermal necrosis resulting in death was reported in a 35 year old patient with AIDS taking several concomitant medications and with a history of multiple cutaneous drug reactions.

Psychiatric: Emotional upset, depression, psychosis, aggression, hyperactivity, hostility, and behavioral deterioration.

Musculoskeletal: Weakness.

Hematologic: Thrombocytopenia and inhibition of the secondary phase of platelet aggregation may be reflected in altered bleeding time, petechiae, bruising, hematoma formation, epistaxis, and frank hemorrhage (see **PRECAUTIONS - General and Drug Interactions**). Relative lymphocytosis, macrocytosis, hypofibrinogenemia, leukopenia, eosinophilia, anemia including macrocytic with or without folate deficiency, bone marrow suppression, pancytopenia, aplastic anemia, and acute intermittent porphyria.

Hepatic: Minor elevations of transaminases (eg, SGOT and SGPT) and LDH are frequent and appear to be dose-related. Occasionally, laboratory test results include increases in serum bilirubin and abnormal changes in other liver function tests. These results may reflect potentially serious hepatotoxicity (see **WARNINGS**).

Endocrine: Irregular menses, secondary amenorrhea, breast enlargement, galactorrhea, and parotid gland swelling. Abnormal thyroid function tests (see **PRECAUTIONS**).

There have been rare spontaneous reports of polycystic ovary disease. A cause and effect relationship has not been established.

Pancreatic: Acute pancreatitis including fatalities (see **WARNINGS**).

Metabolic: Hyperammonemia (see **PRECAUTIONS**), hyponatremia, and inappropriate ADH secretion.

There have been rare reports of Fanconi's syndrome occurring chiefly in children.

Decreased carnitine concentrations have been reported although the clinical relevance is undetermined.

Hyperglycinemia has occurred and was associated with a fatal outcome in a patient with preexistent nonketotic hyperglycinemia.

Genitourinary: Enuresis and urinary tract infection.

Special Senses: Hearing loss, either reversible or irreversible, has been reported; however, a cause and effect relationship has not been established. Ear pain has also been reported.

Other: Anaphylaxis, edema of the extremities, lupus erythematosus, bone pain, cough increased, pneumonia, otitis media, bradycardia, cutaneous vasculitis, and fever.

OVERDOSAGE

Overdosage with valproate may result in somnolence, heart block, and deep coma. Fatalities have been reported; however patients have recovered from valproate levels as high as 2120 µg/mL.

In overdose situations, the fraction of drug not bound to protein is high and hemodialysis or tandem hemodialysis plus hemoperfusion may result in significant removal of drug. The benefit of gastric lavage or emesis will vary with the time since ingestion. General supportive measures should be applied with particular attention to the maintenance of adequate urinary output.

Naloxone has been reported to reverse the CNS depressant effects of valproate overdosage. Because naloxone could theoretically also reverse the antiepileptic effects of valproate, it should be used with caution in patients with epilepsy.

DOSAGE AND ADMINISTRATION

DEPAKOTE ER is an extended-release product intended for once-a-day oral administration. DEPAKOTE ER tablets should be swallowed whole and should not be crushed or chewed.

Migraine

The recommended starting dose is 500 mg once daily for 1 week, thereafter increasing to 1000 mg once daily. Although doses other than 1000 mg once daily of DEPAKOTE ER have not been evaluated in patients with migraine, the effective dose range of DEPAKOTE (divalproex sodium delayed-release tablets) in these patients is 500-1000 mg/day. As with other valproate products, doses of DEPAKOTE ER should be individualized and dose adjustment may be necessary. If a patient requires smaller dose adjustments than that available with DEPAKOTE ER, DEPAKOTE should be used instead.

Epilepsy

DEPAKOTE ER is indicated as monotherapy and adjunctive therapy in complex partial seizures in adult patients, and in simple and complex absence seizures in adult patients. As the DEPAKOTE ER dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected (see **PRECAUTIONS -- Drug Interactions**).

Complex Partial Seizures for adult patients:

Monotherapy (Initial Therapy) : DEPAKOTE ER has not been systematically studied as initial therapy. Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50 to 100 µg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made.

The probability of thrombocytopenia increases significantly at total trough valproate plasma concentrations above 110 µg/mL in females and 135 µg/mL in males. The benefit of improved seizure control with higher doses should be weighed against the possibility of a greater incidenceof adverse reactions.

Conversion to Monotherapy: Patients should initiate therapy at 10 to 15 mg/kg/day. The dosage should be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100 µg/mL). No recommendation regarding the safety of valproate for use at doses above 60 mg/kg/day can be made. Concomitant antiepilepsy drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at the initiation of DEPAKOTE ER therapy, or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur during a reduction. The speed and duration of withdrawal of the concomitant AED can be highly variable, and patients should be monitored closely during this period for increased seizure frequency.

ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
PRINTED IN U.S.

Patient Information Leaflet

Important Information for Women Who Could Become Pregnant About the Use of DEPAKOTE® ER (divalproex sodium) Tablets for Migraine

Please read this leaflet carefully before you take DEPAKOTE® ER (divalproex sodium) tablets. This le provides a summary of important information about taking DEPAKOTE ER for migraine to women who c become pregnant. DEPAKOTE ER may also be prescribed for uses other than those discussed in this leafl you have any questions or concerns, or want more information about DEPAKOTE ER, contact your doct pharmacist.

Information For Women Who Could Become Pregnant

DEPAKOTE ER is used to prevent or reduce the number of migraines you experience. DEPAKOTE ER ca obtained only by prescription from your doctor. The decision to use DEPAKOTE ER for the preventic migraine is one that you and your doctor should make together, taking into account your individual needs medical condition.

Before using DEPAKOTE ER, women who can become pregnant should consider the fact that DEPAK has been associated with birth defects, in particular, with spina bifida and other defects related to fal of the spinal canal to close normally. Although the incidence is unknown in migraine patients treated DEPAKOTE, approximately 1 to 2% of children born to women with epilepsy taking DEPAKOTE in first 12 weeks of pregnancy had these defects (based on data from the Centers for Disease Control, a agency based in Atlanta). The incidence in the general population is 0.1 to 0.2%.

Information For Women Who Are Planning To Get Pregnant

- Women taking DEPAKOTE ER for the prevention of migraine who are planning to get pregnant sh discuss with their doctor temporarily stopping DEPAKOTE ER, before and during their pregnancy.

Information For Women Who Become Pregnant While Taking DEPAKOTE ER

- If you become pregnant while taking DEPAKOTE ER for the prevention of migraine, you should contact doctor immediately.

Other Important Information About DEPAKOTE ER Tablets

- DEPAKOTE ER tablets should be taken exactly as it is prescribed by your doctor to get the most benefits fr DEPAKOTE ER and reduce the risk of side effects.
- If you have taken more than the prescribed dose of DEPAKOTE ER, contact your hospital emergency ro or local poison center immediately.
- This medication was prescribed for your particular condition. Do not use it for another condition or give drug to others.

Facts About Birth Defects

It is important to know that birth defects may occur even in children of individuals not taking any medications without any additional risk factors.

Facts About Migraine

About 23 million Americans suffer from migraine headaches. About 75% of migraine sufferers are women. migraine is described as a throbbing headache that gets worse with activity. Migraine may also include naus and/or vomiting as well as sensitivity to light and sound. Migraine usually happens about once a month, but so people may have them as often as once or twice a week. Often, the symptoms from a migraine can cause peo to miss work or school.

If you have frequent migraines, or if acute treatment is not working for you, your doctor may prescribe preventative therapy. Preventative (prophylactic) treatment is used to prevent attacks and reduce the frequency a severity of headache events.

This summary provides important information about the use of DEPAKOTE ER for migraine to women who cou become pregnant. If you would like more information about the other potential risks and benefits of DEPAKO ER, ask your doctor or pharmacist to let you read the professional labeling and then discuss it with them. If y have any questions or concerns about taking DEPAKOTE ER, you should discuss them with your doctor.

03-5235-R4

Revised: January, 2003

Manufactured by:

ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.

PRINTED IN U.S.

REDACTED - LTCPP-Clinical Project Manager
"LTCPP-CPM"

From: REDACTED - LTCPP-NDCPD
Sent: Wednesday, January 21, 2004 10:41 AM
To: REDACTED - LTCPP-CPM
Subject: FW: Abbott Mailing Content

REDACTED - LTCPP-CPM

Items included in the Depakote-ER mailer:

- Cover Letter
- Depakote-ER Package Insert (Mail Marketing will have to reprint)
- Consultant Pharmacist Journal: Tom Snader article (get permission and/or reprints from ASCP starting at 10,000. Check for a price break at 5000 and over)
- Depakote-ER Monograph (Mail Marketing will have to reprint)

REDACTED should be finalizing the data analysis today, then REDACTED - LTC-NAM and I will determine the total quantity for the mailed pieces.

Thanks,
REDACTED - LTCPP-NDCPD

-----Original Message-----
From: REDACTED - LTC-NAM@abbott.com [mailto REDACTED - LTC-NAM@abbott.com]
Sent: Tuesday, January 20, 2004 9:10 PM
To: REDACTED - LTCPP-NDCPD
Subject: RE: Mailing Content

Hi REDACTED - LTCPP-NDCPD
I bet she knows some good words. Well when REDAC is gone she won't have him to cuss. I have a transition conference call with her and REDAC next Fri.

Will have to work on the PI. Don't know if we have a 2 pg one..what if we don't? I would rather come up with a publication/reprint that was a little more independent and less an Abbott marketing piece. I am still thinking of Snader's Sept Depakote ER article in the Cons Pharmacist...can you get that fairly quickly to make a Feb mailing...I just think whatever we send needs to have some meat. If needed I can talk to REDACTED about it.

Any word on the # Docs for the mailing? That and a budget and I can get things rolling for a check.

Did REDACTED have numbers on the # of letters sent by the CPs for new Depakote patients?..I have to believe REDACTED asked.

Weather better for golf than fishing. A lot of wind. Nice this afternoon. All the conditions were good but fish hard to find. One small Mako shark. Nasty little 3 footer. We are hoping for a nice full day of fishing tomorrow.

Call me if we need to discuss this or other. I have my cell REDACTED

REDACTED - LTC-NAM
LTC National Account Manager
Abbott Laboratories
Phone: REDACTED
Fax: REDACTED
REDACTED - LTC-NAM@abbott.com

'REDACTED - LTCPP-NDCPD@REDACTED - LTCPP.com>

01/20/2004 02:18 PM

To: REDACTED - LTC-NAM@abbott.com'" <REDACTED - LTC-NAM@abbott.com>
cc:
Subject: RE: Mailing Content

REDACTED - LTC-NAM

Well REDACTED was still complaining on the growth contract issue and cussed you once or twice, but other than that all went OK.

- The PI you sent is the 27 page version. I need the 1 or 2 page version.
- "Improving Quality of Life: Use of Mood Stabilizers in Senior Care" is an Abbott publication. I'll send it to you when you return.
- I'll add the Depakote Monograph in place of the sprinkle sheet.
- Med-asses corrected to Med-passes. (that would have been VERY embarrassing!, thanks)

Here's to Good Fishing!
REDACTED - LTCPP-NDCPD

-----Original Message-----
From: REDACTED - LTC-NAM@abbott.com [mailto REDACTED - LTC-NAM@abbott.com]
Sent: Tuesday, January 20, 2004 11:27 AM
To: REDACTED - LTCPP-NDCPD
Subject: Mailing Content

REDACTED - LTCPP-NDCPD
I will be fishing in the warm waters of the FL keys all this week. Call me on my cell anytime you need to REDACTED. Let me know as soon as you have a Doc list and a budget.
See thoughts and questions below in red.

Thanks for all your support. (Please put in a good word for me and Depakote at the vendor meetings this week)

REDACTED - LTC-NAM

REDACTED - LTC-NAM
LTC National Account Manager
Abbott Laboratories
Phone: REDACTED
Fax: REDACTED
REDACTED - LTC-NAM@abbott.com

'REDACTED - LTCPP-NDCPD@REDACTED - LTCPP.com>

01/14/2004 03:39 PM

To: REDACTED - LTC-NAM@abbott.com" <REDACTED - LTC-NAM@abbott.com>
cc:
Subject: RE: LTCPP Depakote data request

Mr Depakote:

If you can interrupt your *ice* (foolish) fishing for a moment,

Here's the letter I will include in the mailer along with the PI and need your thoughts on an appropriate study to include as well.
I have a publication from the CNS/LTC entitled:
Special Report: "Improving Quality of Life: Use of Mood Stabilizers in Senior Care" that I can fax if needed or I'm open to suggestions. I do not have this and would like to read it. (This is not one of those Abbott sponsored publications is it?) Will try and find a fax machine in FL if I need to.

So far Items included in the mailer are:

- Cover Letter Looks excellent! One typo on bullet point w/ med-Passes
- PI Attached
- Clinical Study or review publication (TBD)
- Depakote Sprinkle Administration sheet that has the chart of Depakote benefits listed vs. VPA on the reverse side Good idea...or maybe we send the REDACTED - LTCPP Depakote ER monograph...that might help us more with new RXs. That would also have the conversion table (Docs might well keep the piece in their office as a reference to) OR we can send them both.
  Do you have an e-copy of the 1 page Depakote-ER PI? Attached below

  Thanks for the support!
  REDACTED - LTCPP-NDCPD

-----Original Message-----
From: REDACTED - LTC-NAM@abbott.com [mailto REDACTED - LTC-NAM@abbott.com]
Sent: Tuesday, January 13, 2004 2:27 PM
To: REDACTED; REDACTED; REDACTED; REDACTED
Cc: REDACTED - Abbott s LTC Dir. of Sales; REDACTED - LTCPP-NDCPD; REDACTED; REDACTED
Subject: LTCPP Depakote data request

Hi Everyone,

I had a chance to put the together the analysis and comparisons that were requested during our meeting on December 18th.

- Slide #1 shows the kgs/bed for each of the LTCPPs. 3/4 LTCPPs have virtually identical amounts of Depakote used per serviced bed. One LTCPP falls slightly below the others. This information would suggest that the opportunity for Depakote growth is similar for all major LTCPPs
  - Slide #2 illustrates the average annual growth rates for the LTCPPs. Two LTCPPs had higher rates of growth in 2002 than in 2003 and the other two LTCPPs had higher

growth rates in 2003 vs 2002. REDACTED - LTCPP's growth in 2002 was significantly greater than in 2003, and I believe this was due primarily to the successful conversion of VPA to Depakote to Depakote ER. The average rate of growth through Q3 2003 for the other LTCPPs averaged 9%. I did receive some information for Q4 2003 for LTCPP "C" and the growth rate was 15% for the quarter and this is reflected in Slide #3

- Slide #3 indicates the growth of the LTCPPs by quarter. Slide #4 shows the rate of ER conversion by quarter through Q3 2003

Depakote growth continues to be steady across the LTC channel. Abbott is fully committed to our partnership with REDACTED - LTCPP with regards to Depakote. Significant opportunity remains for Depakote's use in LTC and I believe that if we execute our planned strategy our successes will continue in 2004 and beyond.
I will be working at all levels to help ensure the success of the Depakote Initiatives.

Please feel free to contact me with any questions on the information

Regards,
REDACTED - LTC-NAM

REDACTED - LTC-NAM
LTC National Account Manager
Abbott Laboratories
Phone: REDACTED
Fax: REDACTED
REDACTED - LTC-NAM@abbott.com

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REDACTED

REDACTED - LTCPP-CPM

From: REDACTED - LTCPP-NDCPD
Sent: Tuesday, January 06, 2004 2:50 PM
To: REDACTED - LTC-NAM@abbott.com
Cc: REDACTED - LTCPP-CPM
Subject: RE: REDACTED - LTCPP mailing-follow up questions

REDACTED - LTC-NAM

Happy New Year! Are you sober yet?

The mailer can be done as soon as the materials are developed and drop shipped to the printer. That entails:

- Data pull to determine the scope of the project (assume 10,000 joint prescribers of benzos and aytpicals)
- Just a PDF of the Depakote PI will do. The printer will reproduce the qty. we need.
- Getting enough reprints for the project will be the time limiting factor if we need to obtain and pay for publishing rights then print 10,000.
- Assuming all goes smoothly, Feb. 1 is a good date for the release.

REDACTED - LTCPP-CP and I will begin working on the mailer and REDACTED - LTCPP-CP will be our primary point person.

We'll work with REDACTED (our account executive in Texas) on the Daybreak project. His contact numbers are attached below.

Thanks Depakote Man!
PS. What happened to Michigan??

-----Original Message-----
From: REDACTED - LTC-NAM@abbott.com [mailto REDACTED - LTC-NAM@abbott.com]
Sent: Monday, January 05, 2004 7:16 PM
To: REDACTED - LTCPP-NDCPD
Subject: REDACTED - LTCPP mailing-follow up questions

Thanks REDACTED for the examples.

- I would like to put together a proposed budget for the mailing ASAP. How does this work? I guess we need to target the top high prescibers of benzodiapines and atypicals. How many would that be would you guess? I would guess that in addition to your cover/positioning letter you would need the Depakote ER package insert. Would you also include a clinical reprint as well to reinforce the cover/positioning letter?
  - How long does it take to set up and complete a mailing? I would like to get it done ASAP
    - On an unrelated note, we definately want to sponsor the April program for REDACTED with the customer (REDACTED) you mentioned when we met in Tampa. Who do I work with to get the program set up? I know that I can run the program funding through you.

Thanks

REDACTED - LTC-NAM
LTC National Account Manager
Abbott Laboratories
Phone: REDACTED
Fax: REDACTED
REDACTED - LTC-NAM@abbott.com

"REDACTED - LTCPP-NDCPD@REDACTED - LTCPP.com>

12/19/2003 01:58 PM

To: REDACTED - LTC-NAM (E-mail)" REDACTED - LTC-NAM
cc:
Subject: REDACTED - LTCPP mailer - examples

REDACTED - LTC-NAM

As we discussed:

<REDACTED mailer cover letter FINAL.doc>>
<< REDACTED .pdf>>

REDACTED - LTCPP-NDCPD
REDACTED - LTCPP
National Dir.of Clinical Program Development
REDACTED ext REDACTED

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REDACTED

REDACTED - LTCPP-CPM

From: REDACTED - LTCPP-NDCPD
Sent: Tuesday, February 03, 2004 9:12 AM
To: REDACTED - LTCPP-CPM
Subject: RE: permission to reprint article

REDACTED - LTCPP-CP,

Just follow the guidelines as indicated, especially inclusion of the tag line with each reprinted article.
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-----Original Message-----
From: REDACTED - LTCPP-CPM
Sent: Friday, January 30, 2004 10:42 AM
To: REDACTED - LTCPP-NDCPD
Subject: FW: permission to reprint article

REDACTED - LTCPP-NDCPD

I understand permission was granted to reprint the article, however can you be specific as to what I need to do with REDACTED at Mail Marketing with this?

REDACTED - LTCPP-CPM
Clinical Project Manager
REDACTED - LTCPP

-----Original Message-----
From: REDACTED @ascp.com]
Sent: Thursday, January 29, 2004 4:48 PM
To: REDACTED - LTCPP-CPM
Subject: Re: permission to reprint article

REDACTED - LTCPP-CP,
Sorry for the delay in responding to your request. We are granting you permission to reprint the article. Please see the terms below.

American Society of Consultant Pharmacists
Reprint Permission Terms

I am pleased to grant your recent request for permission to reprint the article(s) listed below from The Consultant Pharmacist :

September 2003 issue of the Consultant Pharmacist on: Divalproex Sodium Use in the Elderly: A New Formulation Offers New Opportunities. This article was written by Thomas C. Snader, PharmD.

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Thank you for your interest in ASCP's publications.

REDACTED

American Society of Consultant Pharmacists REDACTED
REDACTED

America's Senior Care Pharmacists (tm)

From: "REDACTED - LTCPP-CPM" <CMC4211@REDACTED - LTCPP.com>
Date: Wed, 21 Jan 2004 10:49:44 -0500
To: REDACTED
Subject: permission to reprint article

REDACTED,

I am requesting permission to reprint an article in the September 2003 issue of the Consultant Pharmacist on: Divalproex Sodium Use in the Elderly: A New Formulation Offers New Opportunities. This article was written by Thomas C. Snader, PharmD. The purpose is to copy this article and sent it out in a mailer to our pharmacists.

Thank you.

REDACTED - LTCPP-CPM

Clinical Project Manager

REDACTED - LTCPP

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REDACTED

REDACTED - LTCPP

January 2004

Dear Health Care Professional:

As you are aware, REDACTED - LTCPP has developed a geriatric-specific drug formulary. We would like to share some important information about our Select Formulary with you. Our preferred pharmaceutical products are selected through a three-tier evaluation process that begins with review by an expert external national Pharmacy and Therapeutics (P&T) Committee. Based on the P&T Committee's evaluation and further analysis of pharmacoeconomic and cost data, REDACTED - LTCPP selects the most appropriate products for elderly residents to include within the Select Formulary.

Depakote and its derivatives have FDA approval for a variety of indications including bipolar disorder, seizure disorders, and migraine headache prophylaxis. In addition to these uses, Depakote and Depakote-ER are being used with increasing frequency to treat/manage agitation, anger, and hostility associated with dementia in the elderly. For elderly residents requiring therapy for a dementia related behavior disorder, **Depakote ER®** has been granted preferred status on the PharMerica's formulary. Depakote ER® is a logical cost-effective choice for treating elderly patients with these challenging behavioral symptoms.

Depakote ER® should be considered for patients with dementia related behaviors including:

- Initial therapy for patients with agitation anger, and hostility symptoms
- Adjunctive therapy for patients partially responsive to an atypical antipsychotic (antipsychotic can be tapered to a lower dose or eliminated after stabilization of behaviors)
- Replacement therapy for patients receiving benzodiazepines

- **Depakote ER®** can be dosed once daily and has improved side effects profiles vs the original Depakote DR (delayed release) with significant decreases in sedation and gastrointestinal complaints.

- **Depakote ER®** 500mg costs less than equivalent doses of the original Depakote DR (delayed release) with additional pharmacoeconomic savings in decreased med-passes and increased quality of life.

- Use of **Depakote ER®** instead of atypical antipsychotics and benzodiazepines can also positively impact the nursing facilities Quality Indicator Report.

Physician prescribing in compliance with the formulary can maintain or improve resident outcomes while containing costs. This also will minimize the number of calls and interventions from nursing and pharmacy to change prescriptions to formulary-preferred drugs. We appreciate your support of these formulary preferences for our long-term care patients.
Enclosed you will find complete prescribing information that will be helpful.

If you have any questions, please contact the REDACTED - LTCPP consultant pharmacist in the facility where you practice.

Sincerely,

REDACTED - LTCPP-NDCPD

National Director of Clinical Program Development
Chair, P&T Liaison Committee

Disclaimer: Information contained in this letter is for general guidelines only. Prescribing and dosing should be based on individual patient conditions. Portions of the accompanying literature have been supported by an unrestricted educational grant from Abbott Laboratories.

From: REDACT
ED /lake/ppd/abbott;nsf REDACTED @abbott.com;smtp
To: REDACTED lake/ppd/abbott@abbott;
REDACTED lake/ppd/abbott@abbott; REDACTE
RED /lake/ppd/abbott@abbott; REDACTED
REDAC /lake/ppd/abbott@abbott; REDACTED /lake/ppd/abbott;
REDACTED /lake/ppd/abbott@abbott; REDACTED
REDACTE /lake/ppd/abbott
Cc: REDACTED /lake/ppd/abbott@abbott;
REDACTED /lake/ppd/abbott; REDAC
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REDACTED /lake/ppd/abbott; REDACTED /lake/ppd/abbott;
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REDACT /lake/ppd/abbott; REDACTED /lake/ppd/abbott;
REDACTED /lake/ppd/abbott; REDACT
REDACTED /lake/ppd/abbott
Bcc:
Subject: REDACTED Depakote ER Mailing to Prescribers
Date: Sun Mar 21 2004 17:23:59 EST
Attachments: Top 5000 PrescribersAtypicals&BenzosQ4-03.xls

Managers,

This past week REDACTED sent out a targeted Depakote ER mailing to the top 4,000 prescribers of atypicals and top 1000 prescribers of benzodiazepines within REDACTED facilities. This was based on Q4 2003 data and was measured in days of therapy for the two drug categories for the time period. They did not break out the physicians by drug class, but I think it is probably safe to assume that the higher days of therapy is more likely related to atypical use. I would expect that many of the higher ranking physicians are probably already LTC targets, but the rankings may give some additional insight as to their prescribing prowess in a particular area.

The purpose of the mailing is to help increase the overall use of Depakote ER vs the atypicals and benzodiazepines for patients with dementia related behaviors as well as boost the percentage of patients being converted from DR to ER.

The mailing included 3 items:
A cover letter from REDACTED (National Director of Clinical Programs)
REDACTED Depakote ER monograph (includes conversion guidelines)
The Consultant Pharmacist Article by Tom Snader (Sept 2003) : Divalproex Sodium Use in the Elderly: A New Formulation Offers New Opportunities

The cover letter strongly positions Depakote ER vs the atypicals, emphasizes the excellent side effect profile of Depakote ER, and also references the advantages to the facilities in terms of reduced med passes. It also discusses how the use of Depakote ER instead of the atypicals and the benzodiazepines can positively impact the nursing facilities' Quality Indicator Report. I am working to provide this letter to the consultant pharmacists for them to able to give to prescribers and other caregivers in situations where it would be helpful.

Please feel free to share this information with your respective teams to make them aware of physicians in their territories who have received the mailing. I have sorted it by state to make it more useful to you. Again, this is data only from REDACTED facilities. A physician may have Rxs going to additional LTCPPs. Any feedback from the field on how physicians are responding to the mailing would be greatly

appreciated. Please let me know if you have any questions on the mailing.

Thanks (as always) for your strong support of the REDACTED Depakote Initiative!

REDAC

REDACTED
LTC National Account Manager
Abbott Laboratories
Phone: REDACTED
Fax: REDACTED
REDACTED @abbott.com

From: REDACTED
To: REDACTED /lake/ppd/abbott;nsf REDACTED @abbott.com;smtp
Cc: REDACTED /lake/ppd/abbott@abbott
Bcc:
Subject:
Date: Wed Oct 29 2003 17:14:42 EST
Attachments: REDACTED LTC 102903.ppt

24-25

REDACTED
Abbott Laboratories - Pharmaceutical Products Division
Business Unit Director: Neurology, Long Term Care, & Medical Liaisons
REDACTED

Depakote Long Term Care

2004 Strategic Investment Proposal

October 30, 2003

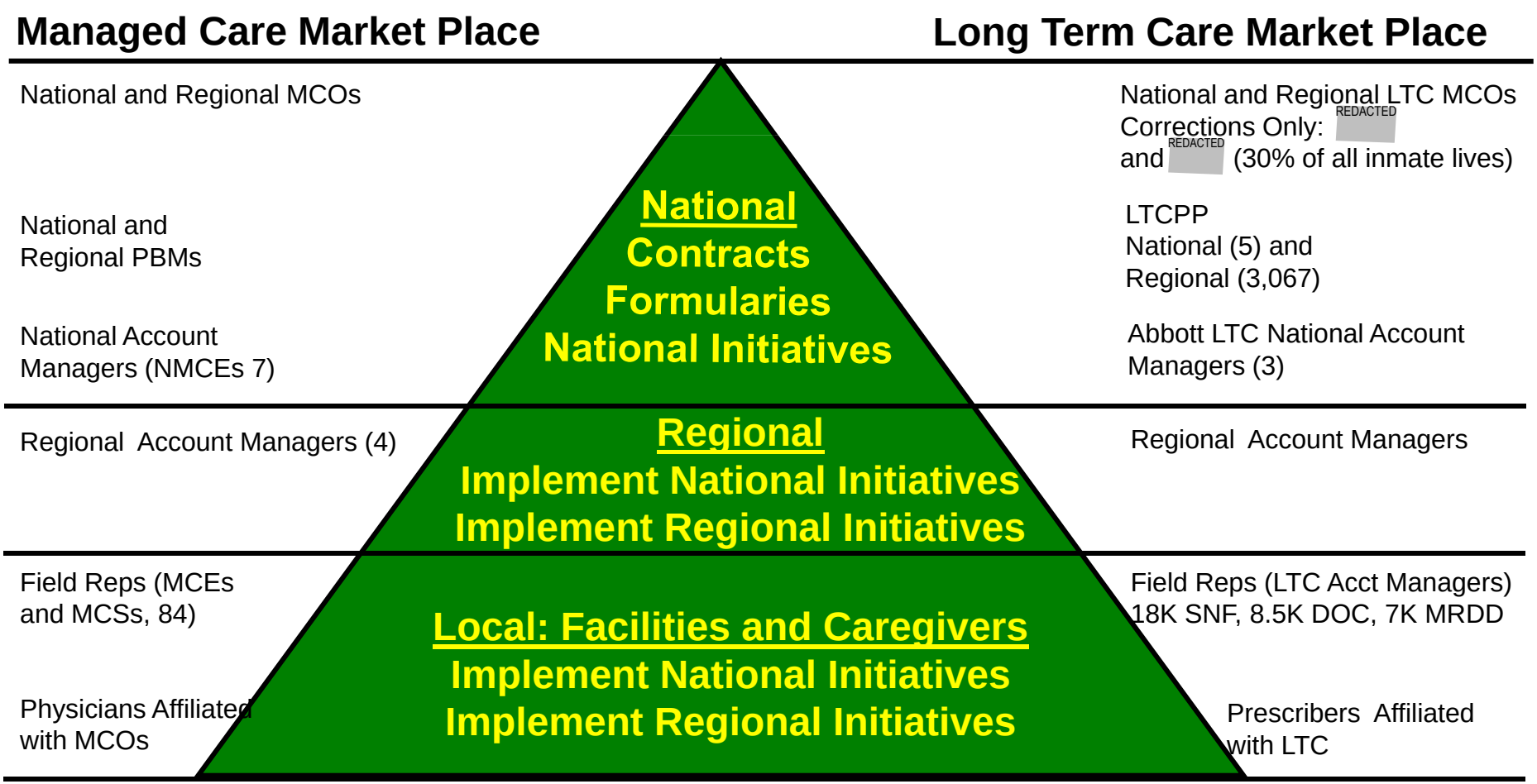
Depakote LTC Strategic Plan Background

- **2003 Depakote LTC**
  - Revenue: $129 MM
  - Salesforce Efficiency: $2.4 MM/FTE
  - Focus: Skilled Nursing Facilities messaging on agitation/aggression due to historical indication pursuit

- **Q2 2003 Market Research to Explore LTC Growth Opportunities**
  - MRDD: Mentally Retarded Developmentally Disabled Facilities
    - » Epilepsy and Agitation/Aggression prevalent, 25% and 22% respectively
    - » Once daily Depakote ER advantages: side effects, and med passes.
  - DOC: Department of Corrections Facilities
    - » Bipolar and Agitation/Aggression prevalent, 21% and 31% respectively
    - » Once daily Depakote ER advantages: tolerability and med passes.
  - SNF: Skilled Nursing Facilities
    - » Bipolar and Epilepsy prevalent, 13% and 10% respectively.

- **Q3 2003 HPR Salesforce Analysis**
  - Incremental revenue can be achieved through optimization

LTC Similarities with Managed Care

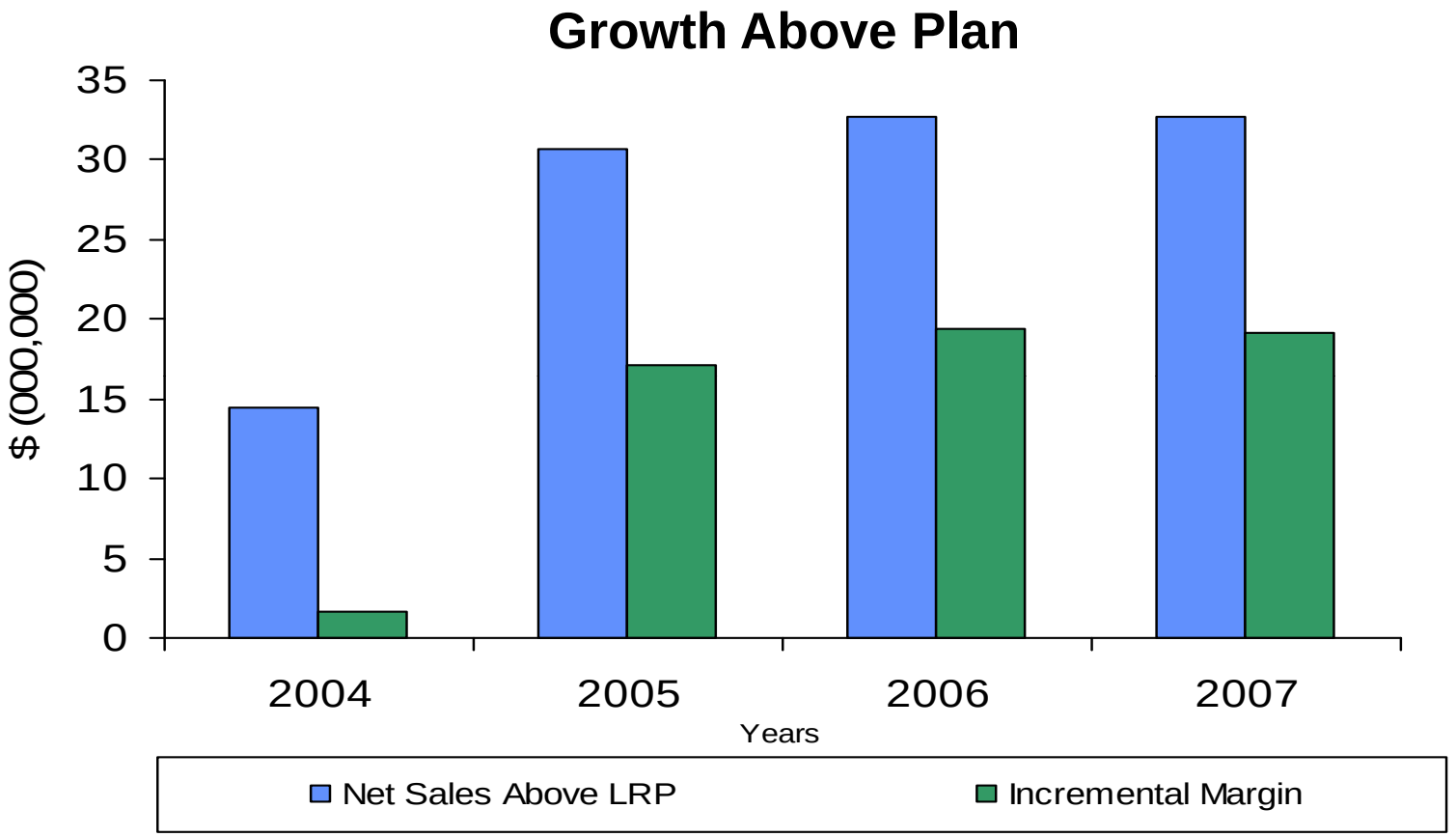


Sources:LTC Scenario Data Pull, October 2002; REDACTED *The customer universe here was defined by Abbott sales reps (SNAP database) and includes only customers with significant LTC business; thus, for example, the PCP universe here includes only those PCPs that prescribe in SNFs.

Depakote LTC Optimization Strategic Objectives

- **Provide incremental revenue and margin**
  - Incremental revenue of **$120.3** million over LRP
  - Incremental margin of **$62.9** million over LRP
- **Reduce promotional risk**
  - W/O Optimization: Promotion based on **agitation/aggression**
  - With Optimization: Promotion based on **epilepsy and bipolar disorder** with dissemination of agitation/aggression information.
- **Create organization capable of supporting the most profitable segments of LTC**
  - Marketing and IIS support of SNF, DOC and MRDD
  - RAMs to pull through national programs to local level and support regional and independent pharmacy providers
  - Sales representatives to cover highest value facilities/caregivers

Depakote LTC Optimization Can: Provide Incremental Revenue and Margin



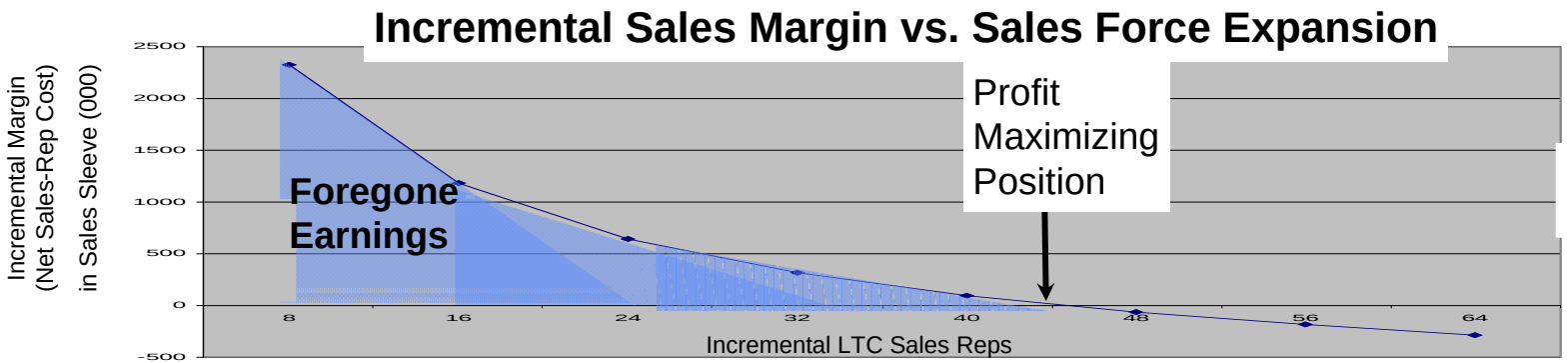
Targeted investment in LTC can increase sales by **$120.3 million**, with incremental margin of **$62.9 million** over the LRP.

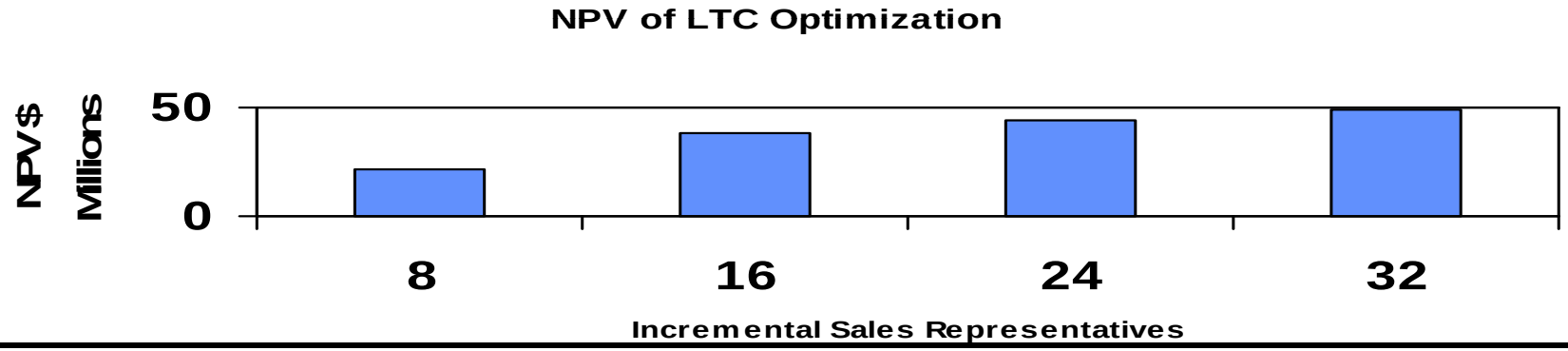
- Note: 2004 Reflects the plan numbers. Year 2005-2008 are LRP numbers.

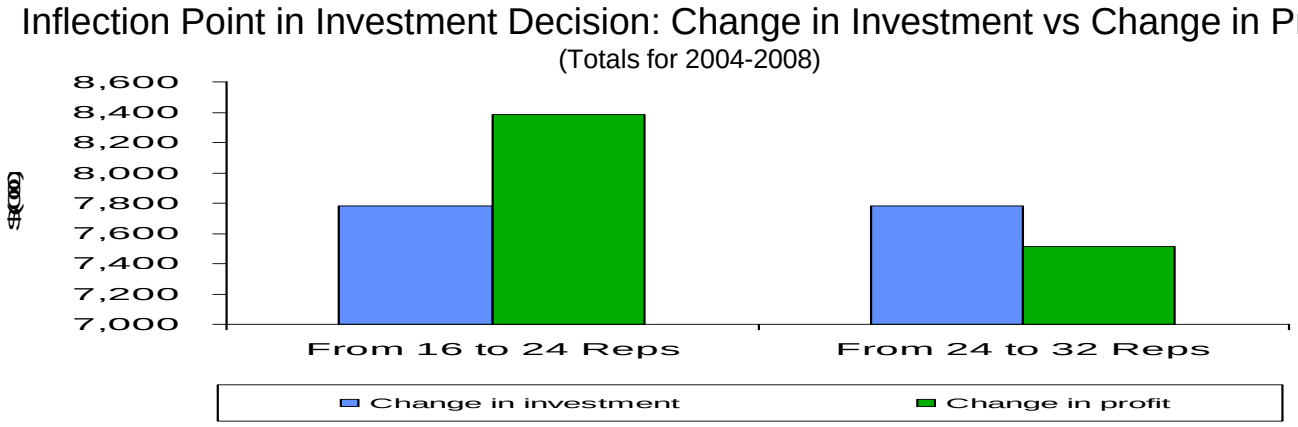
Three strategic LTC investments are required to deliver incremental revenue of $120 MM.

		2004	2005	2006	2007	2008	TOTAL
Sales & Marketing Optimization							
Sales Force Optimization							
• Increase field based reps from 55 to 79, add 3 DM • 8 RAMs, 1 RM	Investment	$7.7MM	$8.1MM	$8.2MM	$8.3MM	$2.5MM	$34.8MM
Marketing Expansion							
• Add 2 additional staff and Increase the promotional budget by 2.8 MM (Total 38 FTE)	Investment	$3.2MM	$3.2MM	$3.2MM	$3.2MM	$1.0MM	$13.8MM
New Sales		**$14.5**	**$29.4**	**$29.9**	**$31.1**	**$8.6**	**$112.6**
Clinical Data Investment							
• Fund relevant DOC, MRDD and SNF IIS	Investment	$1.0MM	$0.5MM	$0	$0	$0	$1.5MM
New Sales		**$0**	**$1.3**	**$2.8**	**$2.5**	**$1.1**	**$7.7**
Total Incremental Sales		**$14.5**	**$30.7**	**$32.7**	**$33.6**	**$ 9.7**	**$120.3**
Total Incremental Investment		$11.9	$11.8	$11.4	$11.5	$ 3.5	$50.1
Total Incremental Margin		$1.6	$17.1	$19.4	$19.2	$ 5.6	$62.9

Sales Force Optimization Analysis: Target Addition of 24 LTC Sales Representatives







Benchmarking LTC Sales Efficiency: Additional 24 representatives

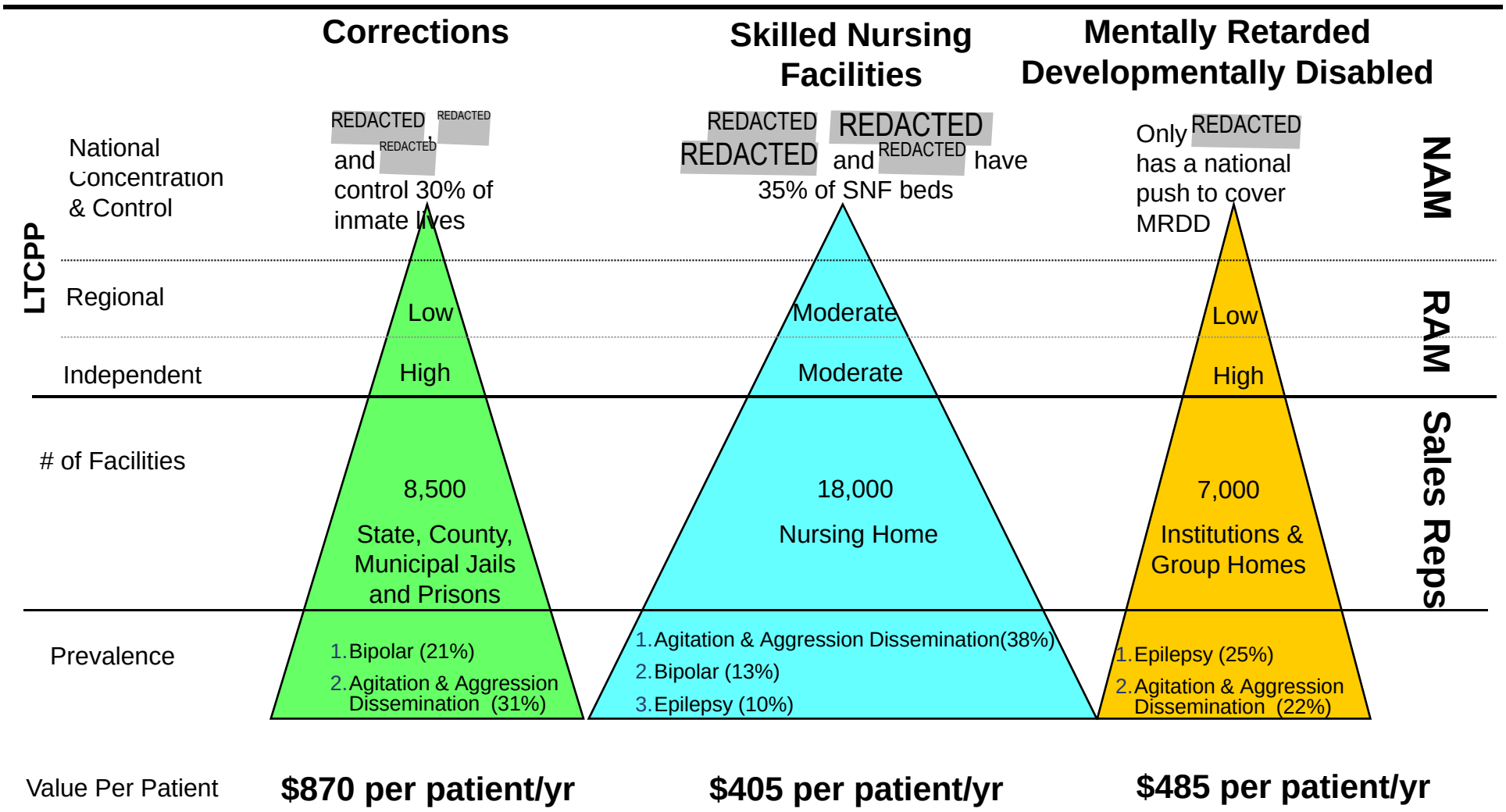
Local Field Sales Coverage

(FTE Representatives)

Average WAC Per Day of Therapy		$ Per FTE/ Per Year	$ Per FTE/ Per Year (Price Adjusted to REDACTED WAC)
$10.69	REDACTED: 176 FTEs /263 Reps	$2.8 MM	$2.8 MM
$2.60	Abbott Today: 55 FTES/Reps	$2.4 MM	$9.9 MM
$5.08	REDACTED: 80 FTE / 160 Reps 5 NAMs / RAMs unknown	$2.0 MM	$4.2 MM
$2.60	Abbott Proposed Expansion: 79 FTEs/Reps 3 NAMs / 8 RAMs	$1.9 MM	$7.8 MM
$7.77	REDACTED: 188 FTE / 280 Reps 8 NAMs and 10 RAMs for REDACTED alone	$1.8 MM	$2.5 MM

Sources: REDACTED, Abbott field Interviews, REDACTED primary market research conducted for Abbott in June 2003. FTE counts were achieved by taking 70 % of total rep numbers to account for the primary detail on the atypical antipsychotic.

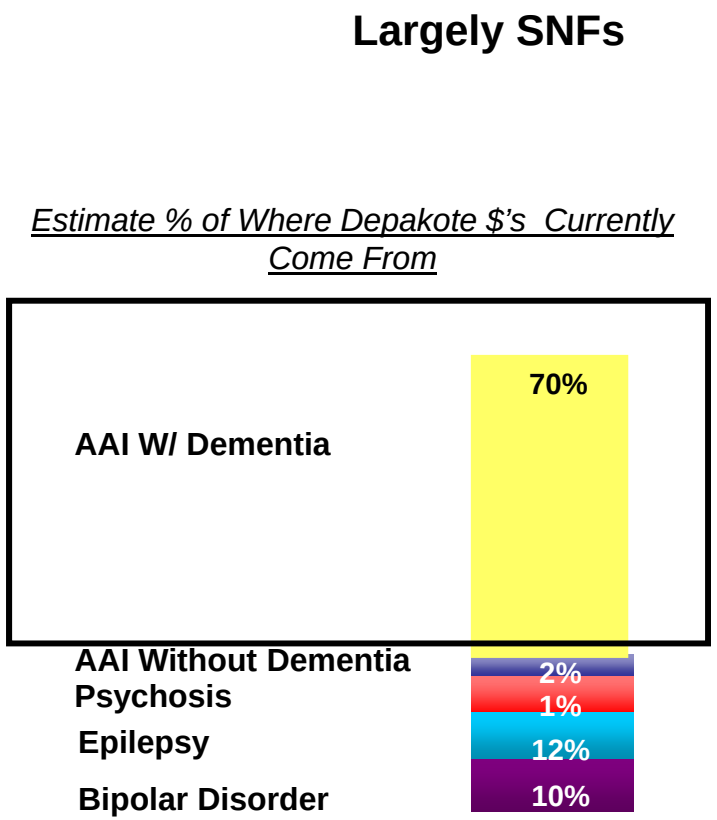
Depakote LTC Optimizaton: Expanding focus from SNF to: DOC, MRDD and SNF.



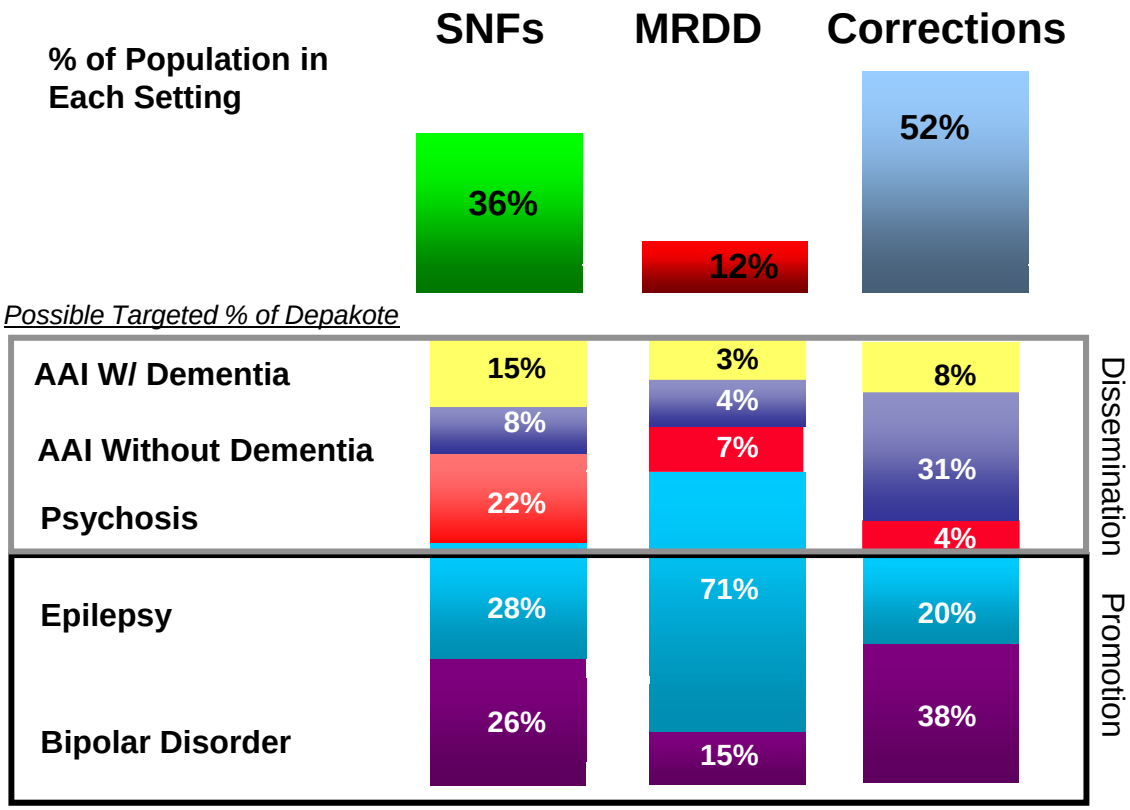
Sources: REDACTED, Abbott field Interviews, REDACTED primary market research conducted for Abbott in June 2003.

Depakote LTC Optimization Can: Reduce Promotional Risk

LTC W/O Optimization



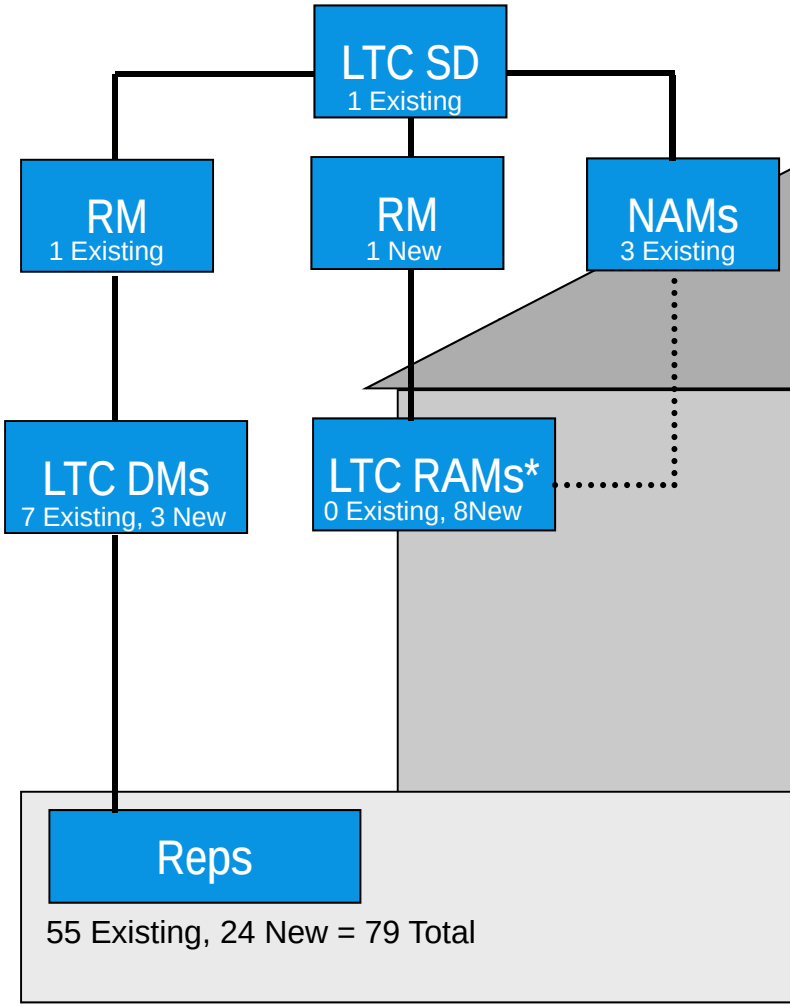
LTC Optimization



Sources: Current sales by condition from Abbott qualitative analysis. Optimizes sales by condition from REDACTED supplied primary data (QA). Presented results have been rounded from final REDACTED findings.

New LTC field resources will provide greater coverage within relevant LTC market segments.

Proposed LTC Field Organization



Realigned Account Responsibilities

National Account Managers (NAMs)

- Support national VPs of LTCPPs
- Establish contracts
- Monitor contract performance
- Launch major programming/initiatives
- Monitor national sales trends and practices

LTC Regional Account Managers (RAMs)

- Support regional VPs at the National LTCPPs
- Develop regional initiatives & assure implementation of national initiatives
- Maintain relationships with major independents
- Call on State & large county DOCs and their pharmacies
- Maintain key state-level association relationships

LTC Specialists

- Call on target pharmacies and outlets
- Detail relevant prescribers
- Educate key influencers and care givers

Depakote LTC Optimization Can: Create organization capable of supporting the most profitable segments of LTC

- **Summary of Optimization Changes**
  - Channel align marketing and sales activities to highest opportunity channels within LTC
    - » SNF
    - » MRDD
    - » DOC
  - Establish LTC IIS Funding for Channel Specific Studies
    - » 2004
    - » 2005
  - Expand pull through organization
    - » NAM — National Account Management
    - » RAM — Regional Account Management
    - » LTC Sales Representative — Account based selling

2004-2008 P&L Assumptions

- **Sales Force Optimization Includes:**
  - $18,000 per rep,$45,000 per RAM and $150,000 per NAM war chest allotment
  - Voucher allotments per reps can be covered by the current franchise allotment, no samples
  - $168,000 fully loaded costs per year for for reps
  - $259,000 fully loaded costs per year for NAMs, RAMs and DMs
  - 40% rep effectiveness in 2004 and 100% effectiveness in remaining years

- **Marketing Expansion Includes:**
  - A marketeering program budget return of 1.5:1 per Abbott promotional analytical average ROI experience with Abbott marketing programs
  - $207,000 fully loaded costs per year for an SPM
  - $187,000 fully loaded costs per year for PMs

- **Clinical Data Investments Include:**
  - 75% percent chance of study success
  - Similar sales return as produced by the introduction of the two previously incomplete sets of clinical trial data into the SNF market place

- **Margin calculations include a 6% reduction for cost of goods sold, freight and other miscellaneous PPD distribution allocations**

New LTC Clinical Data Will Drive Additional LTC Growth

Three substantial investigator initiated studies will drive $7.7 MM in incremental revenues through 2008, for $1.5 MM investment.

			2003	2004	2005	2006	2007	2008
Total of three studies ***Assuming 75% probability of success:***		**Total Revenue** *(Current sales force)*		**$0.0**	**$1.3**	**$2.8**	**$2.5**	**$1.1**
		Total Cost		**$1.0**	**$0.5**			
Detail by strategic component:	***Study description:***							
As monotherapy, demonstrate efficacy, superior tolerability, and cost-effectiveness vs. atypicals, VPA or other AEDs. As adjunctive therapy, demonstrate efficacy and safety.	**IIS Study 1: Depakote ER in MRDD**	**Study Revenue** *(Current sales force)*			**$.43**	**$.62**	**$.56**	**$.25**
		Study Cost		**$0.33**	**$0.25**			
	IIS Study 2: Depakote ER in DOC	**Study Revenue** *(Current sales force)*			**$.43**	**$1.09**	**$.99**	**$.44**
		Study Cost		**$0.33**	**$0.25**			
As adjunctive therapy, demonstrate efficacy & safety in patients whose symptoms are inadequately controlled by atypicals	**IIS Study 3: Depakote ER as adjunctive to atypicals in elderly agitation**	**Study Revenue** *(Current sales force)*			**$.43**	**$1.09**	**$.99**	**$.44**
		Study Cost		**$0.33**				

KOLs advise that clinical data specific to each Sector is needed to best impact Depakote business in the DOC and MRDD Markets.

- **For the DOC Sector :**
  - **The DOC represents a unique group of patients with biological and environmental issues contributing to patient condition**
  - **Pharmacological treatment decisions for DOC patients can be different than for those in the general population:**
    - » **Severity of condition can be greater in the DOC environment**
    - » **Patient compliance can be more problematic**
    - » **Consequences of treatment failures more severe**
  - **Studies in the DOC patient population most relevant to practitioners**

- **For the MRDD Sector:**
  - **The MRDD patient population is unique and represents a group that can have severe handicaps**
  - **Identification and appropriate classification of patient conditions is problematic due to the patient's inability to articulate symptoms**
  - **Pharmacologic treatment decisions for MRDD patients can be different due to the nature of the patient's condition**

Source: Abbott Conducted Qualitative Research with Key Opinion Leaders, Summer 2003

Proposed IIS LTC Study Descriptions in Correctional Facilities

- **Conditions Assessed:**
  - Agitated/Aggressive/Impulsive behaviors with or without head injuries
  - (per REDACTED)Bipolar Disorder with at least one comorbidity (have a laundry list that could include:
    - » Agitated/Aggressive/Impulsive behaviors
    - » MRDD
    - » head injury
    - » substance abuse
    - » ADHD
    - » Others (DR. REDACTED noted that the design could resemble the abulatory study she is currently doing for Psychiatry Team)
- **Type of Study:**
  - Prospective (Note: Informed consent requirements and advocacy oversight may require that any prospective study use two active agents.)
- **Study Setting:**
  - Jails
  - Prisons
  - Probation catchment (DR REDACTED suggested that if getting IRB approved for prison population is a problem, it would be possible to screen probation patients or patients with a prison/jail record)
- **Primary Assessment:**
  - Efficacy
    - » Improvement in Bipolar
    - » Decreased frequency and severity of behaviors; patients “less triggered” by stressors
    - » Decreased frequency and severity of comorbid condition
  - Also measure side effects, safety, tolerability

Source: Abbott Conducted Qualitative Research with Key Opinion Leaders, Summer 2003

Proposed IIS LTC Study Descriptions in Correctional Facilities (continued)

- **Primary endpoints:**
  - YMRS
  - Overt Aggression Scale and others
  - Staff keeps log of frequency of behaviors; measure Vs. staff assessment
    - Use of restraints
    - Time in isolation or solitary confinement
    - Number of medication passes required
  - Seizure measurement scales
  - Other scales relevant to comorbid conditions
  - Cost savings due to better compliance, fewer side effects, fewer relapses etc
- **Time period for study:**
  - Jails: 4 week study
  - Prisons: 4 week study (but could be longer due to inmate length of stay)
  - Probation: 8 week study
- **Patient Inclusion Criteria:**
  - See primary assessment
- **Treatment Arms:**
  - Depakote ER vs placebo or Loading dose Depakote ER vs. Non-Loading Dose DepakoteER (per DR. REDACTED
  - Depakote ER Vs. valproic acid
  - Depakote ER Vs. an antipsychotic (Zyprexa: could show results and differences in side effect profiles)

Source: Abbott Conducted Qualitative Research with Key Opinion Leaders, Summer 2003

Proposed IIS LTC Clinical Study Descriptions in MRDD

- **Conditions assessed:**
  - Agitated/Aggressive/Impulsive behaviors with or without seizures
- **Type of Study:**
  - Prospective (per MD respondents)
  - Retrospective ok (per REDACTED pharmacist)
- **Primary Assessment:**
  - Efficacy
    - » decrease frequency and severity of behaviors; patients “less triggered” by stressors
    - » decrease frequency and severity of seizures
- **Primary endpoints:**
  - Overt Aggression Scale and others
  - Staff keeps log of frequency of behaviors; measure Vs. staff assessment
  - Seizure measurement scales
- **Time period for study:**
  - 3-6 months (it was noted that there is a seasonal response: patients have more behavioral problems in the Spring/Summer versus Fall/Winter. Therefore a study of 1 yr... or more would eliminate the seasonality)
- **Patient Inclusion Criteria:**
  - Patients are required to have failed behavioral therapy or behavioral therapy must have been ruled out as an option in order to begin pharmacotherapy.
  - It was also suggested that patients could be those who previously failed treatment on a low dose of an antipsychotic
- **Treatment Arms:**
  - Depakote ER Vs. behavioral therapy (double blind)
  - Depakote ER Vs. an antipsychotic (Zyprexa: could show results and differences in side effect profiles)
  - AP therapy Vs. AP plus Depakote ER
  - Depakote ER Vs. another AED

Source: Abbott Conducted Qualitative Research with Key Opinion Leaders, Summer 2003

KOLs also advise that the best development path for Depakote in elderly agitation would be adjunctive studies with atypicals.

- **Two major clinical studies of Depakote monotherapy were discontinued, for reasons unrelated to efficacy:**
  - **M97-738: Depakote in Elderly Mania** – Showed efficacy[1], but discontinued in 1999 because of excessive somnolence
    - » Somnolence was caused by dosing schedule that was too aggressive for an elderly population
  - **M99-082: Behavioral Agitation in Elderly patients with Dementia** – Discontinued in 2001 before any results were available, because recruitment targets could not be met at reasonable cost
    - » Recruitment was very slow because inclusion criteria were too restrictive: in particular, patients on antidepressants were excluded, thus reducing the eligible population by around 50%

- **Key opinion leaders therefore advise an adjunctive study as the best development path for Depakote in BDD:**
  - **Investigators unlikely to be willing to conduct further Depakote monotherapy trials**, because of prior experiences
  - **The adjunctive market is large:** Geriatric psychiatry advisors estimate 50-70% of patients require polypharmacy for management of aggression
  - **Adjunctive Depakote works:** Existing data[2] shows that Depakote + atypical combination is effective in patients unresponsive to monotherapy or taking multiple atypicals
  - **Recruitment will be easier:** The majority of BDD patients are already treated with antipsychotics, so the eligible population will be large
  - **Drop-outs due to adverse events can be minimized:** Availability of ER 250 mg and a better understanding of tolerability issues in the elderly means the side-effects caused M97-738 to be discontinued can be avoided

Sources: (1) Tariot *et al.*, Curr. Therapeutic Res. 2001, 62: 51-67; (2) Narayan & Nelson, J. Clin. Psychiatry, 1997, 58: 351-4; M99-082 Study protocol; Draft FDA submission prepared by Abbott proposing label change to Depakote for indication in elderly agitation; Neuroscience clinical team, strategic review document

Proposed IIS LTC Clinical Study Descriptions in Elderly Agitation

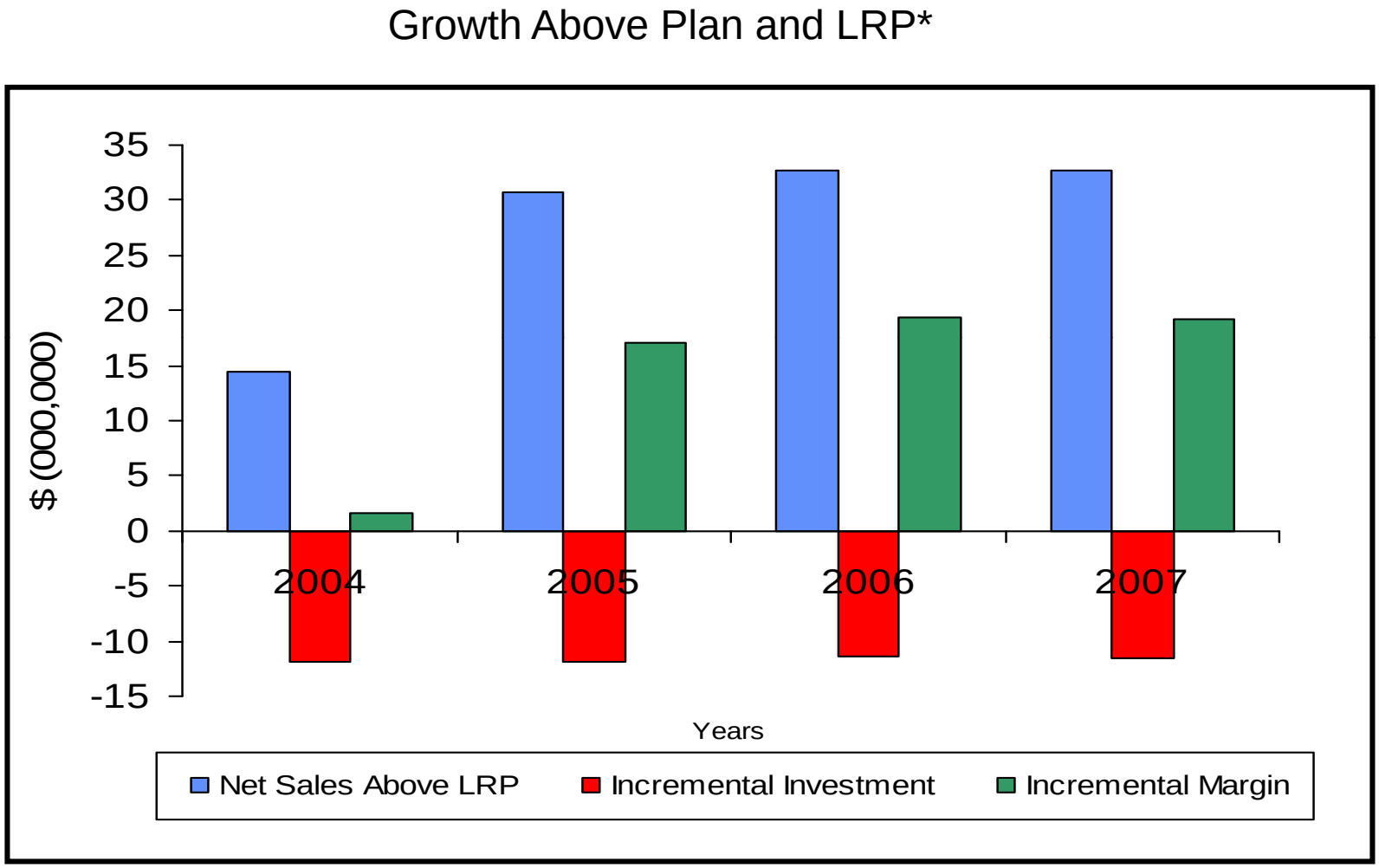
- **Conditions assessed:**
  - Agitated/Aggressive/Impulsive behaviors with or without seizures
- **Type of Study:**
  - Prospective open label
- **Primary Assessment:**
  - Efficacy as measured by the PANSS Excited Component, which includes measurement of the following:
    - impulse control
    - tension
    - hostility
    - degree of cooperativeness
    - excitement
- **Primary endpoints:**
  - PANSS Excited Component
- **Time period for study:**
  - 12 months
- **Patient Inclusion Criteria:**
  - Probable or possible Alzheimer's
  - Probable or possible vascular dementia
- **Treatment Arms:**
  - Depakote ER and atypical, vs. atypical + atypical , vs. atypical alone; n=30-40 each group

Source: Abbott Conducted Qualitative Research with MLs and Key Opinion Leaders, Fall 2002.

LTC Strategic Investment Summary: Grow sales by focusing on Department of Corrections, Mentally Retarded Developmentally Disabled and Skilled Nursing Facilities.

- **Refocus today's largely SNF directed sales and marketing efforts towards a more expansive set of targets: DOC, MRDD and SNF**
  - Corrections: deliver core bipolar message
  - Mentally Retarded Developmentally Disabled: deliver core epilepsy message
  - Skilled Nursing Facility: increase bipolar and epilepsy messaging
  - Target all three channels with additional marketing programs
- **Generate in 2004: $14.5 MM in new LTC sales from $11.9 MM in new investments with a positive margin of $1.6MM:**
  - $3.2 in additional marketing resources: 2 new FTEs (Channel Aligned to DOC and MRDD) with $2.8 MM in promotional dollars
  - $7.7 MM in additional field resources: 24 reps/3 DMs and 8 RAMs/1 RM
  - $1.0 MM in additional LTC dedicated IIS funding
- **Generate $120 MM in new LTC sales in years 2004-2008 from investment**
  - 2005: $30.7 MM incremental sales: $17.1 MM incremental margin
  - 2006: $32.7 MM incremental sales: $19.4 MM incremental margin
  - 2007: $32.7 MM incremental sales: $19.2 MM incremental margin

Targeted investments in LTC can increase sales over current LRP projections by $120 in five years.



- Note: 2004 Reflects the most recent plan numbers. Year 2005-2008 LRP numbers are likely to be updated in December 2003.

Outline

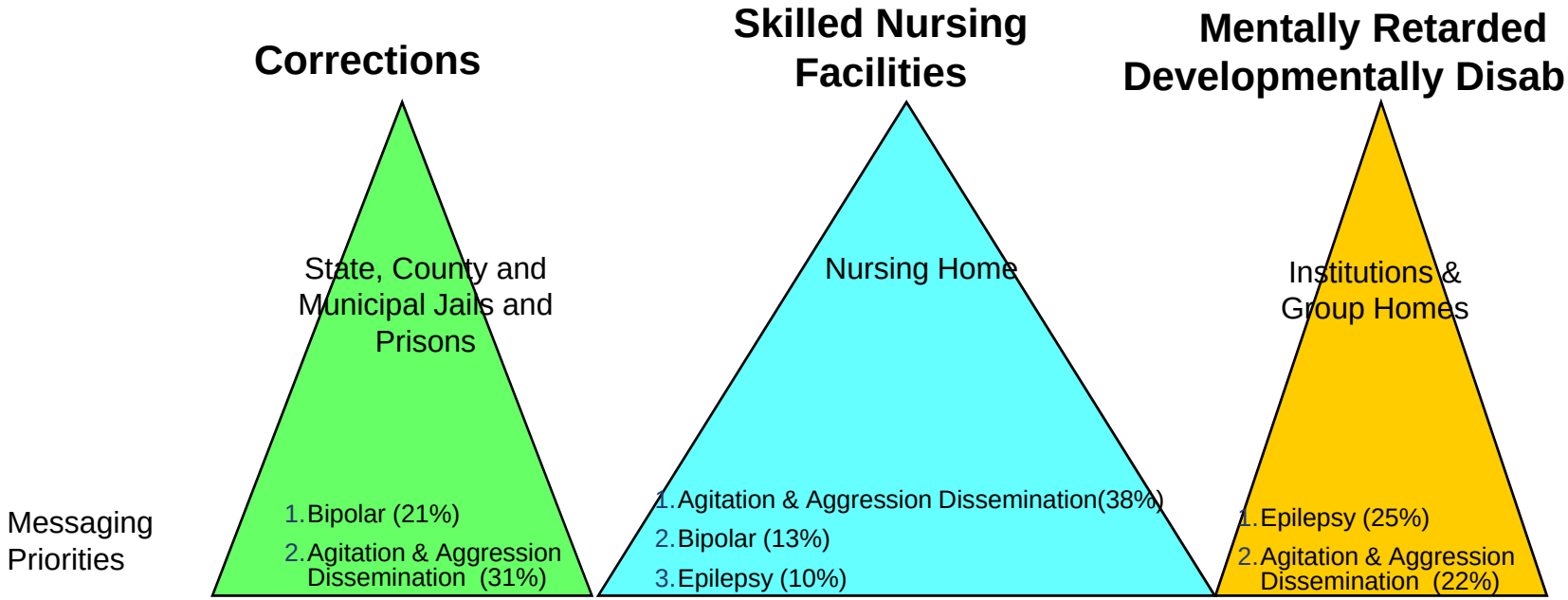
- **Executive Summary of LTC Strategy**
- **Strategic Investment Proposal Framework**
- **Targeted LTC Channels**
- **Sales Force Optimization Summary**
- **Summary of Financial Analysis**

Depakote LTC Optimization Can: Reduce Promotional Risk

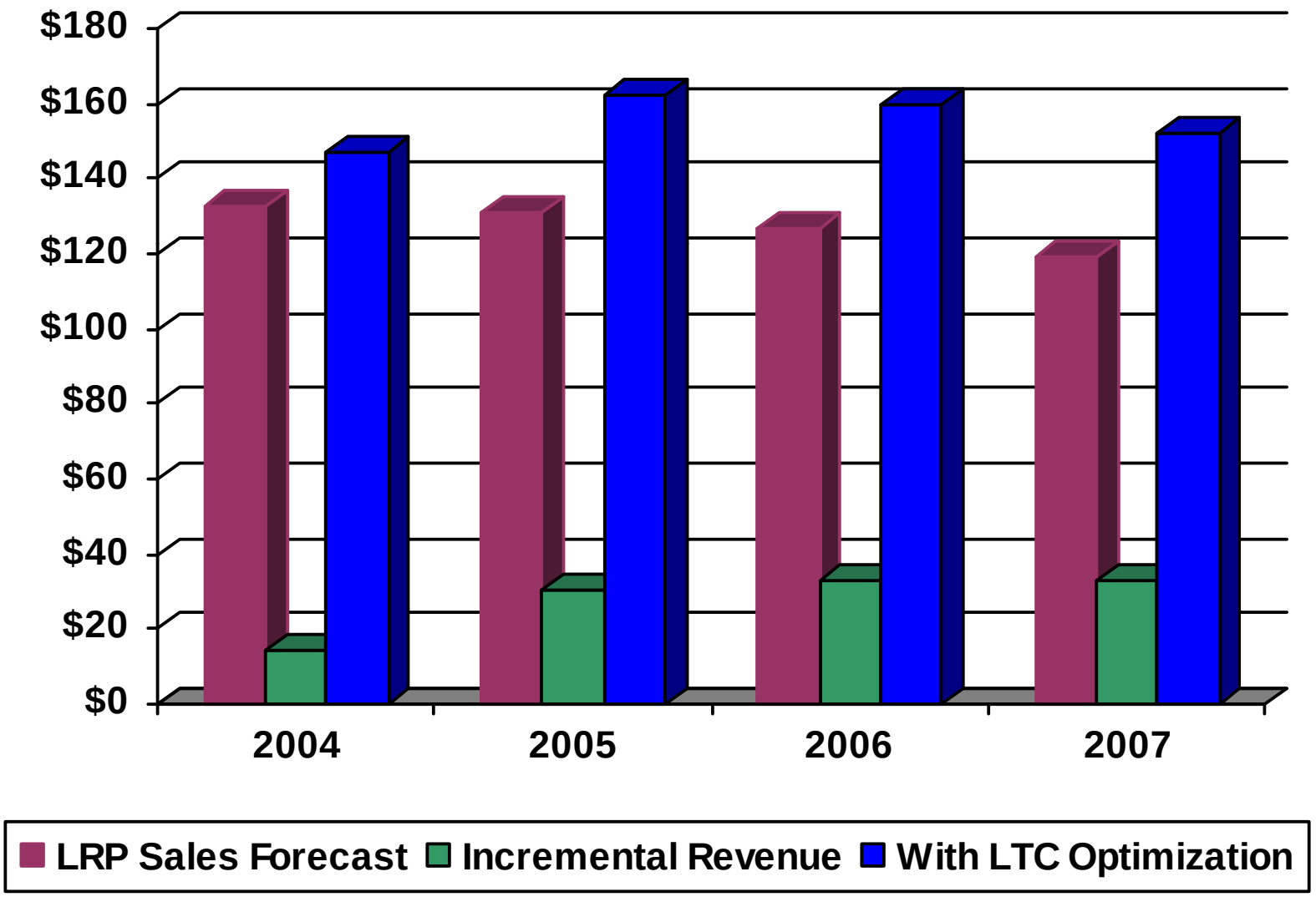
Today



Optimization

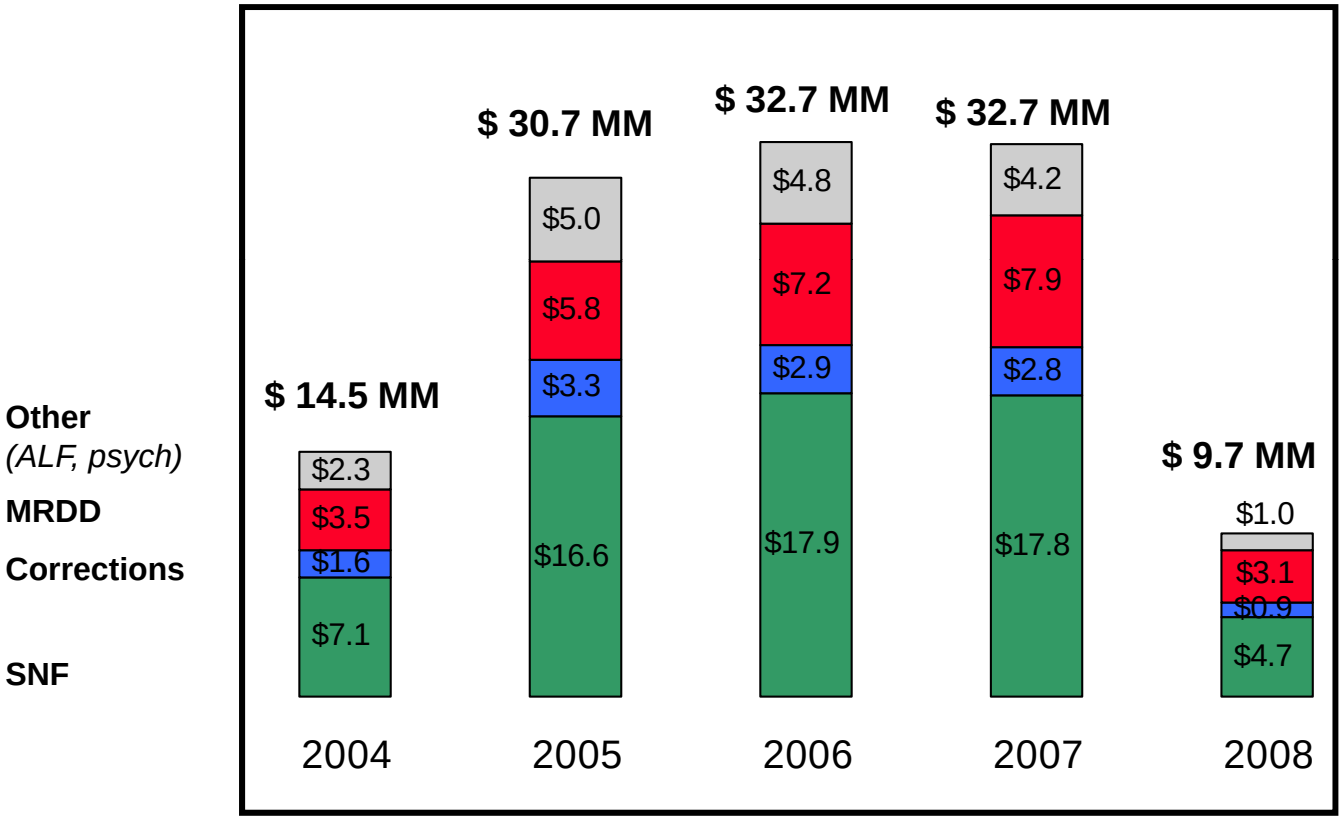


LTC Optimization Provides Incremental Revenue



Where does the growth come from?

Change in Revenues
Over 2004 Plan, 2005-2008 LRP*



*Note: The 2005-2008 LRP will be updated in December 2003.

New LTC Clinical Data Will Drive Additional LTC Growth

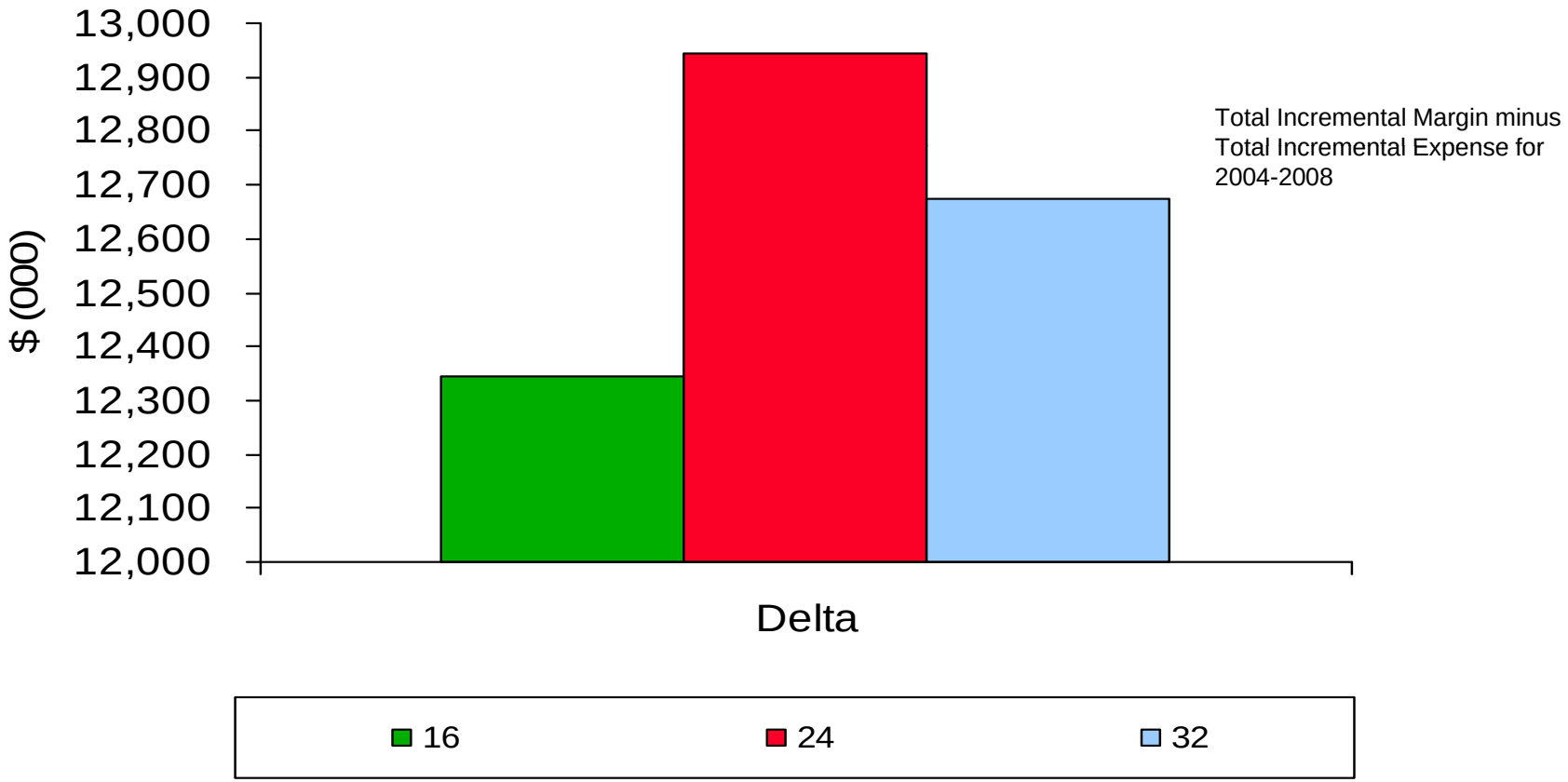
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			2003	2004	2005	2006	2007	2008
Total of three studies ***Assuming 75% probability of success:***		**Total Revenue** *(Current sales force)*		**$0.0**	**$1.3**	**$2.8**	**$2.5**	**$1.1**
		Total Cost		**$1.0**	**$0.5**			
Detail by strategic component:	***Study description:***							
As monotherapy, demonstrate efficacy, superior tolerability, and cost-effectiveness vs. atypicals, VPA or other AEDs. As adjunctive therapy, demonstrate efficacy and safety.	**IIS Study 1: Depakote ER in MRDD**	**Study Revenue** *(Current sales force)*			**$.43**	**$.62**	**$.56**	**$.25**
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As adjunctive therapy, demonstrate efficacy & safety in patients whose symptoms are inadequately controlled by atypicals	**IIS Study 3: Depakote ER as adjunctive to atypicals in elderly agitation**	**Study Revenue** *(Current sales force)*			**$.43**	**$1.09**	**$.99**	**$.44**
		Study Cost		**$0.33**				

Adding 24 additional representatives reaches the inflection point between incremental investment and incremental margin

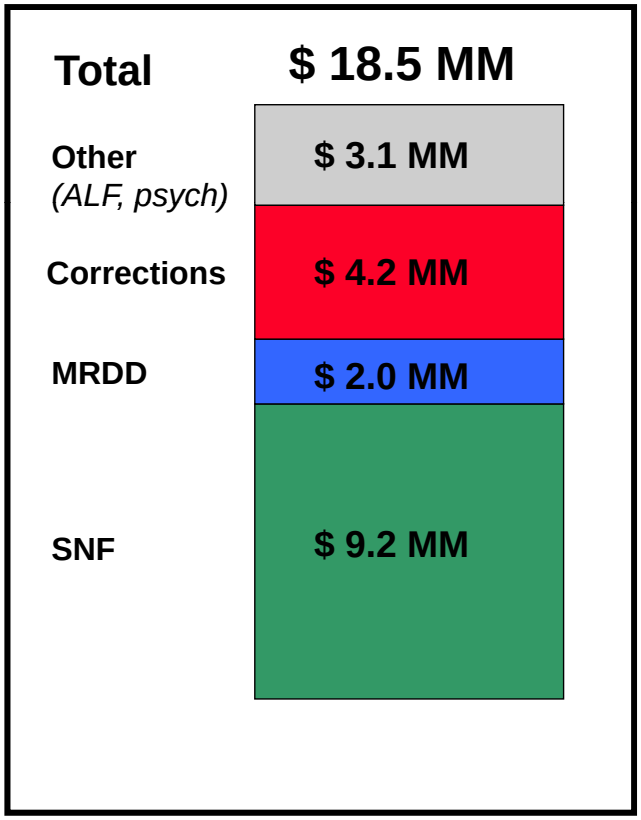
Inflection Point in Investment Decision:

[Total Incremental Contribution Margin-Total Incremental Expense]=Delta



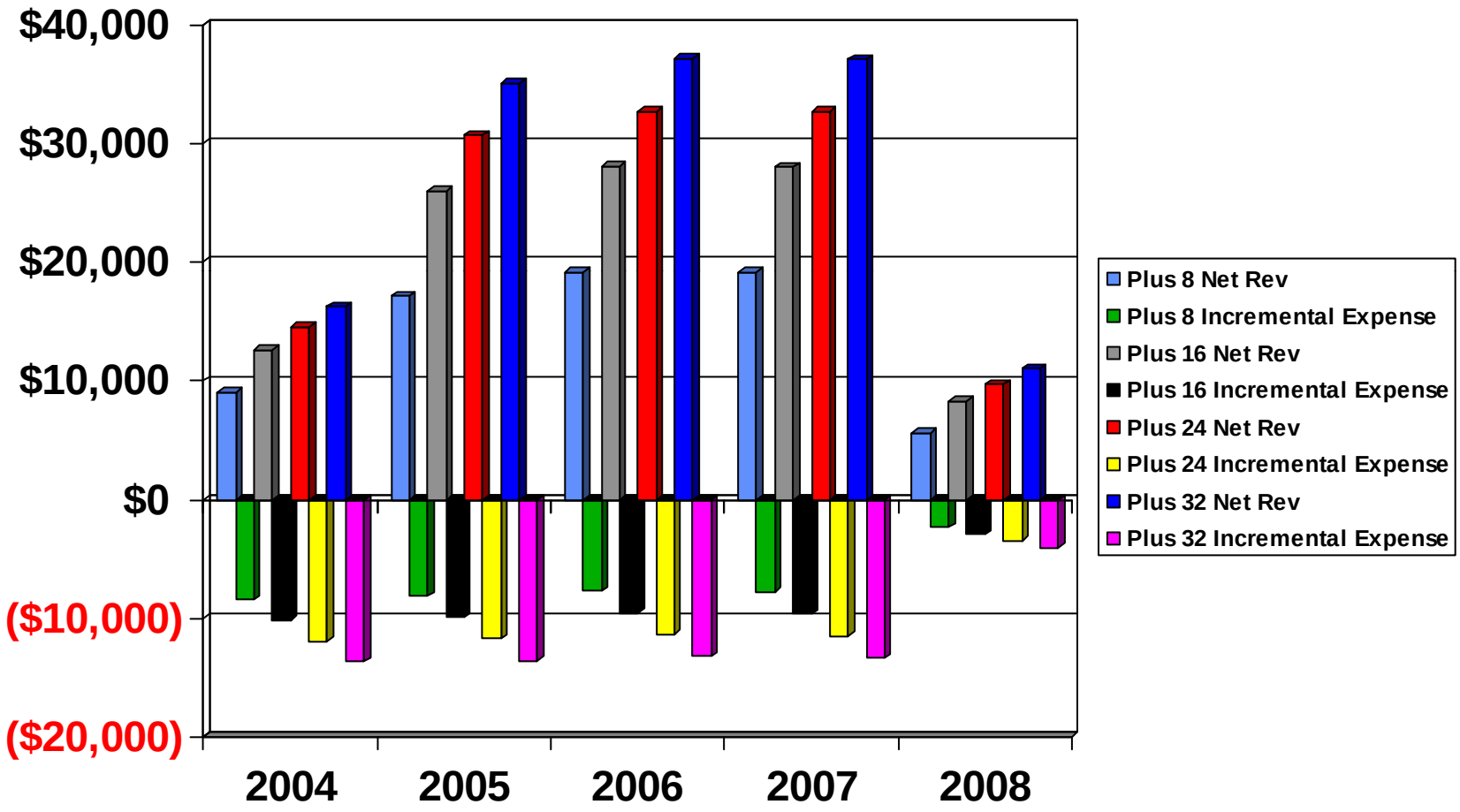
Where does the LTC growth come from (2003-2004)?

Change in Revenues
Over 2003 Actual



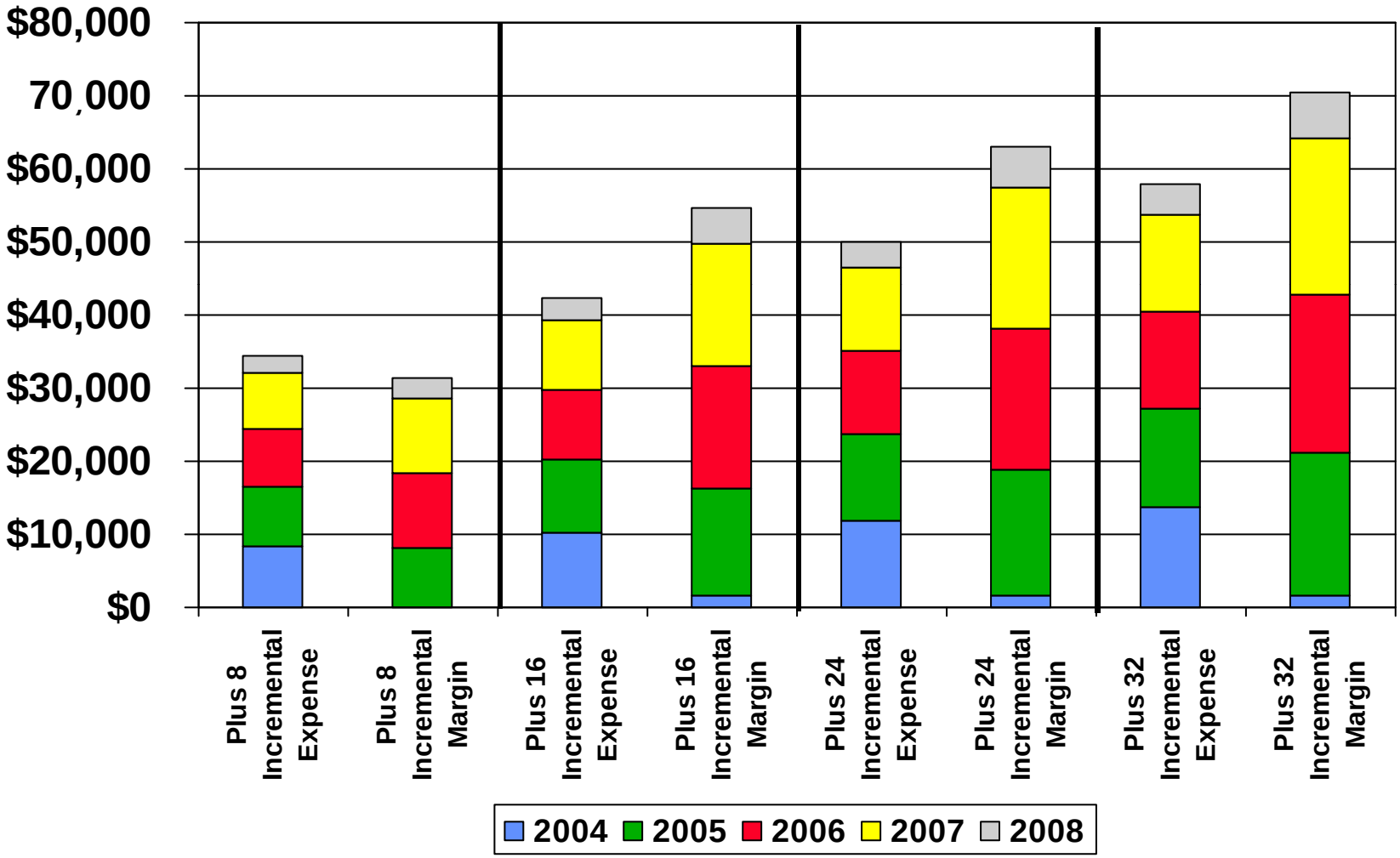
*Note: The 2005-2008 LRP will be updated in December 2003.

Incremental Revenue Compared to Incremental Expenses

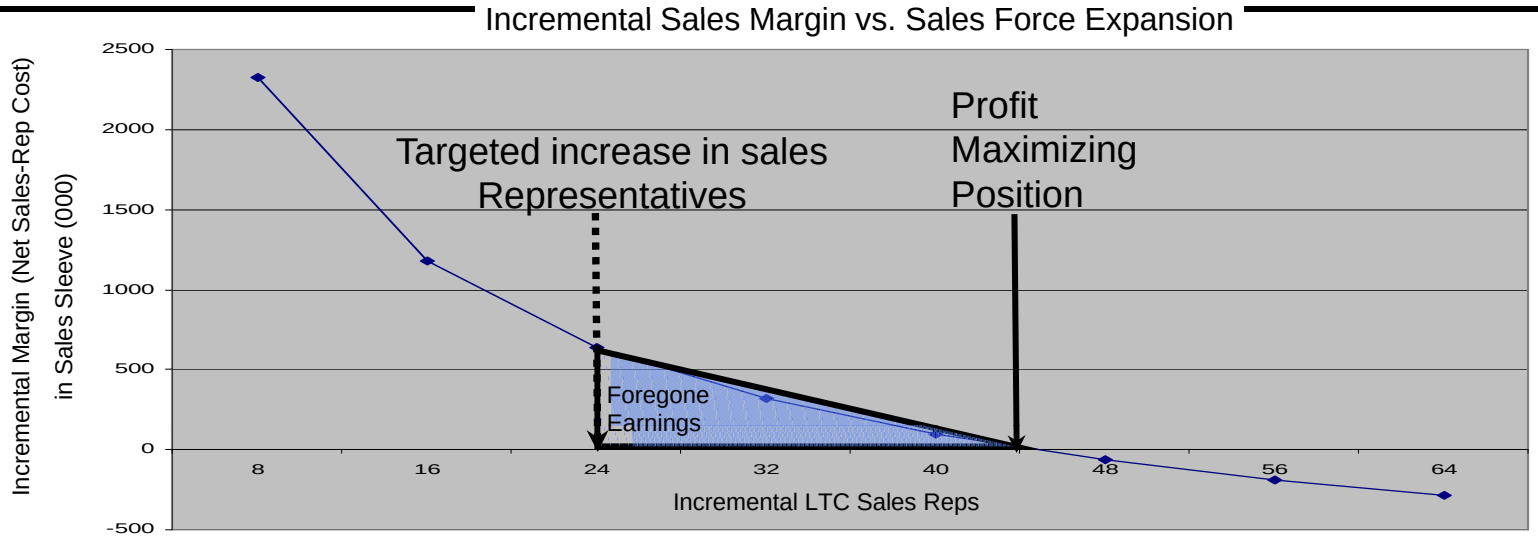


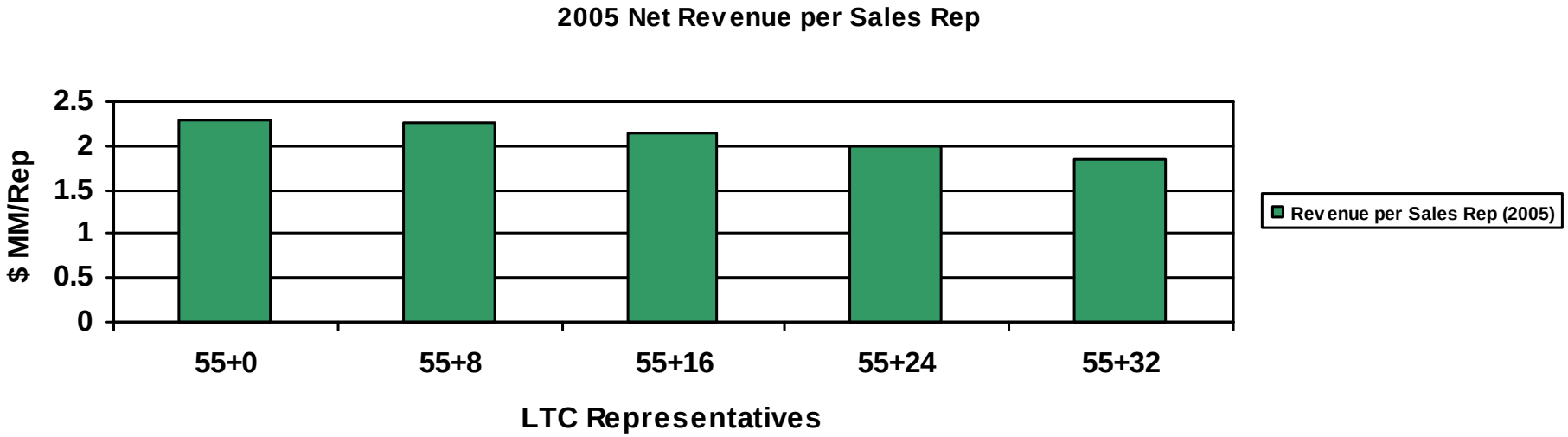
	2004	2005	2006	2007	2008
Plus 8 Net Rev	$9,069	$17,132	$19,188	$19,116	$5,634
Plus 8 Incremental Expense	($8,454)	($8,151)	($7,729)	($7,809)	($2,367)
Plus 8 Incremental Margin	$71	$7,953	$10,308	$10,160	$2,929
Plus 16 Net Rev	$12,633	$26,044	$28,100	$28,028	$8,308
Plus 16 Incremental Expense	($10,190)	($9,951)	($9,556)	($9,663)	($2,931)
Plus 16 Incremental Margin	$1,685	$14,530	$16,858	$16,683	$4,878
Plus 24 Net Rev	$14,493	$30,692	$32,748	$32,676	$9,702
Plus 24 Incremental Expense	($11,927)	($11,751)	($11,383)	($11,517)	($3,496)
Plus 24 Incremental Margin	$1,696	$17,099	$19,400	$19,198	$5,624
Plus 32 Net Rev	$16,252	$35,090	$37,146	$37,074	$11,021
Plus 32 Incremental Expense	($13,664)	($13,551)	($13,210)	($13,371)	($4,061)
Plus 32 Incremental Margin	$1,613	$19,434	$21,708	$21,478	$6,299

Increasing the size of the salesforce from 16 to 32 representatives never reaches the point of inflection where incremental investment drives equivalent incremental earnings (i.e. the 40+ rep scenario)

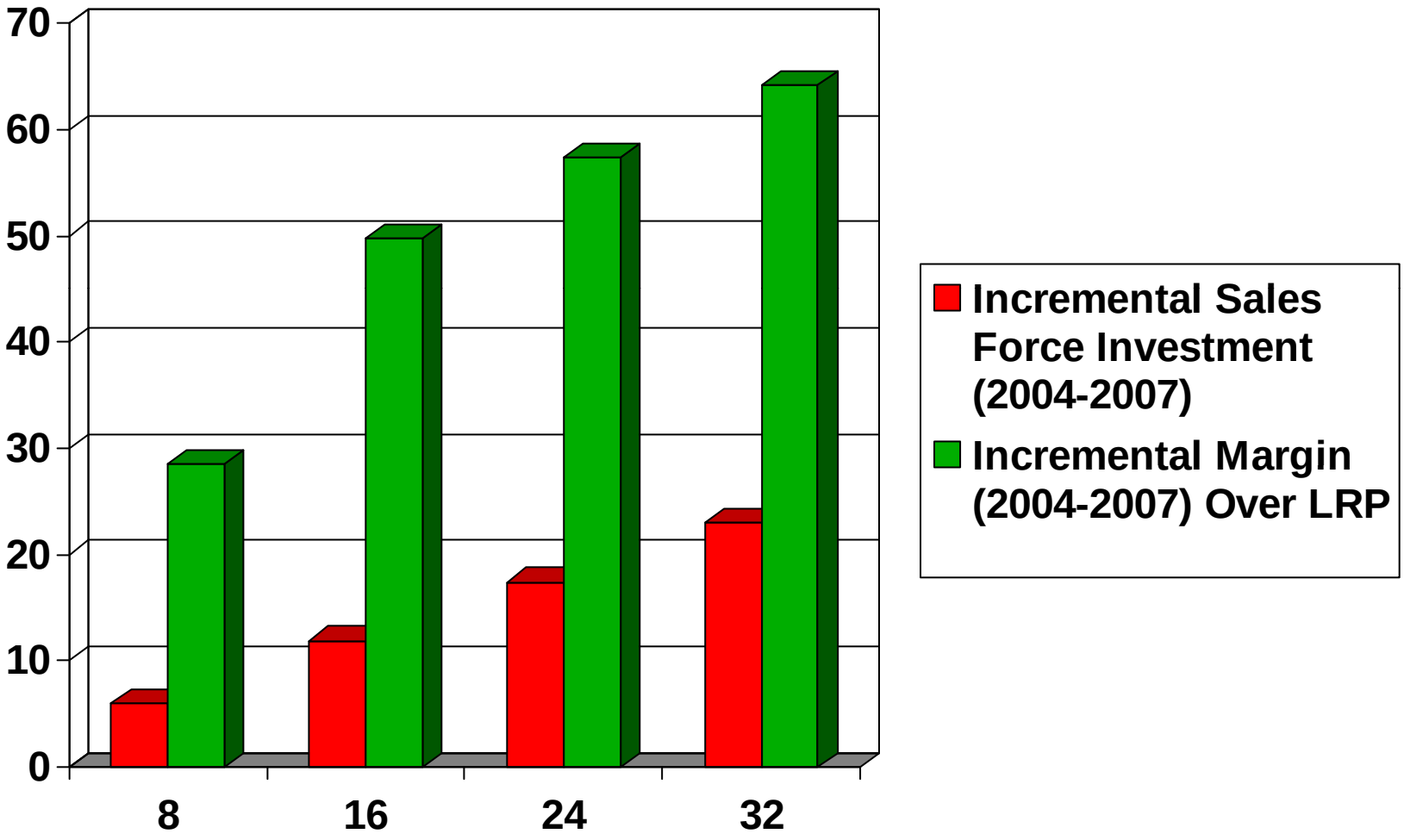


Sales Force Optimization: Target Addition of 24 LTC Sales Representatives

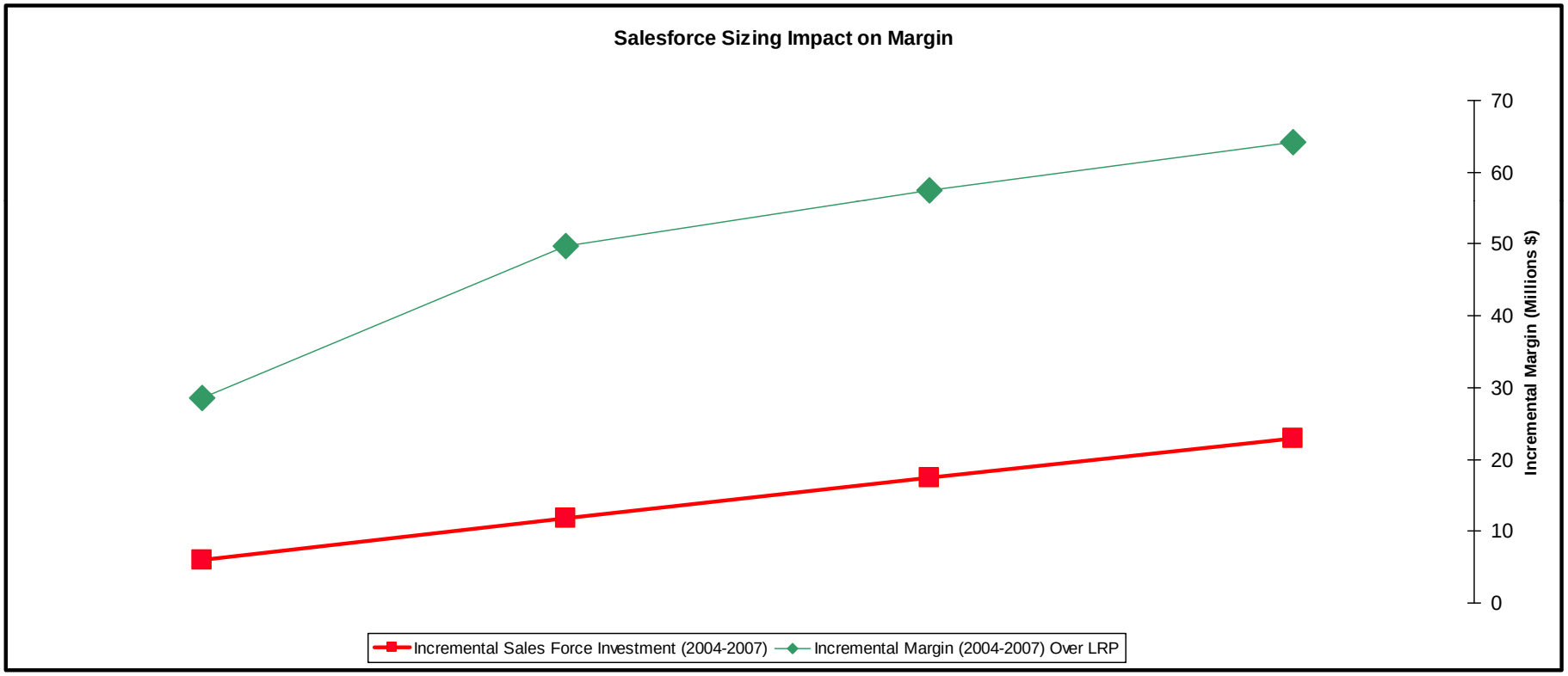




Incremental Margin Improves Over All Scenarios

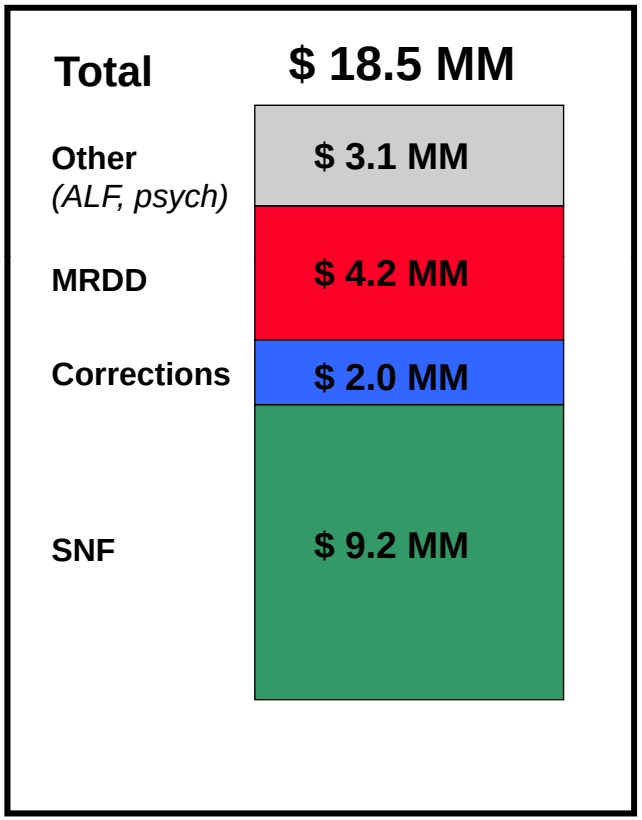


Sales Force Optimization: Target Addition of 24 LTC Sales Representatives

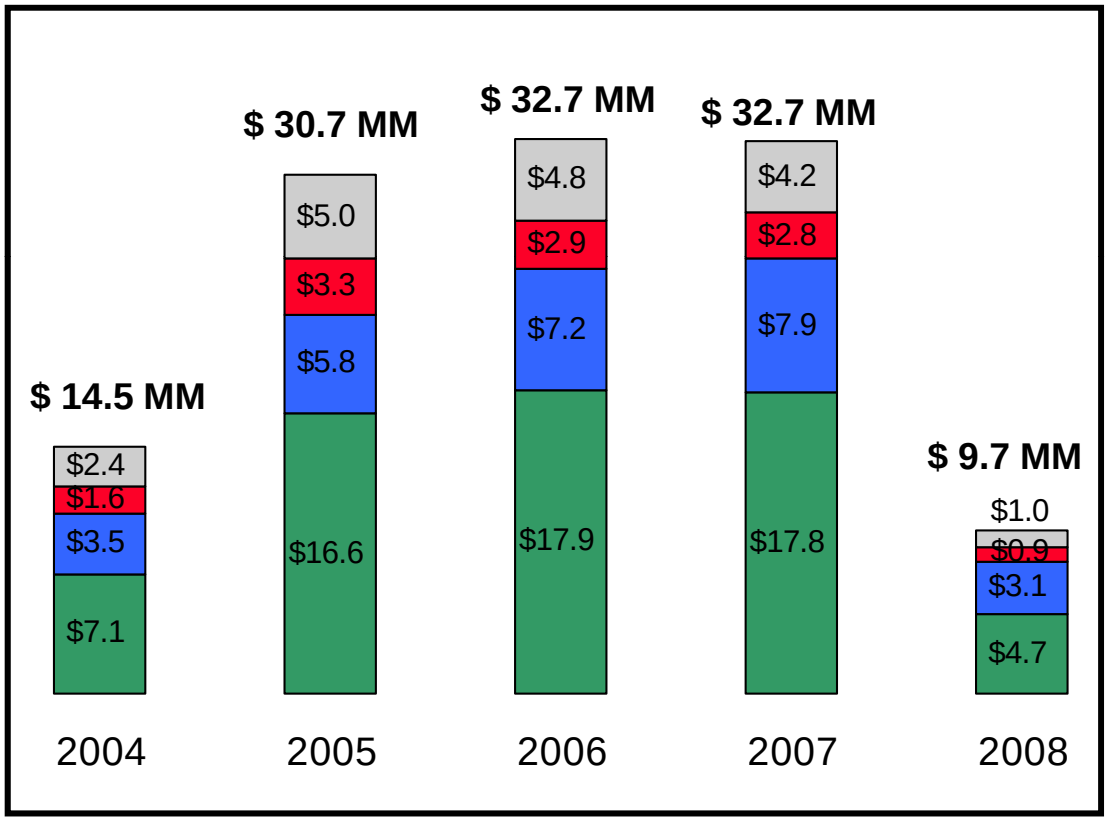


Where does the growth come from?

Change in Revenues
Over 2003 Actual

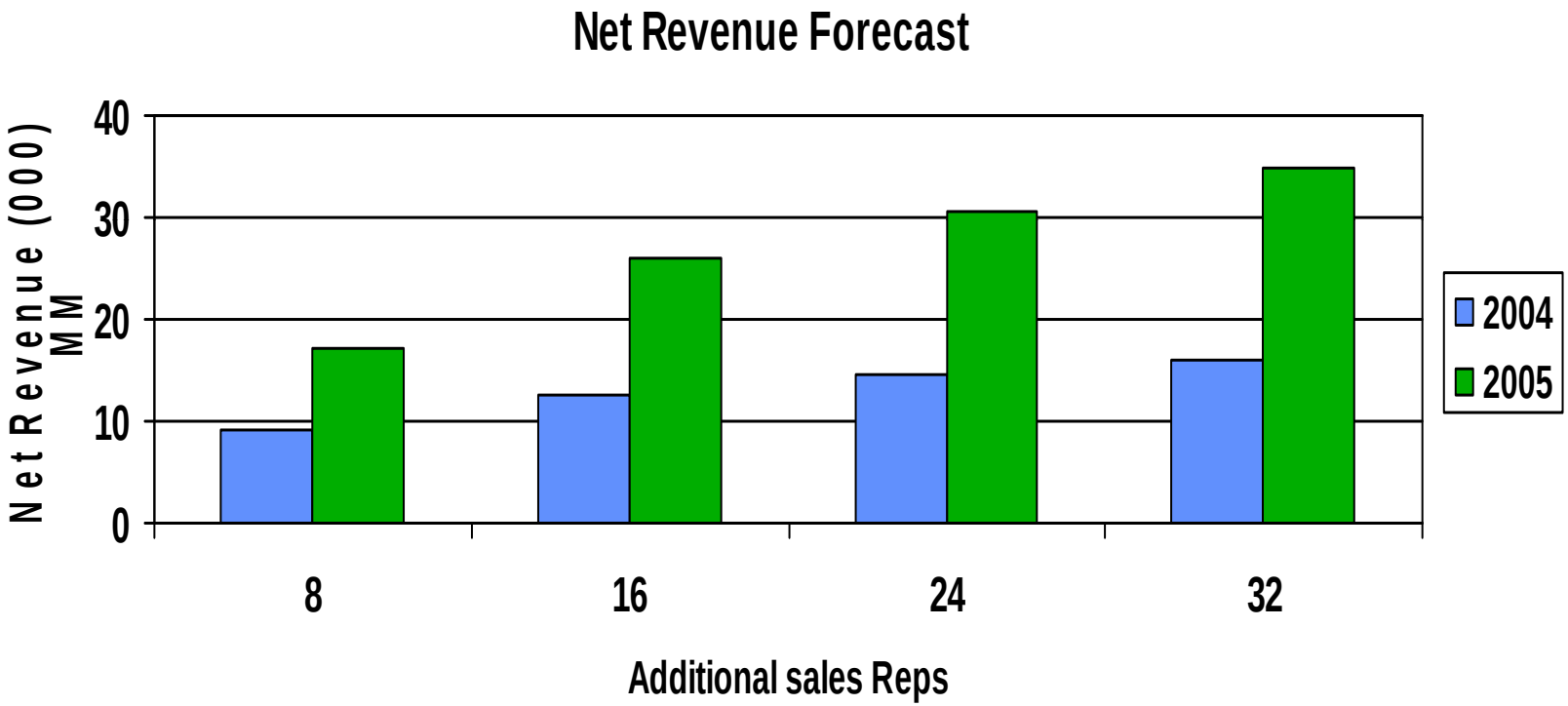


Change in Revenues
Over 2004 Plan, 2005-2008 LRP*



*Note: The 2005-2008 LRP will be updated in December 2003.

Sales Force Optimization: Target Addition of 24 LTC Sales Representatives



Three strategic LTC investments are need to ensure delivery of $120 MM in projected new revenues over the next five years.

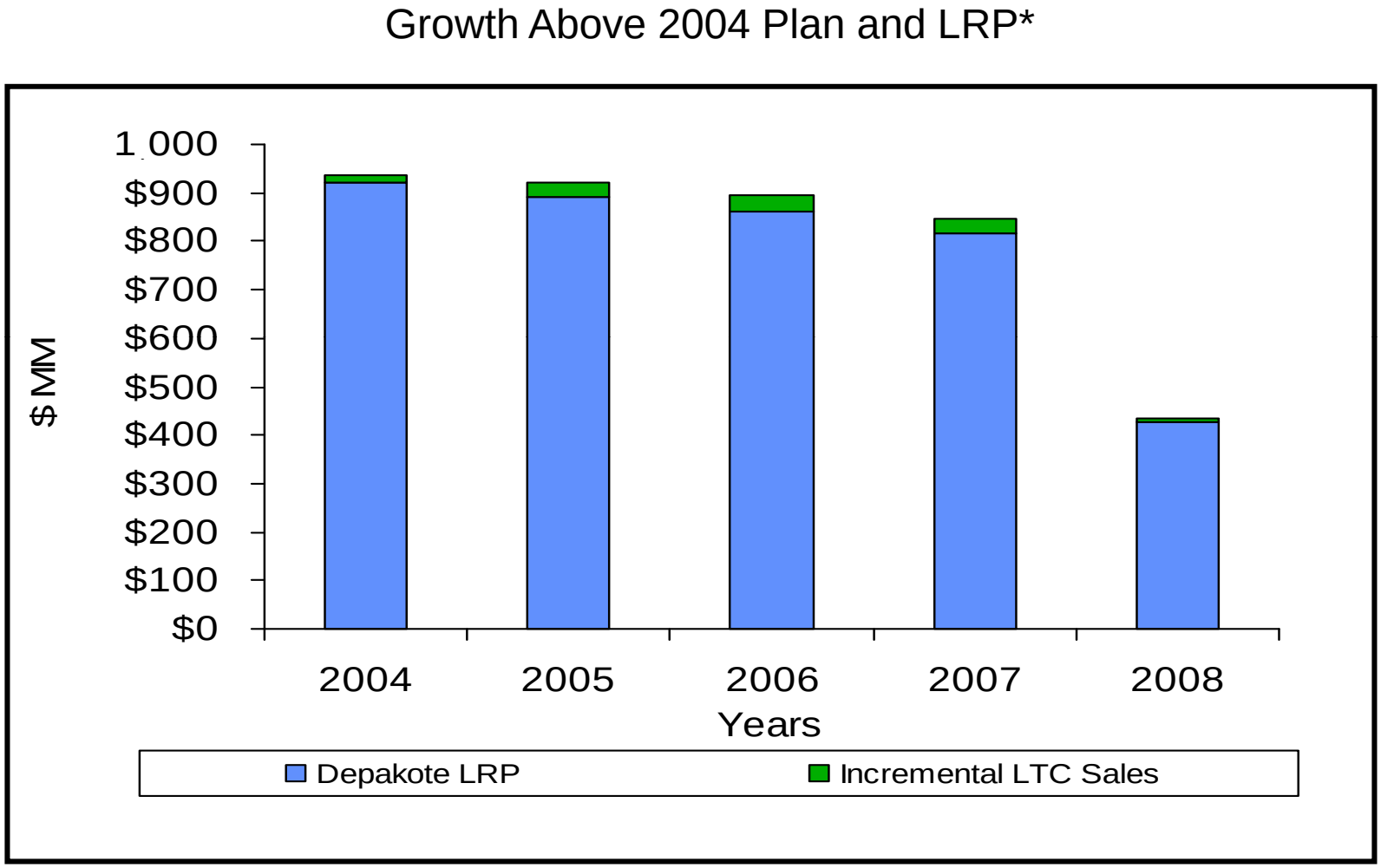
		2004	2005	2006	2007	2008	TOAL
LTC 2004 Buy-Up Needs							
Sales Force Optimization	New Sales	$9.7MM	$24.2MM	$24.2MM	$24.2MM	$7.3MM	$89.6MM
• Increase field based resources from 55 to 77	Investment	$7.7MM	$8.1MM	$8.2MM	$8.3MM	$2.5MM	$34.8MM
Marketing Expansion							
• Add 2 additional staff and Increase the promotional budget by 2.8 MM and initiate corrections contracting	New Sales	$4.8MM	$5.2MM	$5.7MM	$5.9MM	$1.3MM	$23.0MM
	Investment	$3.2MM	$3.2MM	$3.2MM	$3.2MM	$1.0MM	$13.8MM
Clinical Data Investment							
• Fund relevant Corrections, MRDD and SNF investigator initiated studies	New Sales	$0	$1.3MM	$2.8MM	$2.5MM	$1.1MM	$7.7MM
	Investment	$1.0MM	$0.5MM	$0	$0	$0	$1.5MM
TOTAL Sales		**$14.5 MM**	**$30.7 MM**	**$32.7 MM**	**$32.7 MM**	**$ 9.7MM**	**$120.3 MM**
TOTAL Investment		**$11.9 MM**	**$11.8 MM**	**$11.4 MM**	**$11.5 MM**	**$ 3.5MM**	**$50.1 MM**

Proposed 2004 LTC Promotional Budget Allocations

Major Promotional Categories	Key Category Elements	'03 Actual Spend (000's)	2004 Proposed Spend (000's)	2004 Key Category Components*
Sales Force Support	Reprints, Sales Aids, and NAM War Chest	$ 580	$ 700	2 LTC sales aids, 2-4 slim jim like pieces and increased NAM war chest funds to cover corrections
Meetings and Events	Conventions, Meeting Symposia, Advisory Board	$ 1.1	$ 1.7	Reduced SNF meetings, additional Corrections and MRDD Meetings, 2 advisory meetings per market segment
CME Programs		$ 400	$ 1.0	"Key Pharmacoeconomic Concerns in the DOC: Why Branded is Better!", "Differential diagnosis: psychiatric and behavioral disturbances in the mentally retarded and developmentally delayed", "Increased Patient Compliance with QD Dosing."
Grants	Funds for institutes/3rd parties to support product research / foster general company goodwill	$ 300	$ 700	Added support to advocacy organizations to produce patient/care giver materials relevant to Corrections, MRDD and SNF environments.
Consultant Meetings	One on one meetings with key prescribers/influencers	$ 0	$ 675	4 corrections RCMs, 4 MRDD RCMS and 7 SNF DCMs
Agency Fees	PR and Advertising Fees	$ 0	$ 20	Use external PR support to publicize new findings
Market Research	Focus Groups, Studies	$ 225	$ 400	ATU and positioning research for new strategy
Data Purchases	Syndicated and proprietary data purchases	$ 0	$ 300	Annual LTC physician level data, new DNA product and list purchases for Corrections and MRDD
	TOTAL	**$ 2.6**	**$ 5.5**	

* Full program details by sector are found in the appendix.

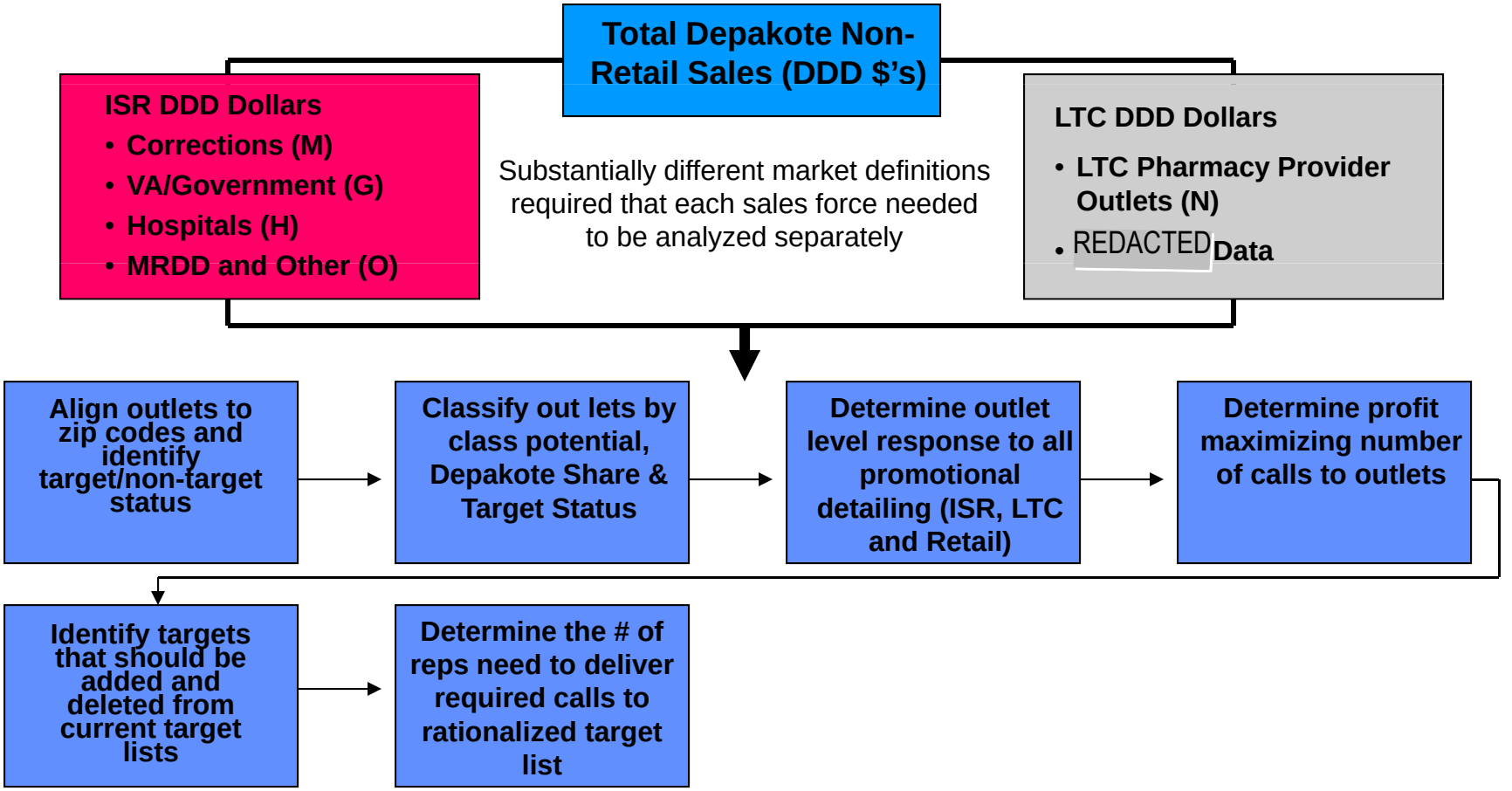
Targeted investments in LTC can boost the Depakote molecule LRP $120 over five years.



- Note: 2004 Reflects the most recent plan numbers. Year 2005-2008 LRP numbers are likely to be updated in December 2003.

Health Products Research Methodology and Results: Non–Retail Sales Force Optimization

Business Question: "Is Depakote optimizing its non-field resources? If not, what is the profit maximizing number of reps and what accounts should they be targeting?

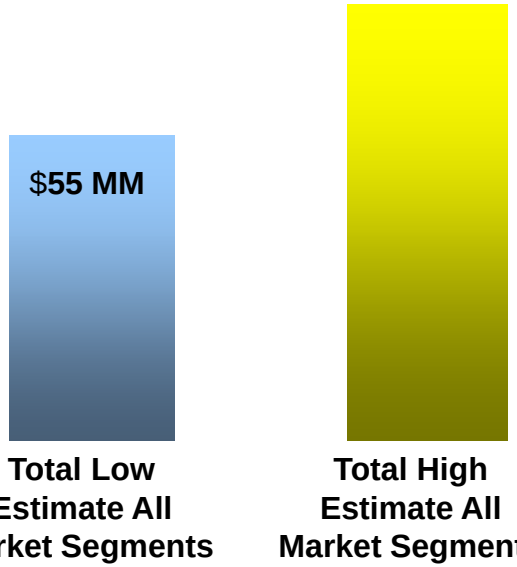


Business Answer: Current ISR reps are sufficient though call lists may need to be slightly readjusted. Current LTC reps are insufficient and should be increased by 24 reps, 1 RTS, 3 DMs, 1 RM and 7 RAMs.

Refocused LTC sales and marketing efforts generates $14.5 MM in new revenue in 2004 and $105.8 MM in years 2005-2008.

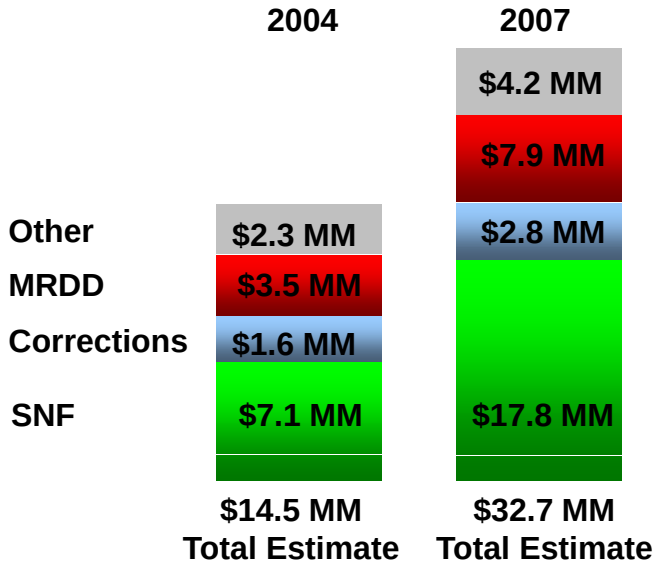
Estimated 2003 Unrecognized LTC Sales

REDACTED *Primary Market Research*



Estimated Attainable New LTC Sales Over Plan/LRP

Abbott Internal Analysis



Factors Affecting Segment Growth Estimates

Corrections	Low base, need to stem VPA growth
MRDD	Small patient base ,more fragmented LTCPP coverage
SNF	Higher current base , strong existing relationships

A larger marketing organization will help increase Depakote's share of voice in LTC and create greater parity in Neuroscience.

Proposed LTC Marketing Organization



LTC Marketing Responsibilities by Channel Increases Efficiency & Effectiveness

- Disease knowledge
- Channel operations
- Channel specific CME planning and execution
- Channel specific meetings and events planning and execution

Neuroscience Promotional Resources

	Mkt. FTEs	Promo $'s	Net Revenue		Mkt. FTEs	Promo $'s	Net Revenue
Psych '03	9	$15 MM	$350 MM	Neuro '03	4	$10 MM	$350 MM
LTC '03	1.5	$2.6 MM	$130 MM				
LTC Proposed	3.5	$5.5 MM	$150 MM				

Back-Up Slides Table of Contents

1. Market Understanding and Defining

2. Abbott's Past Performance in LTC

3. Market Sizing and Future Potential

4. Optimization Supports Need to Realize Incremental Sales
   - Sales Force Optimization
   - Marketing Expansion
   - Clinical Investments

LTC Market Complexities

Market Characteristics

- Patients have greater incidence and prevalence of CNS disorders than the general population
- Degree of unmet medical needs in LTC increases physicians discretionary use of Rx products
- Heavy LTC Prescribers and influencers are usually low-decile writes in retail
- Government regulates initiation and continued use of Rx products in some LTC settings

Long Term Care

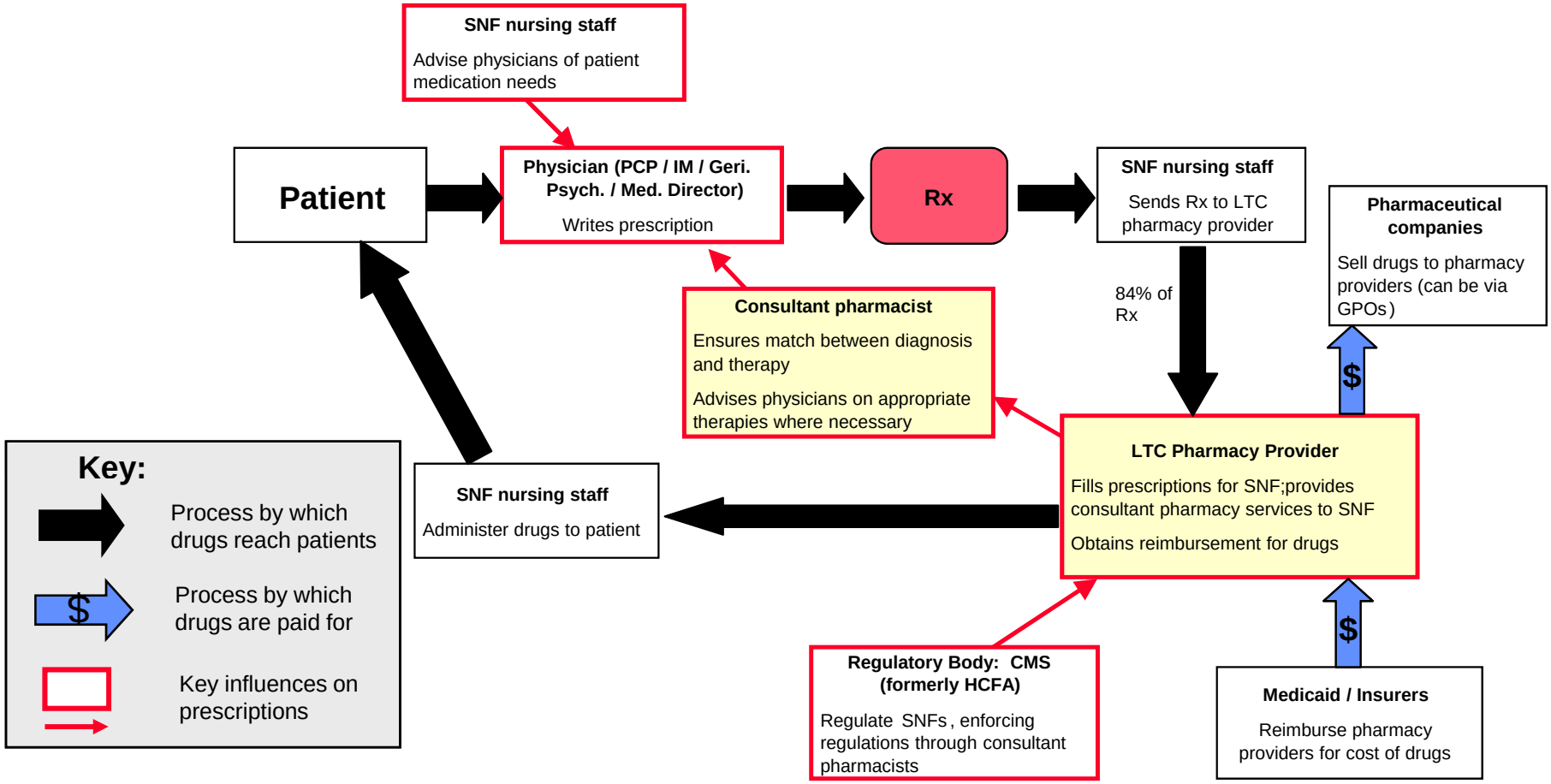
Channel Characteristics

- Long Term Care Pharmacy Providers (LTCPP) fill the majority of LTC Rxs
- LTCPP closed-door services are more involved and expensive than retail services, e.g. consultations
- LTCPP have contractual arrangements with manufacturers
- LTCPP measurements and metrics are much more limited than retail.
- LTC, as a percent of all pharmaceutical sales, has grown from 8% to 13% in the past five years

Source: Abbott interviews, REDACTED, REDACTED

Prescription fulfillment in all LTC settings in very complex.

Example: How Drugs are Prescribed and Paid for in SNFs



Similarly complex process flows exist in other LTC setting segments.

Sources: Abbott Neuroscience LTC Business Review, REDACTED

The LTC market is undergoing growth and change. Depakote LTC, while growing, lags the rest of the market.

Market Issues

- **Pharmaceutical companies and LTCPP are expanding the LTC market**
  - The channel is estimated to offer 2 billion dollars in net sales in 2003
  - Competitors are establishing contracts in other LTC settings, e.g. REDACTED contracts in corrections
  - LTCPP are expanding their reach to serve:
    - ALFs
    - MRDD institutions and group homes
    - Corrections
- **Product competition in the SNF segment of the LTC is intensifying**
  - Risperdal label change has caused prescribers and influencers to rethink medication choices
  - Abilify is publishing LTC data and devoting sales resource to the channel
  - Cholinesterase inhibitors have surpassed Depakote's LTC TRxs and have introduced behavior control data
  - New Alzheimer's products will hit the market in 2004 (Memantine)
- **Channel consolidation is accelerating**
  - REDACTED REDACTED acquired two other national Long Term Care Pharmacy Providers (LTCPP) in 2003 - REDACTED and

Depakote Issues

- **Depakote is the third or fourth medication choice behind antipsychotics for psychiatry needs in LTC**
- **Depakote is in a dead heat with other AEDs as a medication choice for addressing neurology needs in LTC**
- **Depakote has produced much less LTC data than its competitors**
- **Depakote has one of the smaller LTC sales force in the industry**

Abbot's LTC History

Where We've Been

- Neuroscience sales force launched in 1998 with 28 LTC Specialists and 1 National Account Manager (NAM)
- Launched clinical trials – Elderly Mania - in hopes of obtaining an indication for treating aggression and agitation in the elderly
- Sales and marketing efforts 100% focused on treating elderly patients in skilled nursing facilities (SNFs)

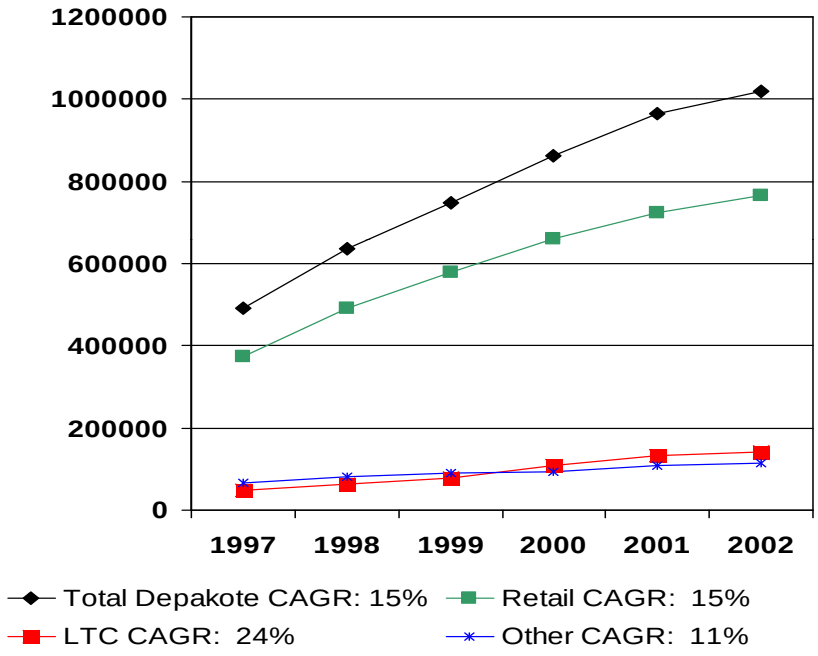
Where We Are

- Neuroscience sales force currently supports 55 LTC Specialists; 3 NAMs – last expansion took place in 2001
- Conducting retrospective analysis and investigator initiated studies to produce LTC data
- Sales and marketing efforts focused:
  - –75% SNFs
  - –15% MRDD
  - –10% ALFs and Other

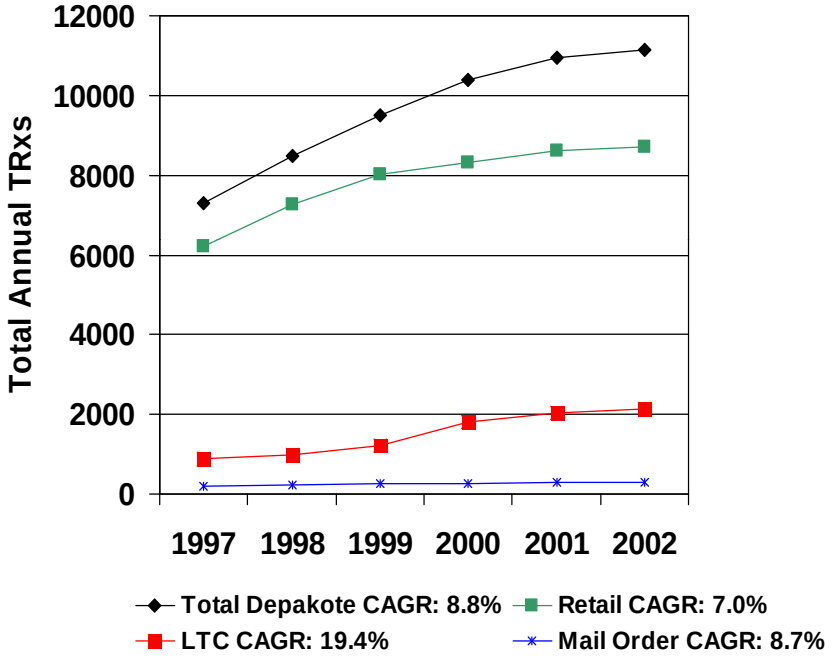
Source: Abbott interviews and historical documentation of channel efforts.

LTC's Past Contribution To Sales

Depakote Gross Sales by Channel



Total RXs



Source: [REDACTED] **Retail & Provider Perspectives. Abbott analysis of DDD LTC sales and LRP LTC Sales.**

In LTC, Depakote faces the same product challenges as it faces in Psych and Neuro markets, plus unique facility based challenges.

Depakote as Compared to Other Products Used in Select LTC Settings

	Efficacy	Safety	Tolerability	Overall Appeal
SNFs	+	+	+	+ **Lack of regulation concerns aids rating**
ALFs	+	-	+	+ **Prescribers lack experience**
MRDD Facilities	+	-	+	+ **Prescribers lack experience**
Correctional Facilities	+ +	+	+ +	+ + **Cost and broad spectrum utility aids rating**

+++ = Superior rating or an attribute
+ = Average rating for an attribute
- = negative product attribute
- - - = Highly negative product attribute

Source: Synthesized from REDACTED supplied primary data (QA).

Neuroscience has redefined LTC to match the extended care market served by LTCPPs - aligning LTC's strategy with the larger brand strategy.

5 MM Total LTC Patients in Select LTC Settings

	Skilled Nursing Facilities (SNFs)	Assisted Living Facilities (ALFs)	Mentally Retarded Developmentally Delayed Facilities (MRDD)	Correctional Facilities
Current Population	• 1.5 MM residents or 28% of all LTC patients • # of beds is flat	• 1 MM residents or 24 % of all LTC Patients • # of beds increasing rapidly	• 450,000residents or 9 % of all LTC Patients • # of beds is flat	• 2 MM residents or 39 % of all LTC Patients • # of beds is moderately increasing
Est. 2007 Population	• 1.6 million residents	• 3 million residents	• 525,000 residents	• 2.3 million residents
Current Payor Mix	• Medicaid - 60% • Medicare - 15% • Private pay / insurance - 25%	• Medicaid/SSI – 10% • Private pay – 88% • LTC insurance – 2%	• Medicaid/SSI – 98% • Private pay – 2%	• Government 100%
Current LTCPP Penetration	• 100%	• 20%	• 15%	• 40%
Prescriber Priorities	• Medical Directors/PCPs • Geriatric Psychiatrists	• PCPs	• PCPs • Neurologists	• PCPs • Psychiatrists

Historic Abbott Market Definition

Sources: Abbott Primary Market Research. REDACTED NCAL Facts and Trends 2001; ALFA Overview of the Assisted Living Industry 2001; REDACTED Abbott Neuroscience Population estimates have been rounded. Business Review, National Center for Health Statistics, Health United States 2001; .

Current LTC secondary data sources limit the ability to understand future sales activity and segment contributions.

Currently Available Secondary LTC Data	Current Data Elements	Limitations
Rx: NPA Provider Perspective (REDACTED –Buy In)	• National accounting of Rxs for total REDACTED Sub Cat N1 – Nursing Home Pharmacy Providers	• Lacks Rx by Sector • Lacks Rx by Diagnosis • Projects for REDACTED (which Abbott buys indecently)
DDD $(REDACTED Sell Out)	• Depakote $ for total N1s Nursing Home Pharmacy Providers • Depakote $'s by Outlet for total LTC	• Lacks Depakote $ by Sector - can not tie outlet dollars to facilities • Lack Depakote $ by Diagnosis • Does not include REDACTED $'s • Can not tie Prescriber relationships to N1 outlets • Can not define dollars by competitor (DDD groups competitors)

Unavailable But Useful Secondary LTC Data

- Lists of MRDD facilities and the dollar volumes they carry
- Complete lists of correctional facilities and the dollar volumes they carry
- Complete lists of nursing home facilities and the dollar volumes they carry
- Complete doctor level data
- Mechanism for link doctor (or other provider / potential target) with facility and/or type of facility
- Dollars by competitor (DDD groups competitors)
- Dollars by competitor by facility type
- Any way to factor data by diagnosis
- Share of voice metric in LTC

Abbott had to conduct primary market research to size the market's potential.

Current LTC Data Limitations

- Actual REDACTED account information only captures sales activity at the pharmacy outlet level.
- No publicly available data tracks sales activity from a pharmacy outlet to the facilities served by these outlets.
- Numerous REDACTED accounts currently categorized as "nursing home providers" are doing the majority of their business in other LTC settings.
- No publicly available LTC data source ties dollar sales to diagnoses in LTC.

The only way to precisely understand where today's Depakote LTC DDD dollar sales requires a unique account profiling exercise:

Each LTC rep would estimate the % of dollars directed to different facilities types affiliated with each outlet in their territory

We recommend pursuing this analysis over the next three months.

Note: Market research sample and methodology details are found in the appendix.

LTC Primary Market Research May 2003: Design and Objectives

Physician Sample

	# of Physicians Completing Study by Facility Type
Total Completed	248
Correctional Facility	***49***
PCP	4
Psychiatrist	45
MRDD	***48***
PCP	44
Neurologist	24
Assisted Living Facility	***65***
PCP	65
Skilled Nursin Facility	***66***
PCP	66

Study Objectives

- **What is the size of the LTC market?**
- **What is the prevalence of Depakote's use in different LTC facilities across select neuroscience conditions?**
- **How is the Depakote brand currently being used in select LTC environments to treat select neuroscience related conditions?**
- **What can Abbott do to increase its usage?**
- **How much can the usage increase?**

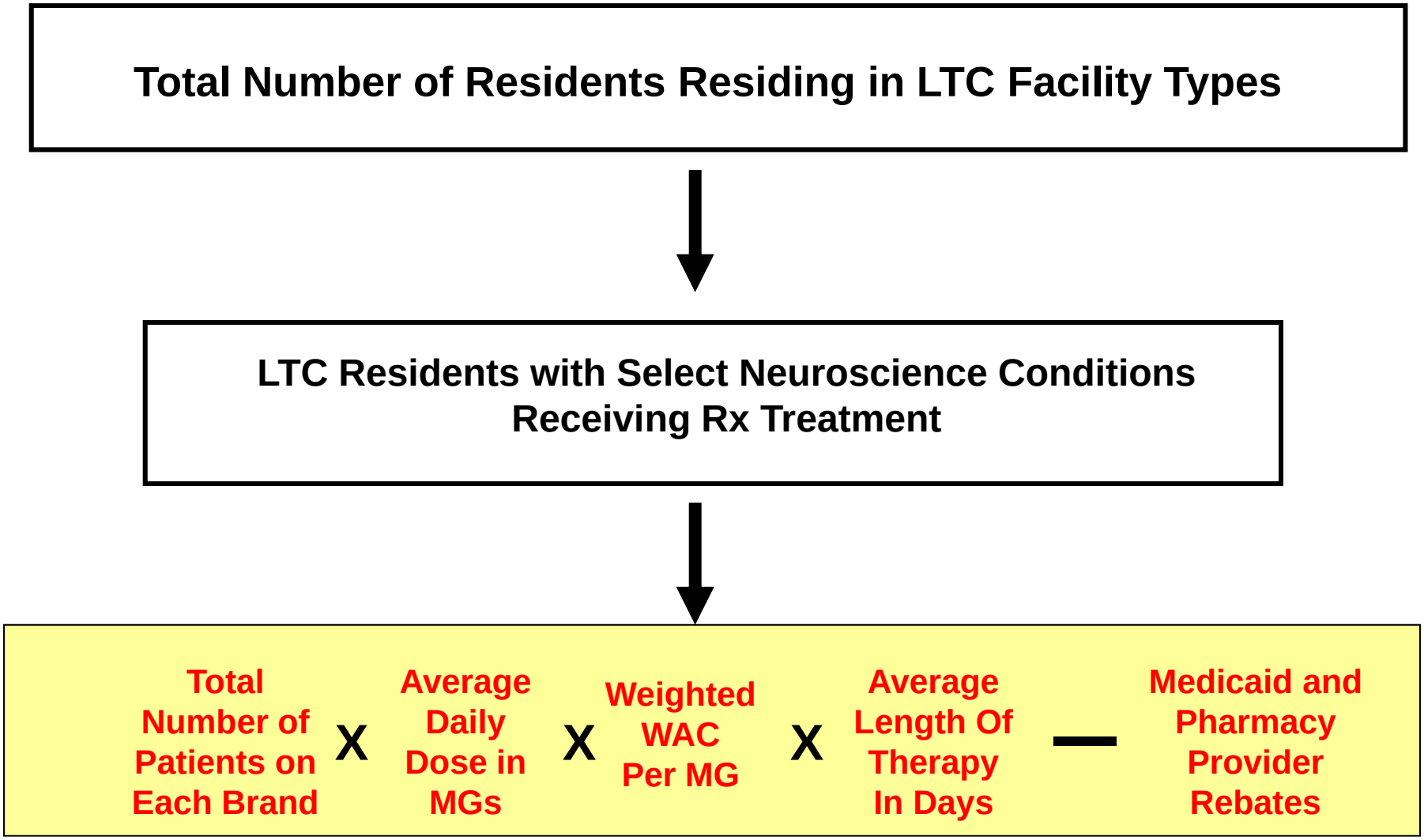
LTC Strategic Considerations

LTC Segment Evaluation Grid

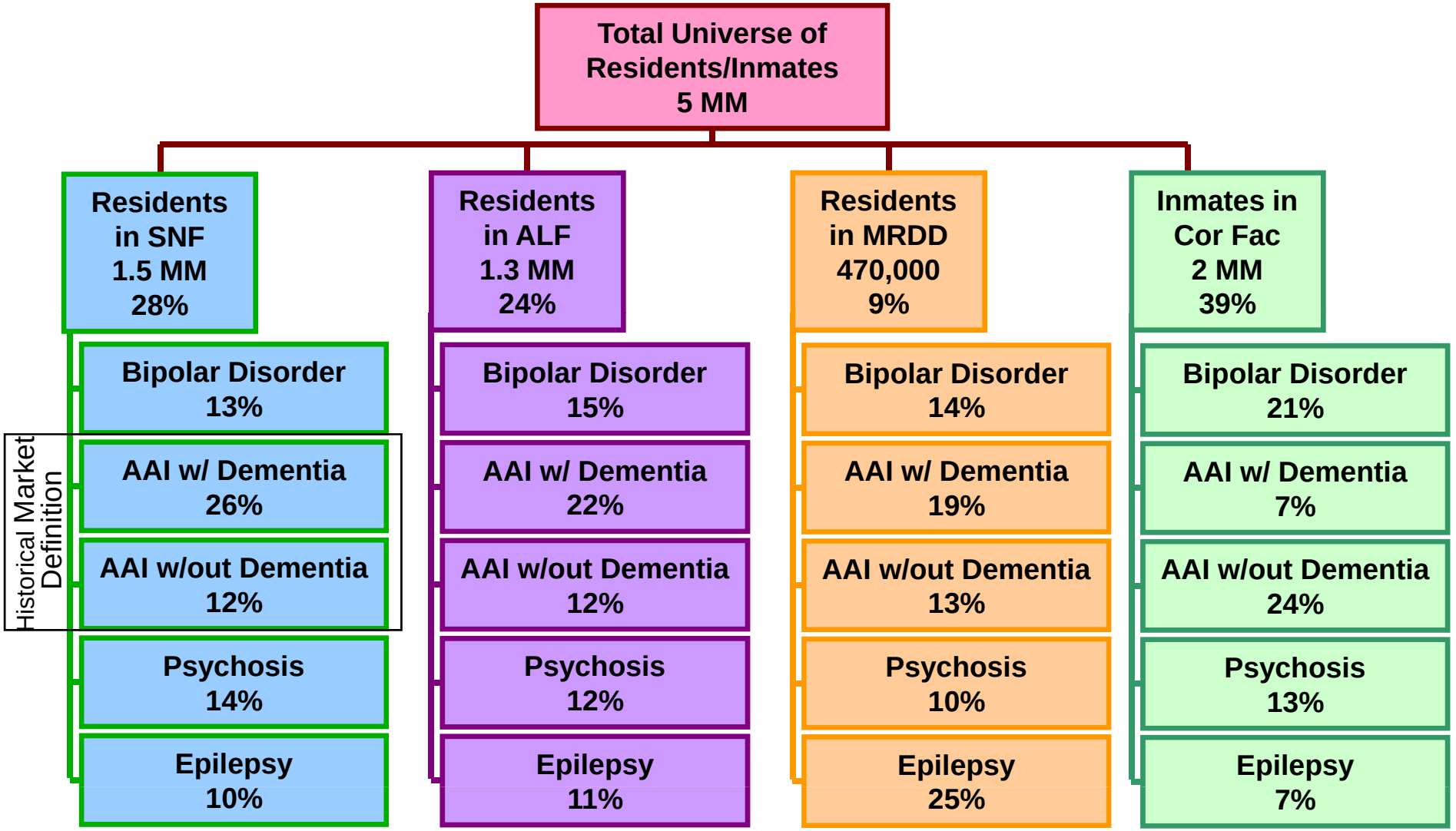
LTC Market Segments	Financial Potential	Promotional Alignment	LTCPP's Ability to Impact Business	Competitive Advantages	Overall Segment Value to Abbott
Skilled Nursing					
Assisted Living					
MRDD					
Corrections					

Source: Abbott analysis.

LTC Segments Financial Potential Analysis



Resident Universe for LTC: Depakote Relevant Segments



Sources: REDACTED, State of the States in Developmental Disabilities Report and Bureau of Justice Statistics. Prevalence of condition data sourced from physician reported, EDACTED supplied primary data (QA).

Additional Prevalence Proof for Neuroscience Conditions in the LTC Marketplace

	SNF		ALF		MRDD		CORR	
	2ndary Res	REDACTED	2ndary Res	REDACTED	2ndary Res	REDACTED	2ndary Res	REDACTED
Bipolar	10%(1)	13%		15%		17%	20% (6)	21%
AAI W/Dementia		26%		22%		15%		7%
AAI W/O Dementia		12%		12%		17%		24%
Psychosis	6% to 10% (2)	14%		12%		14%	10% (7) &(8)	13%
Epilepsy	6% (3) 8% to 15% (4)	10%		11%	14% to 24% (5) 45% to 67% (5)	25%		7%

References for Secondary Prevalence Findings

1 (A) 10% of Nursing Home patients have Bipolar disorder
www.upcmd.com/dot/diseases/01076/disorder_information.html

(B) Lifetime prevalence of Bipolar disorder in the general population has been underdiagnosed; incidence approaches 5% to 8% of the general population: Arnold L Lieber, MD: A Practitioner's Overview of the Soft Bipolar Spectrum:www.psycom.net/depression.central.lieber.html

2 Psychoses prevalence varies from 6% to 10% in the elderly population. Pietro Gareri, Conventional and Atypical Antipsychotics in the Elderly, Clinical Drug Investigation; www.medscape.com

3 Five or 6% of nursing home residents suffer from Epilepsy. K.L. Capozza Epilepsy Drugs Common in Nursing Homes: www.ahealthyadvantage.com/article/hscoutn/103437886

4 Annual Incidence of Epilepsy by age: approximately 8% in 60-69 year olds; approximately 15% in 70-79 year olds; Robert W. Griffith, MD: Epilepsy is Quite Common in Old Age; www.healthandage.com/Home/gid2=734

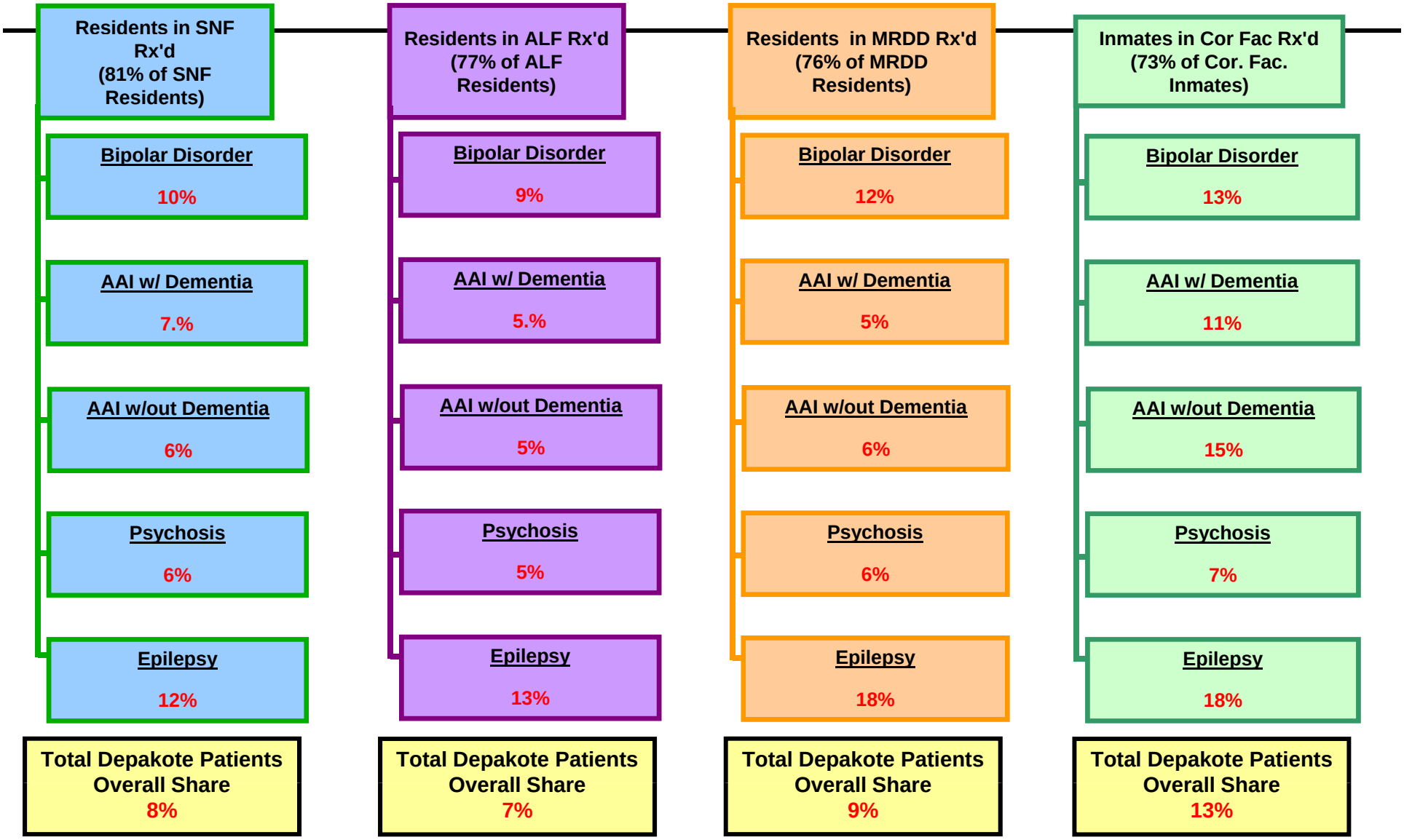
5 14-24% of people with intellectual disability are affected by Epilepsy. 45-67% of people with severe intellectual disability are affected by Epilepsy. National Electronic Library for Health www.minervation.com/ld/healthservices/medical/3.html

6 Prison populations have a four-fold incidence of Bipolar disorder compared to the epidemiology of the general population. (5% Bipolar disorder in general population (reference (1B) above) times 4 = 20%). GN Conacher, Management of the Mentally Disordered Offender in Prison.

7 600,000 to 1 million people jailed have a mental illness: 600000/2million inmates = 30% (combination of Bipolar and Psychosis in REDACTED data = 34%) ; National Council on Disability.

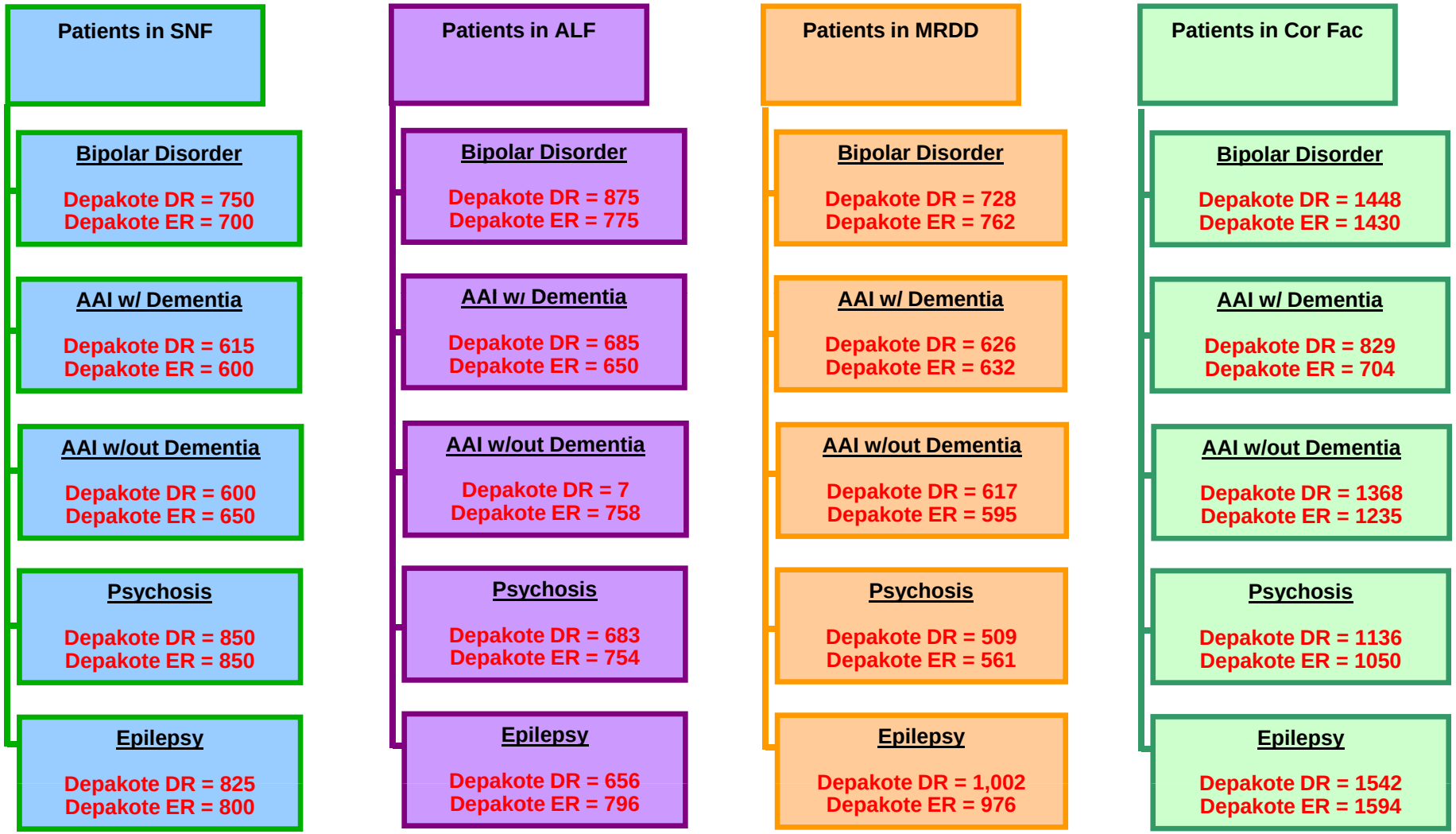
8 7% of sentenced men, 10% of men on remand and 14% of women in both categories were assessed as having a psychotic illness within the past year. REDACTED Severe Mental Illness in Prisoners.

Depakote's RX Share Summary By Condition



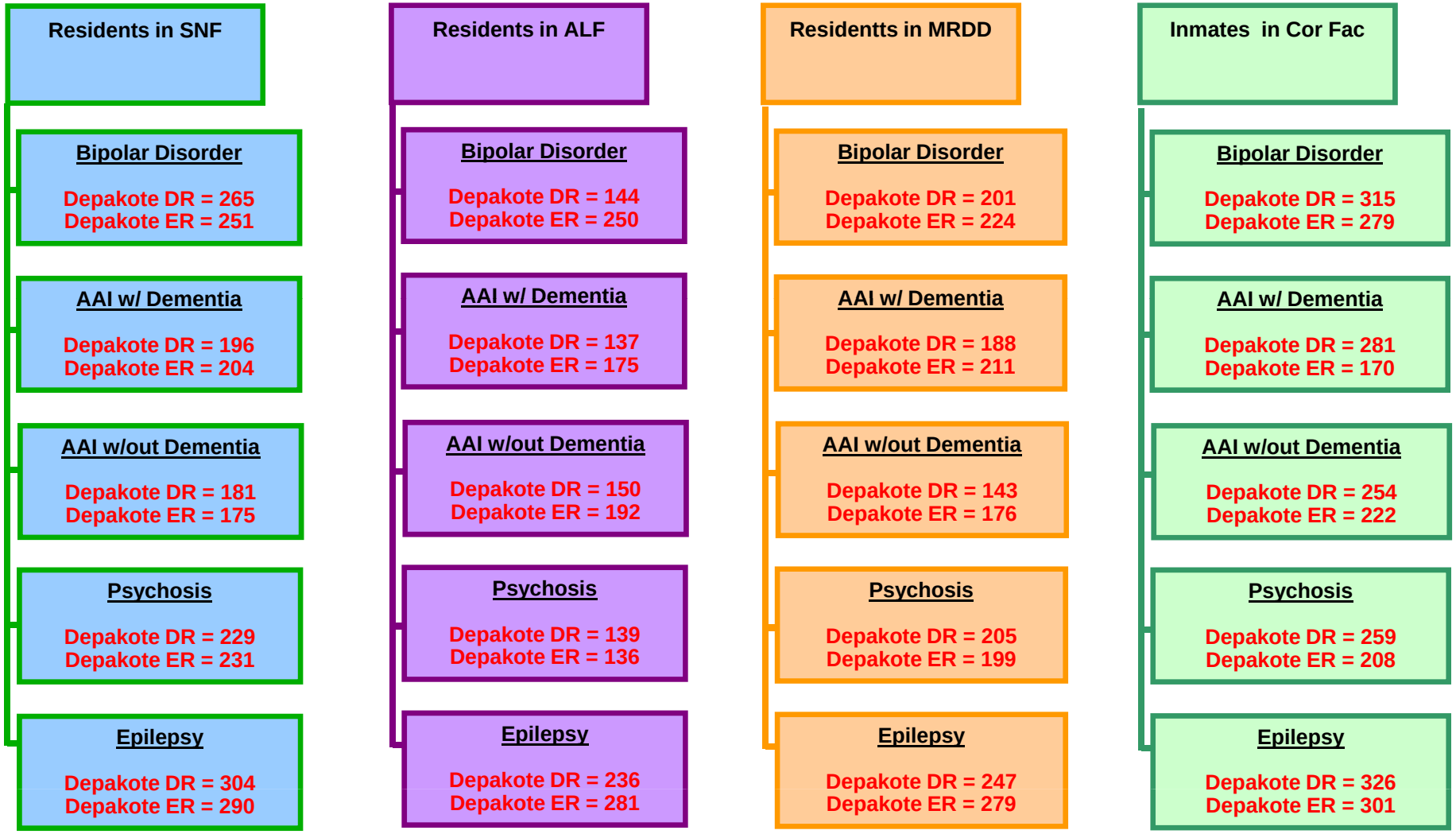
Sources: Facility population counts provided by Abbott. Prevalence of condition data sourced from physician reported, REDACTED supplied primary data (QA).

Depakote Average Daily Dose (in mg) Summary



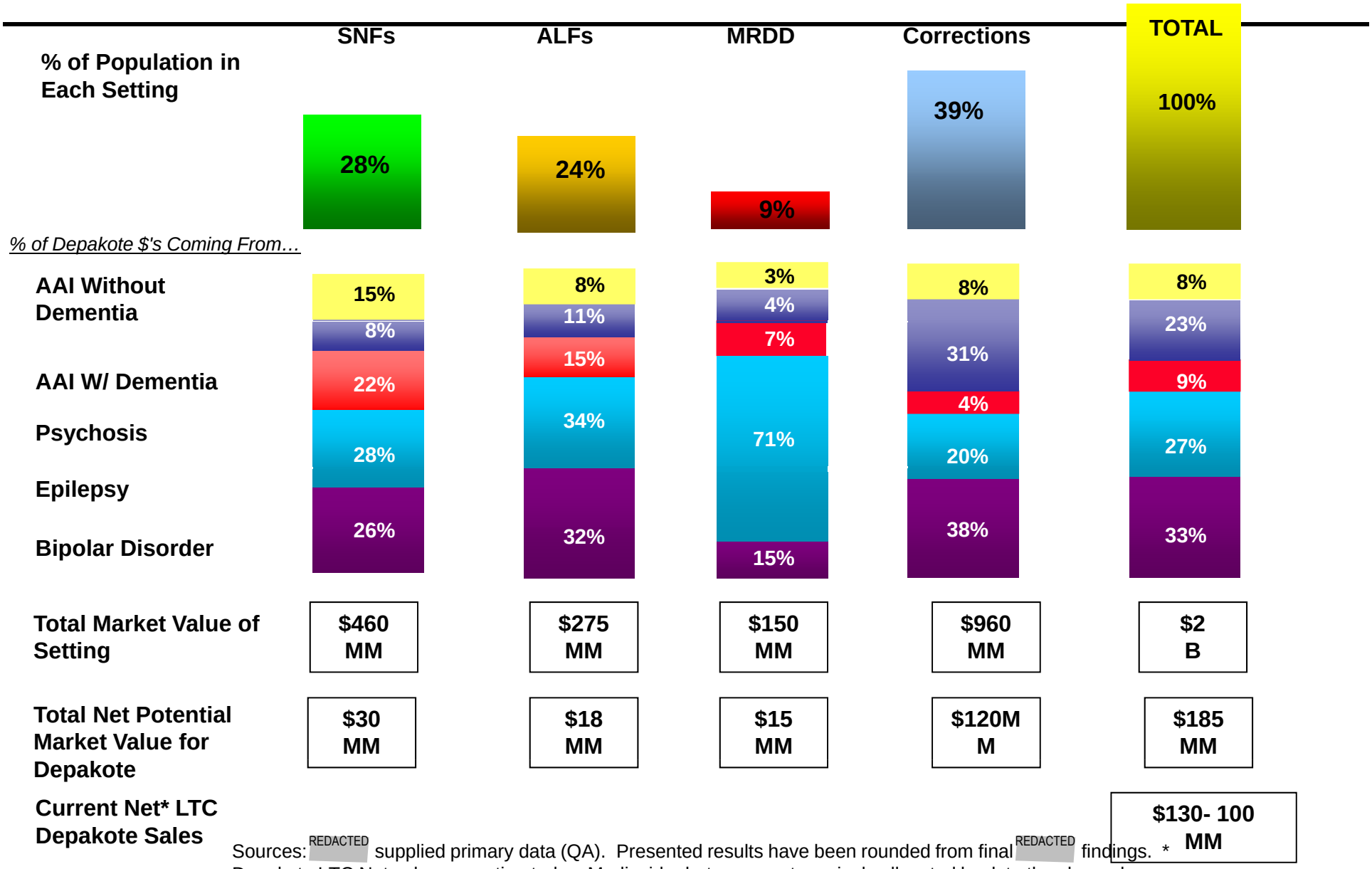
Sources: Facility population counts provided by Abbott. Prevalence of condition data sourced from REDACTED primary data (QA).

Depakote Average Length of Therapy (Days Per Year) Summary



Source: Length of Therapy data sourced from REDACTED primary data (Q7/9).

Primary research suggested that potential Depakote LTC net sales could be $55-$85MM above current net sales.



Sources: REDACTED supplied primary data (QA). Presented results have been rounded from final REDACTED findings. * Depakote LTC Net sales are estimated as Medicaid rebates are not precisely allocated back to the channel.

LTC is seeking to optimize corrections, SNF and MRDD sales and marketing efforts through 2008.

LTC Segment Evaluation Grid

LTC Market Segment	Financial Potential	Promotional Alignment	LTCPP's Ability to Impact Business	Competitive Advantages	Overall Segment Value to Abbott
Skilled Nursing	Moderate $25-30 MM annually	Moderate 54% PI aligned	High	Moderate Antipsychotic regulations give slight advantage	High Represents core LTC business today.
Assisted Living	Moderate $15-40 MM annually	Moderate 66% PI aligned	Low	Low Antipshycotics and cholinestrate inhibitors dominate	Low Growing segment but lacks LTCPP as key element in impacting business
MRDD	Low $15-20 MM annually	High 86% PI aligned	Moderate	High Antipsychotic regulations give advantage	Moderate High strategic fit with Bipolar and Epilepsy.
Corrections	High $120-135 MM annually	Moderate 60% PI aligned	Moderate	High Cost advantages over antipsychotics	High High strategic fit with bipolar and epilepsy. Requires coordination with HIV.

Source: Abbott marketing analysis.

LTC Strategy Execution Drivers

	Corrections	MRDD	SNFs
Depakote Eligible Patient Population	Y% or X MM inmates have conditions that could be treated with Depakote	Y% or X MM residents have conditions that could be treated with Depakote	Y% or X MM residents have conditions that could be treated with Depakote
# of Institutions	8,400 state, county and city jails and prison	7,100 large and small facilities	18,000 Nursing Homes 1.9 Million Beds
Depakote $'s per patient, per year*	$870 a year	$485 a year	$405 a year
LTCPP Coverage	Three national MCOs and their LTCPPs provide drugs to 30% of the market	National LTCPP consolidation is in its infancy	Four national LTCPP provide drugs to 35% of all SNF beds
Depakote Messages	1. Bipolar 2. Agitation & Aggression	1. Epilepsy 2. Agitation & Aggression	1. Agitation & Aggression 2. Bipolar 3. Epilepsey
Promotional Mix (In order of importance)	1. CME 2. RAM coverage 3. Contracting	1. Sales rep coverage 2. CME	1. NAM/RAM coverage 2. Sales rep coverage 3. CME

Source: REDACTED primary market research conduct for Abbott Laboratories, May, 2003.

Note: Prevalence of disease states can be found in the appendix on page _. Marketing plans by setting are found on pages _ - _ of the appendix.

LTC Optimization Supports

Sales Force Optimization

Representative Increase

Management Increases

Key Supports

Marketing Expansion

Marketing Personnel

Marketing Budget

Contracting Expansion

Internal Support Needs

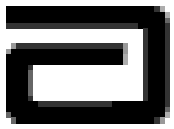
Clinical Data Expansion

Geriatric IIS

Corrections IIS

MRDD IIS

Competitive Field Sales Force Landscape

	LTC	ISRs
REDACTED	**80 FTEs*** **160 FTE Hospital Reps- all 'Hospital' reps are 'Hospital and Long-Term Care' Reps and report through the same structure as the CNS reps.**	
REDACTED	**188 FTEs*** **<u>Elder Care</u>:** **4 Regional Directors, 28 DMs, 280 Reps** **<u>Long Term Care</u>:** **3 Regional Directors, 22 managers**	**<u>Office/Institution</u>:** **58 DMs, 580 Reps.** **16 Institutional account managers, 10 strategic account managers reporting through public sector & institutional business Director.**
REDACTED	**176 FTEs*** **21 District Managers, 263 LTC Reps**	**13 District Managers, 118 ISRs**
	**7 DMs, 55 LTC Sales Representatives**	**9 ISR District Managers, 79 ISRs**

* Note: Total rep counts were reduced by 70% to account for time given to an atypical primary detail to arrive at an adjusted FTE count.

Abbott's Unique LTC Sales Focus

Targets shown are individuals - not accounts or institutions

55 LTC Reps

Account Management Sales flowing through LTCPP, including PCPs, Geri Psychs, Consultant Pharmacists and Nurses

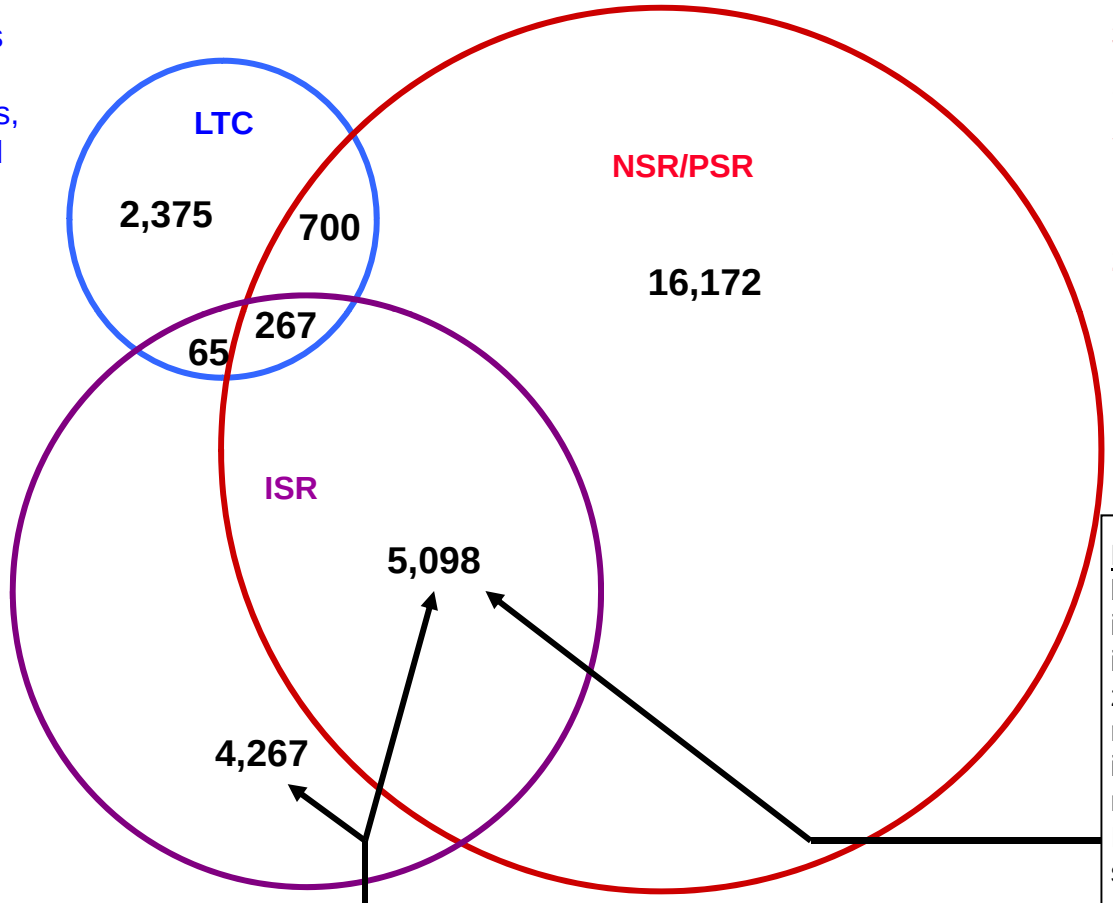
3,407 Targets

79 ISR Reps

Institutional sales flowing through GPOs or IMS non nursing home providers

9,697 Targets

Breakdown of Institutions	
Hospital or Affiliated Clinic/Pharmacy	78%
Psych/MH Center or Affiliated Pharmacy	7%
Correctiosl	4%
MRDD	2%
LTC Facility or LTCPP	2%
Other	9%



300 NSR/PSR Reps

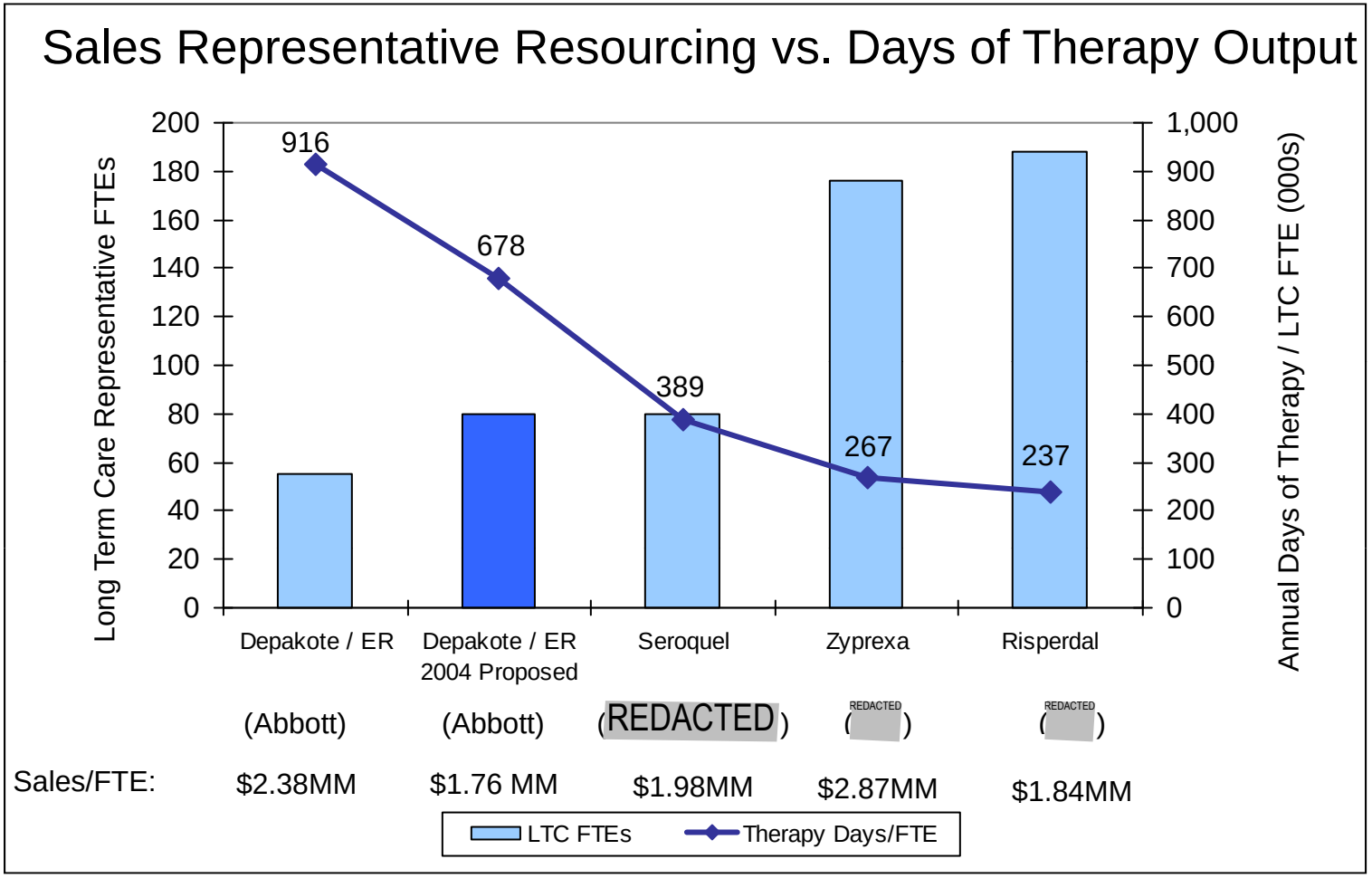
Office based specialist sales focused on psyhciatrists and neurologists

22,777 Targets

Note: Collaboration between SR and ISR reps is motivated by SR incentive plan: SRs are zip aligned and are responsible for all Kg sales in their territories, and so must work closely with ISRs to maximize new starts in institutions that generate spillover.

Note: ISRs alone are responsible for Depacon sales

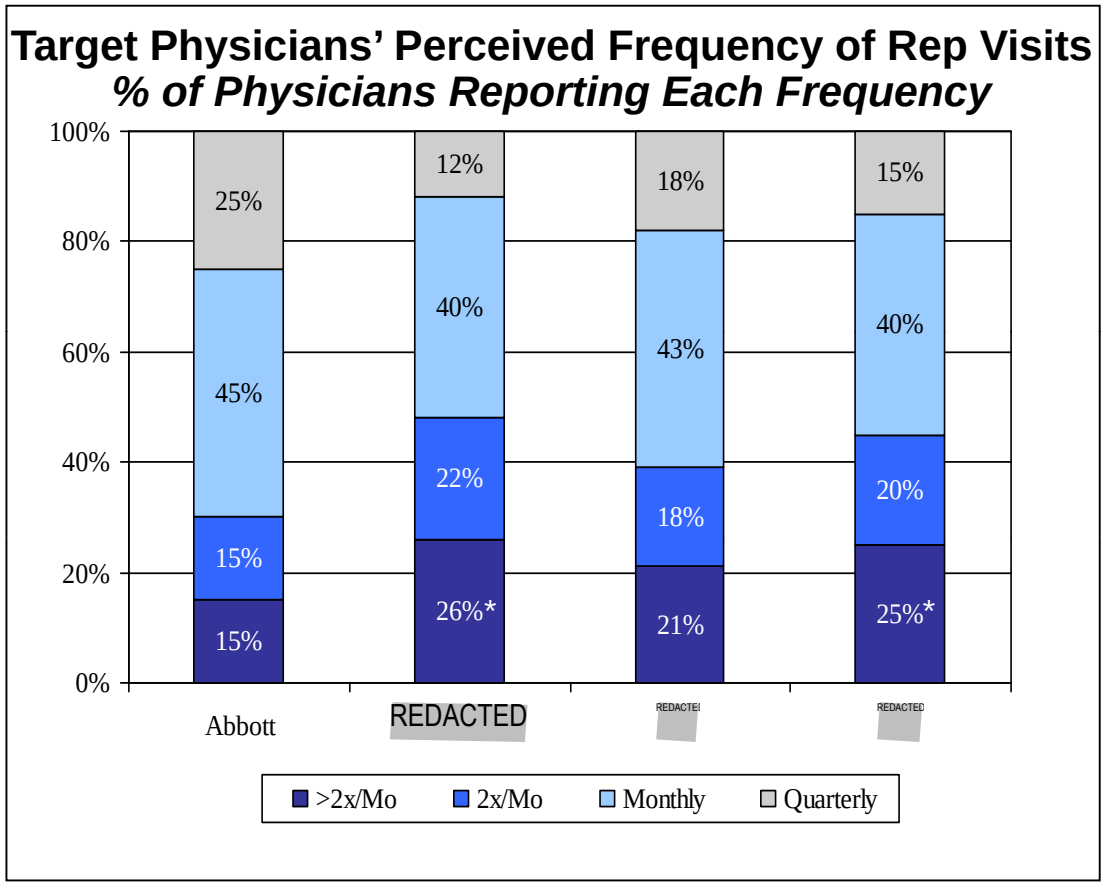
Depakote LTC generates more days of therapy per rep than any major competitors.



Sources: REDACTED REDACTED Commercial Analysis and Marketing assumptions

Note: Depakote: 55 representatives, 100% of time on Depakote/Depakote ER = 55 FTEs. Zyprexa: 263 LTC reps spend 67% of time on Zyprexa = 176 FTEs
Risperdal: 280 Elder Care reps spend 67% of time on Risperdal = 188 FTEs. Seroquel: 100 LTC reps spend 80% of time on Seroquel = 80 FTEs

However, Abbott LTC Reps See Physician Customers Less Frequently than Competitor Representatives



Key Supporting Points

- 16% of Abbott LTC targets surveyed indicated that Abbott reps could be ***more valuable*** by visiting ***more frequently***
- One in five Abbott LTC ***targets*** are satisfied with Abbott reps
- One in ten Abbott LTC ***targets*** can't remember the last time they saw an Abbott rep

*Denotes statistical significance relative to Abbott, p<=0.05
Source: REDACTED ABT Custom Study, May 2003

Recent History of LTC Sales Force Sizing Analyses and Recommendations

- **April 2001**: REDACTED **recommends increasing LTC sales force from 54 representatives to 98 representatives**
- **March 2002**: REDACTED **explores the concept of blending the ISR and LTC sales forces**
- **October 2002**: REDACTED **revises** REDACTED **analysis, keeping LTC sales force separate from ISR sales force.** REDACTED **recommends expanding the LTC sales force to 80 representatives**
- **July-September 2003:** REDACTED **conducts a promotional response analysis within Depakote's non-retails sale groups (ISRs and LTC)to arrive at the number of appropriate target counts, details need per account and number of reps need to address the most profitable targets.**

LTC Market:
Sales Analysis

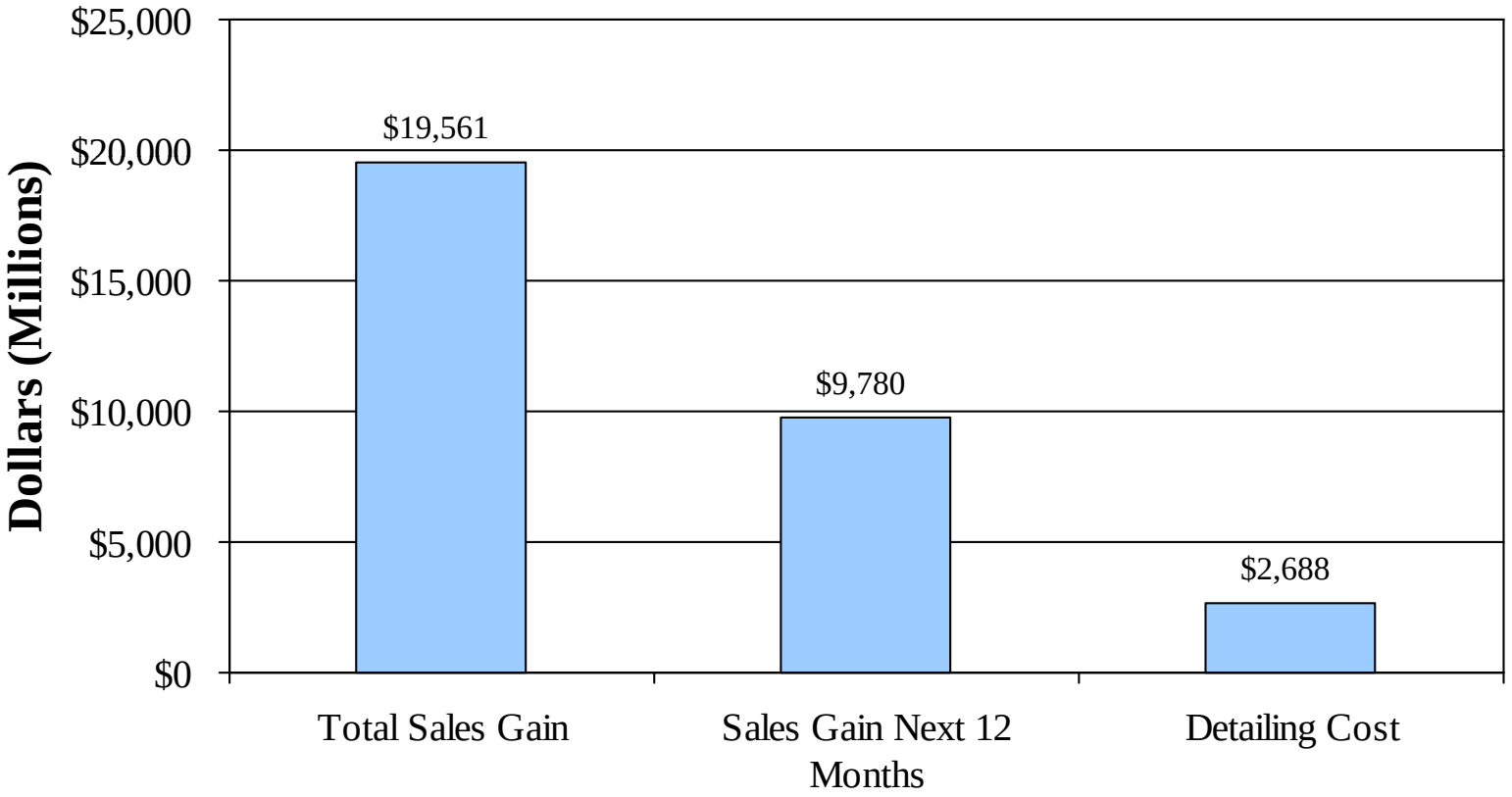
Overview

- **Objective**
  - Calculate the incremental sales by increasing the LTC headcount by 16 reps, 24 reps and 32 reps.

- **Methodology**
  - In all scenarios, the following assumptions apply:
    - » Current Non-Targets are assumed to have already received 20% of their optimal frequency.
    - » LTC reps deliver 1,200 calls / year
    - » Call activity is reallocated away from unprofitable segments
  - Note that, as with the original analysis, the optimal frequency for REDACTED outlets was capped at 2 times their historical LTC call level.
    - » This is due to the historical frequency being significantly below the Non-REDACTED outlets and that both REDACTED and Non-REDACTED outlets were used to derive the response curve.

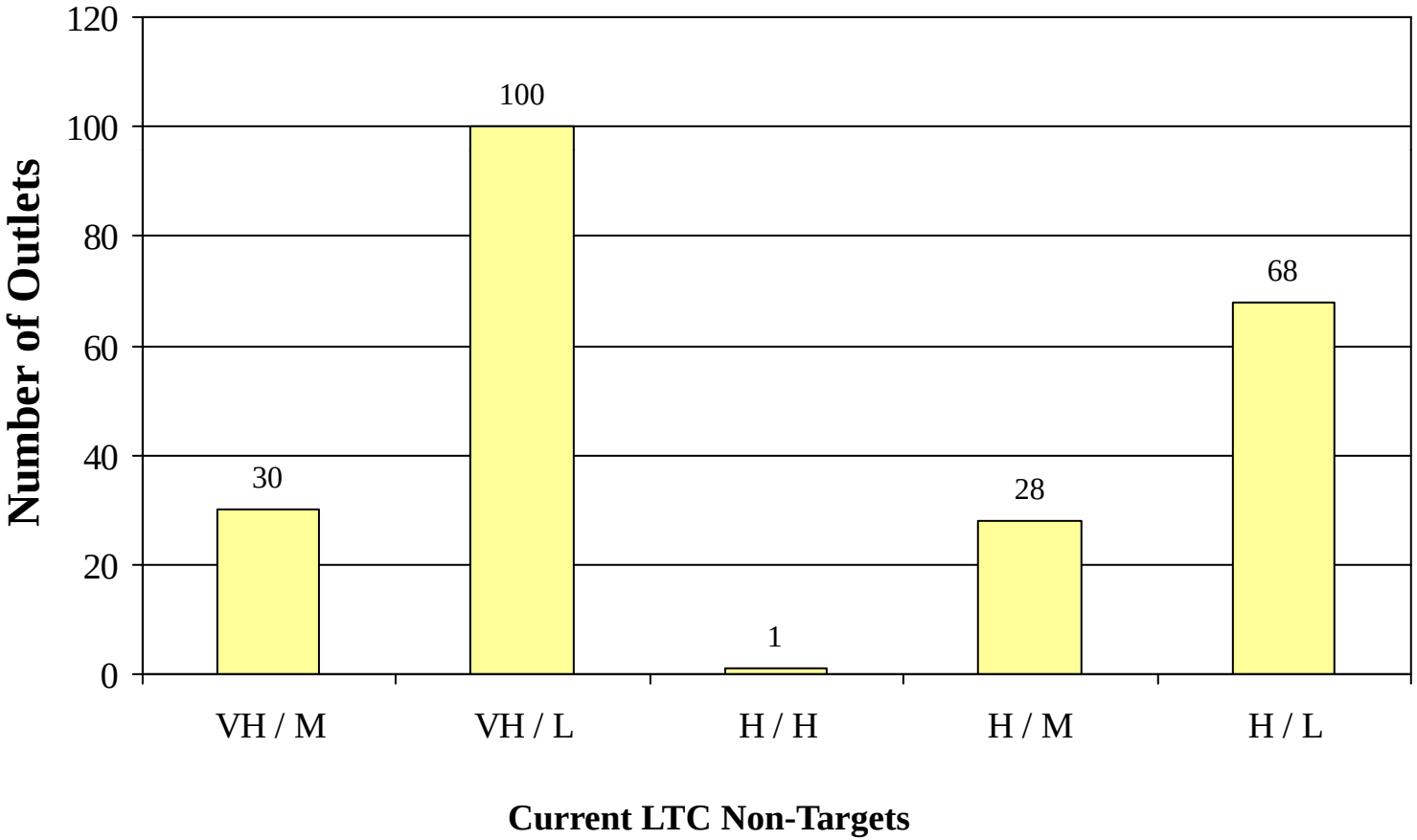
LTC Analysis: Add 16 Incremental LTC Reps

The incremental sales gain over the next 12 months is $9.8MM with a cost of $2.7MM.



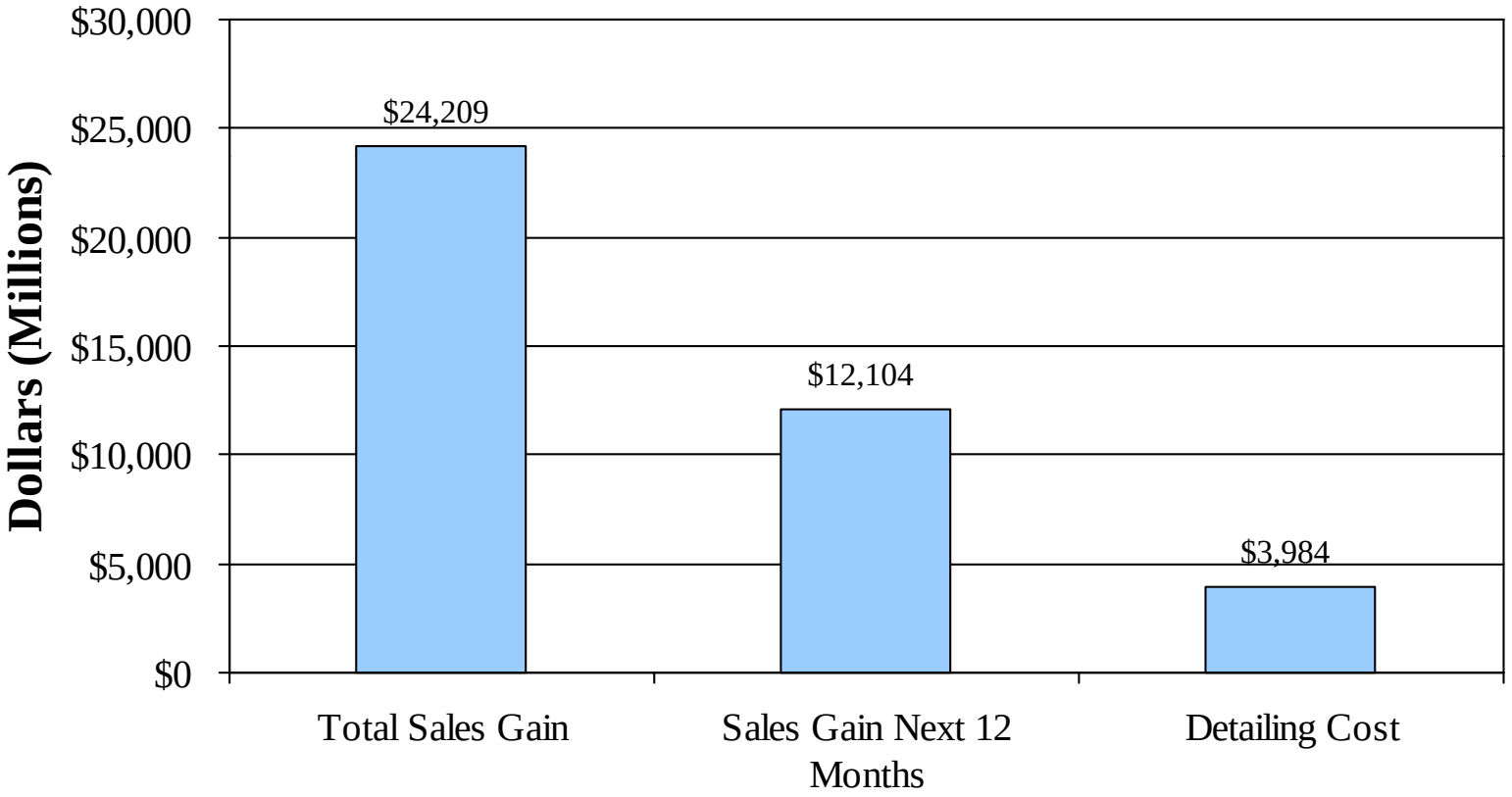
Outlets Added: Add 16 Incremental LTC Reps

The added targets would be selected from the Current LTC Non-Targets.



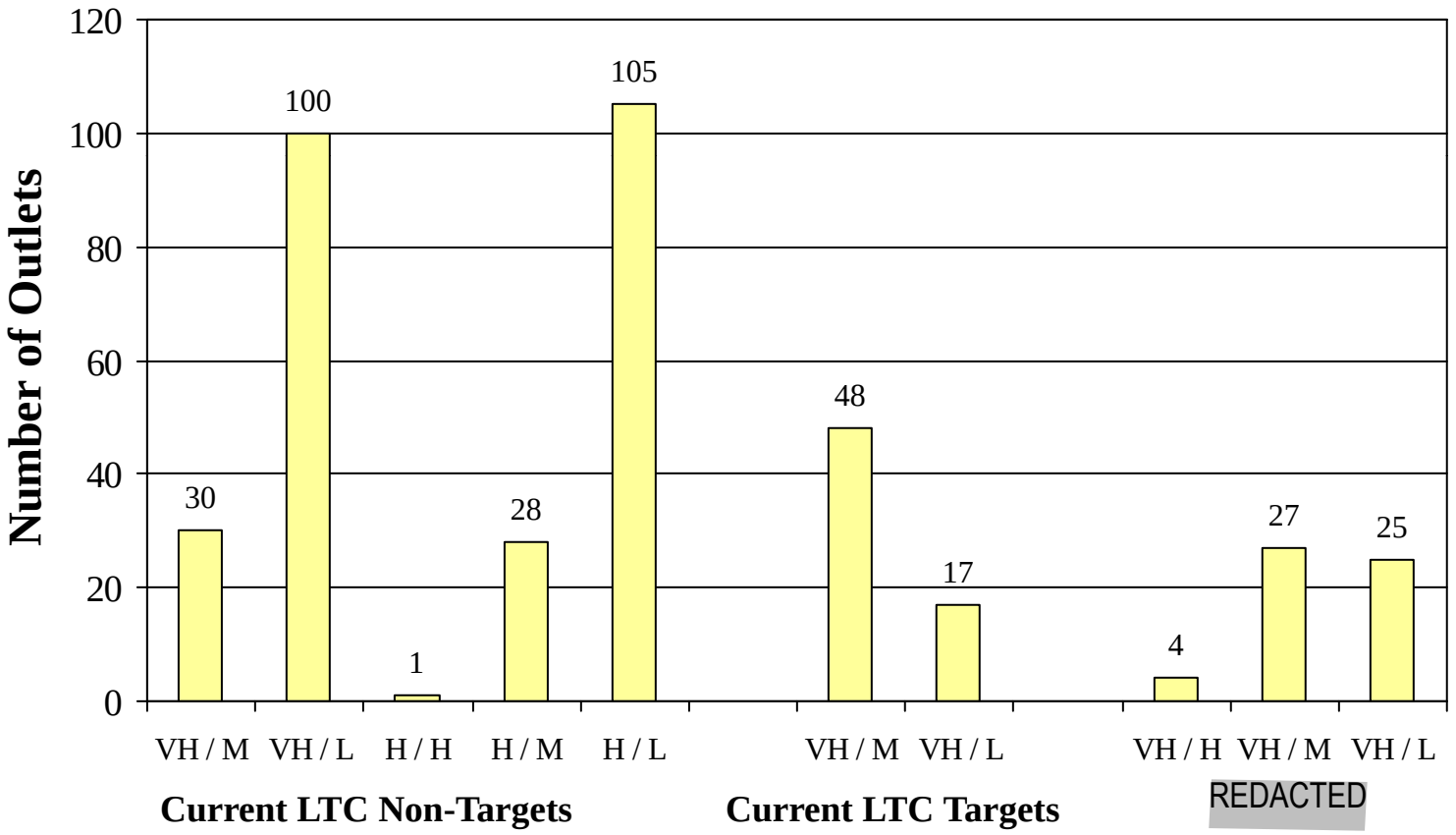
LTC Analysis: Add 24 Incremental LTC Reps

The incremental sales gain over the next 12 months is $12.1MM with a cost of $4.0MM.



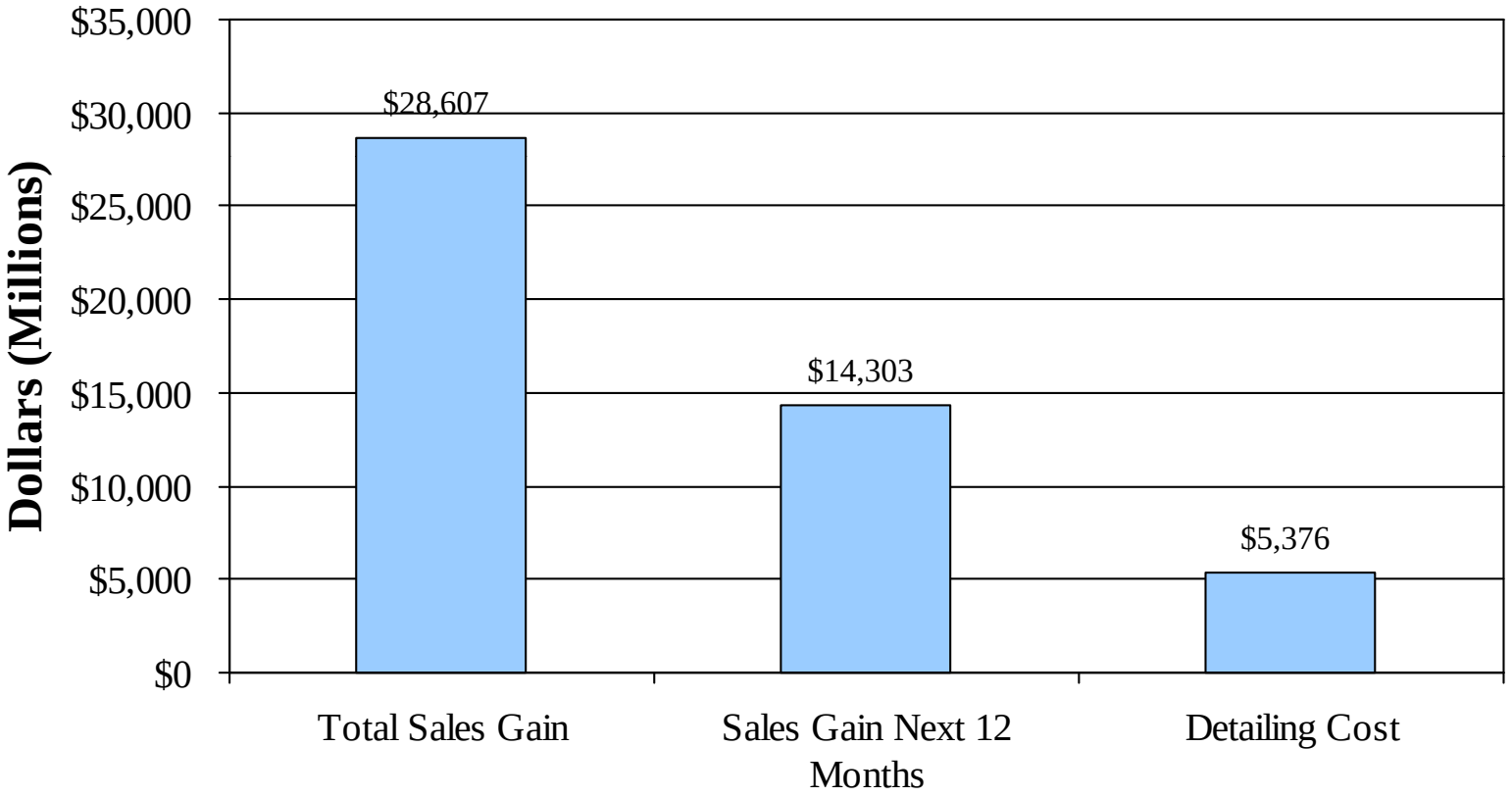
Outlets Added: Add 24 Incremental LTC Reps

The added targets would be selected from the Current LTC Non-Targets, Current LTC Targets, and REDACTED outlets.



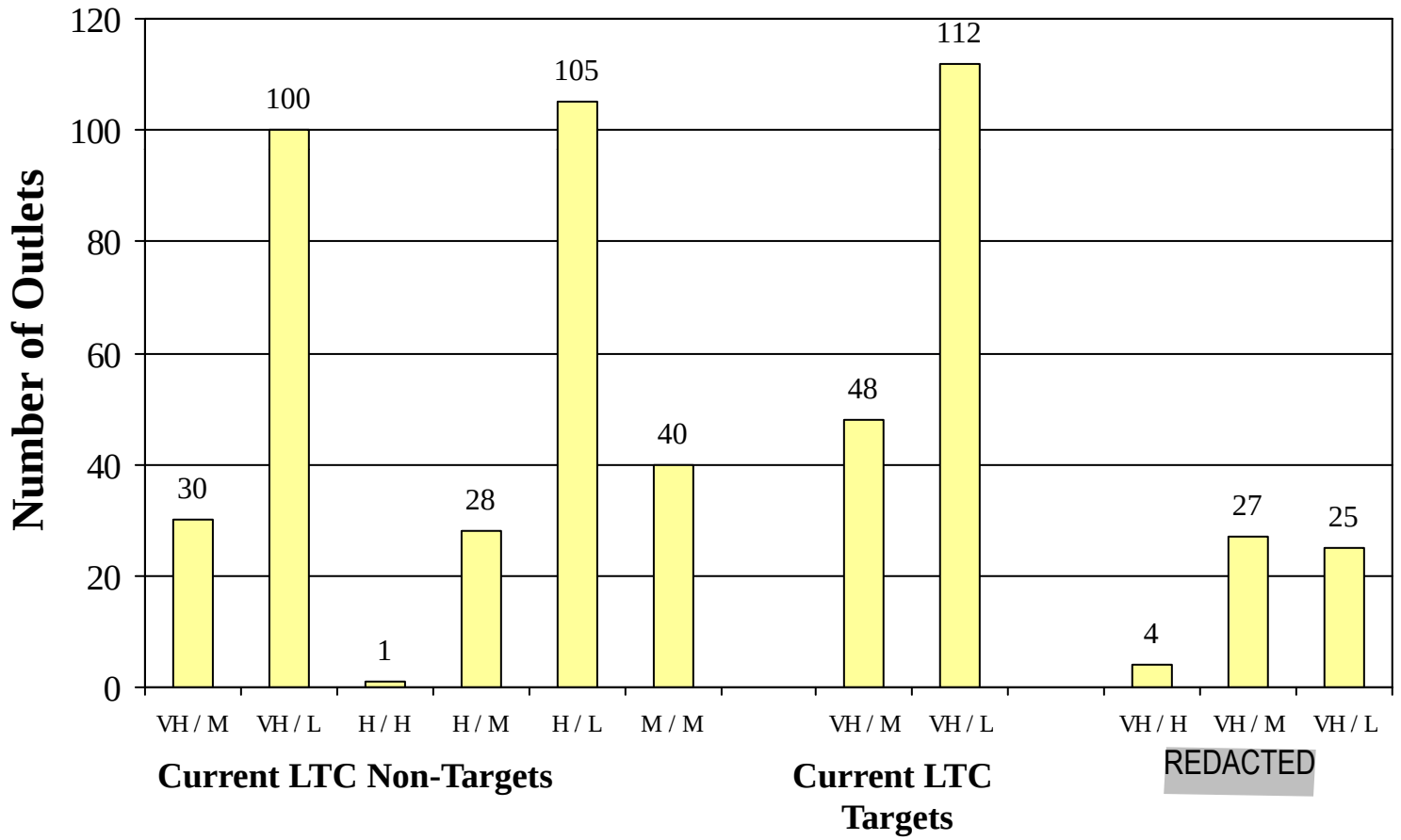
LTC Analysis: Add 32 Incremental LTC Reps

The incremental sales gain over the next 12 months is $14.3MM with a cost of $5.4MM.

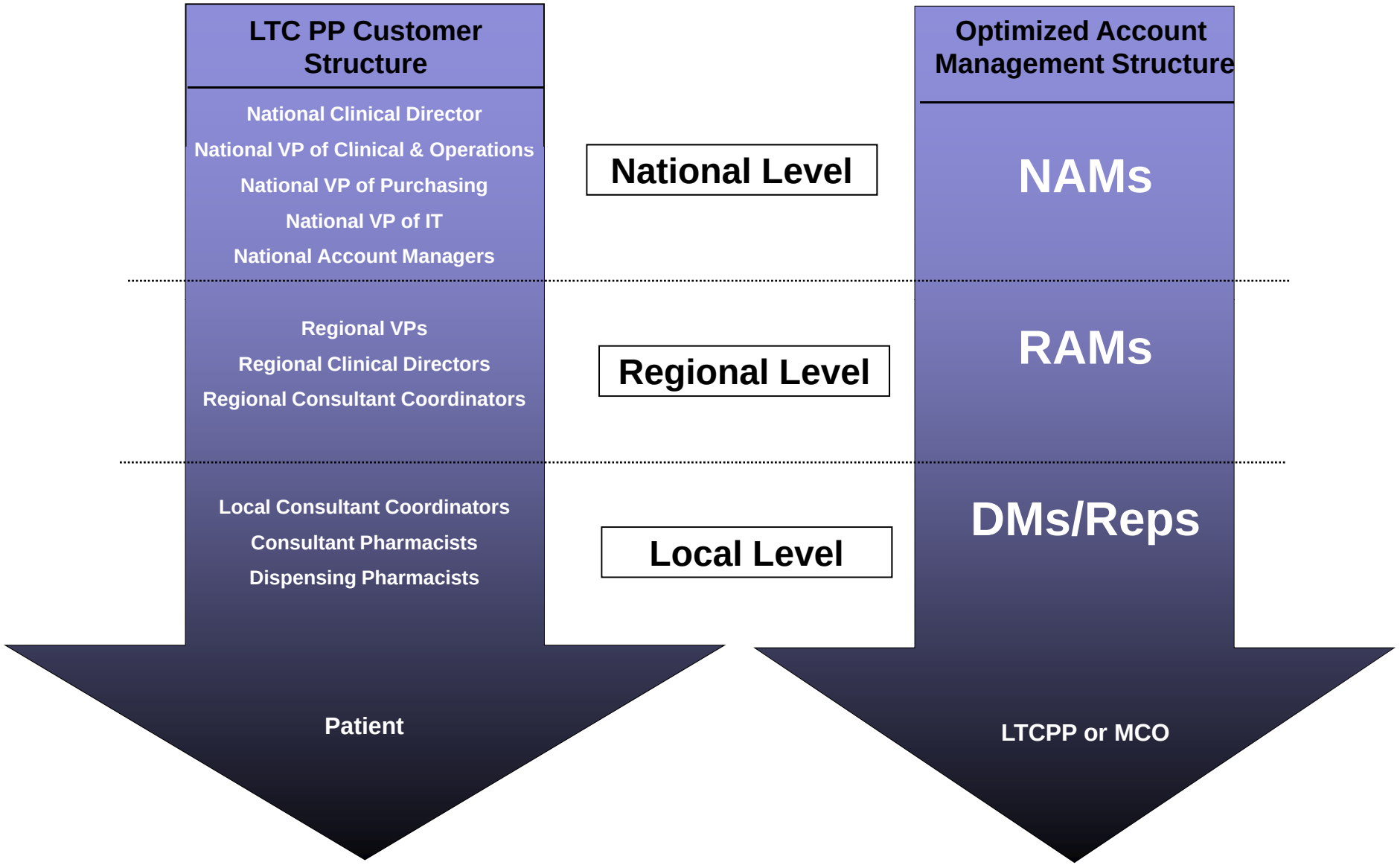


Outlets Added: Add 32 Incremental LTC Reps

The added targets would be selected from the Current LTC Non-Targets, Current LTC Targets, and REDACTED outlets.



Proposed LTC Account Manager Optimization



Example of Western Area (AZ, CA, OR, WA) LTC RAM Responsibilities

National Pharmacy Accounts

- REDACTED **Regional Office**
- **2** REDACTED **Regional Clinical Coordinators**
- REDACTED **Regional Clinical Director**
- REDACTED **Regional VP (WA)**
- REDACTED **Consultant Coordinators (4)**
- REDACTED **Regional Pharmacy Manager (CA)**
- REDACTED **Divisional Sr. Consultant (CA)**

Independent Pharmacy Accounts

- REDACTED **Pharmacy (Van Nuys, CA)**
- REDACTED **Pharmacy (San Diego, CA)**
- REDACTED **Pharmacy (Portland, OR)**

Nursing Home Chains

- **Regional DON –** REDACTED **(CA)**
- **Regional Director -** REDACTED

Department of Corrections

- **CA DOC System**

Developmental Disability Nurse Association Chapters

- **CA and WA DDNA Chapters**

Other

- REDACTED **(In-patient psych –** REDACTED **supplies drug)**

Required LTC Representative Skill Set

- **Account Management Skills**
  - Account Planning Abilities
  - Influence Mapping Expertise
  - Needs Identification Skills
  - Program Design and Delivery Skills
- **Personal Promotion Skills**
  - Integrity selling skills
  - Objection handling abilities for both specialists and generalists
- **Formulary/Reimbursement Knowledge and Understanding**
  - Medicaid Knowledge
  - Medicare Knowledge
  - Dually Eligible (Medicaid/Medicare)
- **Market and Setting Knowledge and Understanding**
  - Demographic understanding of patient types
  - Market drivers of business and medical needs
  - Regulatory understanding
- **Product Understanding**
  - Bipolar Expertise (acute and maintenance)
  - Epilepsy Expertise
  - Agitation and Aggression Expertise
  - Co morbid ConditionEexpertise

LTC New Hire & Existing Filed Sales Representative '04 Training Plan

New Hire	ISTC	Post-ISTC
Hire for Jan 1, 2004 start date	Full Depakote certification	RFT training
Pre-ISTC assignments: Epilepsy, Migraine, Bipolar, MR/DD, DOC and SNF modules	New SNF Training*	LTC Mentor program (30, 90 and 120 days)
	New DOC Training*	Integrity Selling Follow-up teleconferences
	New MR/DD Training*	Field-Based Preceptorships
	Account-Based Selling Advanced Account-Based Selling*	
	Integrity Selling	
	ISTC –Based LTC Preceptiorship	

* Includes existing reps

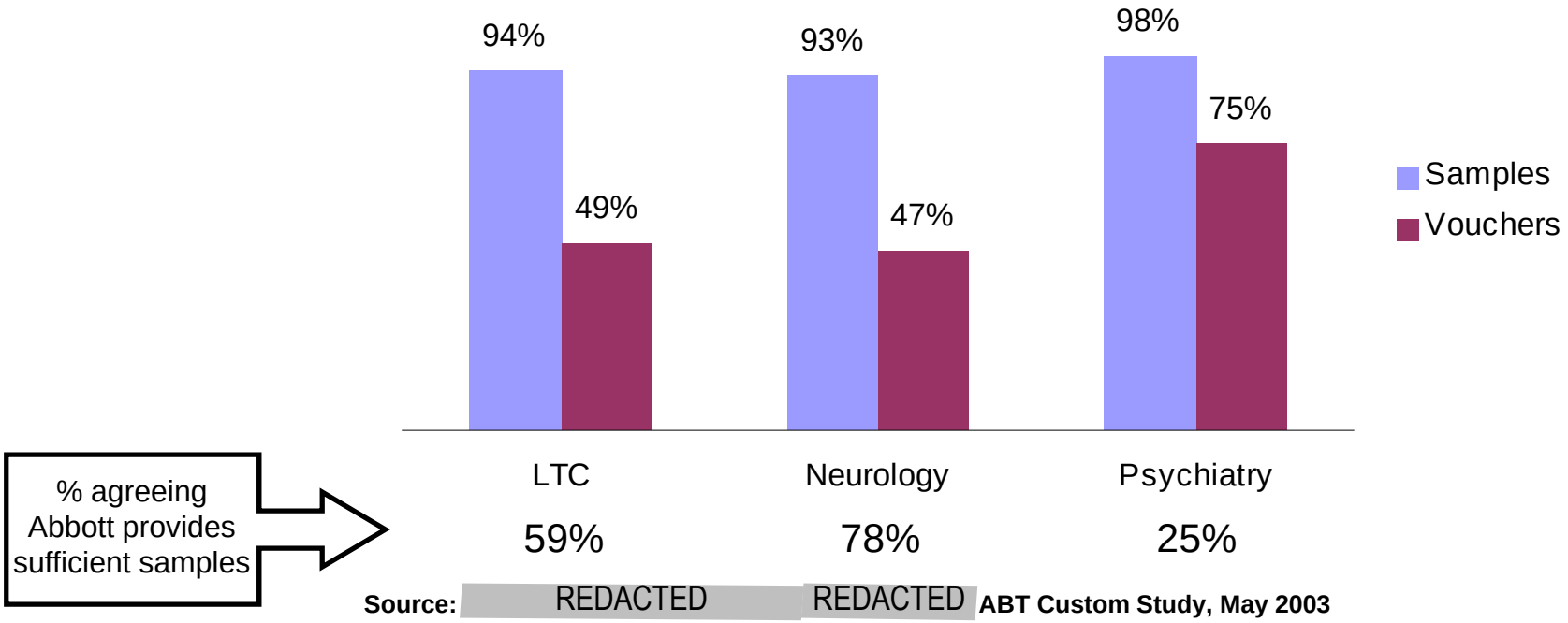
Required LTC Field Sales Support: Data

Data Set	Vendors	Business Uses	Annual Cost*
LTC Exponent	REDACTED	• Provide prescriber level data for a portion of the LTC market • Refine targeting • Refine Q & I requirements for LTC sales organization	$150,000
DNA MD View (Flat File)	REDACTED	• Provide prescriber level data for a portion of the LTC market (largely REDACTED) • Refine targeting • Refine Q & I requirements for LTC sales organization	$100,000
Pharmacist, and Facility Lists	Various	• Provide facility identification data • Provide organizational affiliations for key prescriber and influencers • Assist with direct marketing needs and event targeting	$ 50,000

* Annual costs account for both data acquisition and manipulation related charges should Abbott need to secure outside resources to fulfill programming and analysis needs.

Required LTC Field Sales Support: Vouchers

How Valuable are Samples/Vouchers to You and Your Patients?
(% of Physicians mentioning valuable or very valuable unaided)



Source: REDACTED REDACTED **ABT Custom Study, May 2003**

- **Based 2004 LTC per rep request on:**
  - Abbott's 2003 SR and ISR experience
  - Competitive information
- **Assumed that required vouchers will be funded through Depakote common funds.**

LTC Optimization Supports

Sales Force Optimization

Representative Increase

Management Increases

Key Supports

Marketing Expansion

Marketing Personnel

Marketing Budget

Contracting Expansion

Clinical Data Expansion

Corrections IIS

MRDD IIS

Agitation, Aggression IIS

LTC marketing has developed setting and disease state positioning to ensure fulfillment of LTC's new strategy.

Correctional Facilities

- Hold corrections only RCMs
- Tailor Stahl programming and DLNs to corrections
- Attend key corrections meetings
- Contract with corrections MCOs

Mentally Retarded Developmentally Delayed Facilities (MRDD)

- Hold MRDD only RCMs
- Enhance and expand MRDD Penry programming
- Deliver case-based special populations seizure treatment programming

Skilled Nursing Facilities (SNFs)

- Develop targeted programming for reluctant geri-psychs
- Deliver value added prgms. for CPs and NPs w/ secondary clinical messages, e.g. nurses retention through better behavior mmgt.

Universal Institutional Positioning

- Emphasize cost reduction and pharmacoeconomic messages based on evidenced based medicine in all settings
- Stress the advantages of Depakote ER over VPA and the utility of oral loading for acute treatment

Bipolar LTC

- Deliver core bipolar messages s to corrections, MRDD and SNFs
- Utilize CME to further address bipolar in the elderly or dually diagnosed patient
- Conduct IIS work with incarcerated or probationary bipolar populations

Epilepsy LTC

- Deliver core seizure messages to corrections, MRDD and SNFs
- Utilize CME to address unique seizure types common among MRDD and elderly patients
- Conduct IIS work with specific institutionalized epilepsy populations

Agitation & Aggression LTC

- Communicate symptom relevance from pivotal trials to prescribers
- Utilize CME to disseminate agitation research
- Utilize CME and advocacy ties to address care giver burden issues
- Conduct IIS work addressing common adjunctive therapy approaches - Casey LTC

Proposed 2004 LTC Promotional Budget Allocations

Major Promotional Categories	Key Category Elements	'03 Actual Spend (000's)	2004 Proposed Spend (000's)	2004 Key Category Components*
Sales Force Support	Reprints, Sales Aids, and NAM War Chest	$ 580	$ 700	2 LTC sales aids, 2-4 slim jim like pieces and increased NAM war chest funds to cover corrections
Meetings and Events	Conventions, Meeting Symposia, Advisory Board	$ 1.1	$ 1.7	Reduced SNF meetings, additional Corrections and MRDD Meetings, 2 advisory meetings per market segment
CME Programs		$ 400	$ 1.0	"Key Pharmacoeconomic Concerns in the DOC: Why Branded is Better!", "Differential diagnosis: psychiatric and behavioral disturbances in the mentally retarded and developmentally delayed", "Increased Patient Compliance with QD Dosing."
Grants	Funds for institutes/3rd parties to support product research / foster general company goodwill	$ 300	$ 700	Added support to advocacy organizations to produce patient/care giver materials relevant to Corrections, MRDD and SNF environments.
Consultant Meetings	One on one meetings with key prescribers/influencers	$ 0	$ 675	4 corrections RCMs, 4 MRDD RCMS and 7 SNF DCMs
Agency Fees	PR and Advertising Fees	$ 0	$ 20	Use external PR support to publicize new findings
Market Research	Focus Groups, Studies	$ 225	$ 400	ATU and positioning research for new strategy
Data Purchases	Syndicated and proprietary data purchases	$ 0	$ 300	Annual LTC physician level data, new DNA product and list purchases for Corrections and MRDD
	TOTAL	**$ 2.6**	**$ 5.5**	

* Full program details by sector are found in the appendix.

In corrections, the marketing team will carry out brand new programming for 2004.

	2004 Content Development Tactics for Corrections
Care giver/Patient Education Materials (with or without an association tie in)	Recognition and Appropriate Treatment of Bipolar Disorder/Behavioral Disorders in the Correctional Setting - to be done with National DOC association such as National Committee on Correctional Healthcare and separately with the major MCOs REDACTED , REDACTED REDACTED
	Understanding Bipolar Disorder and How if Affects You
	Formulary Access reference sheets (once Depakote is on formulary for MCOs
	Other spin-offs from CME programs
CME Programs	Best Practices for Management of Bipolar Disorder/Behavior Disorders in the Correctional Setting: New Ideas and Practical Approaches, with Case Discussions
	Seizures in the Correctional Setting: Environmental Triggers and Treatment Options
	Key Pharmacoeconomic Concerns in the DOC: Why Branded is Better!
	How Antipsychotic Overuse is Costing the DOC Time and Money!
Market Research Studies	Positioning Research for the Correctional Setting
	Message/Sales Aid Testing
	Message Recall Study
	ATU
Investigator Initiated Study Topics/Data Requirements	Bipolar Disorder and Comorbid Behavior Conditions with or without Head Injuries
	Efficacy of Depakote when Hepatitis C is present
Training Needs	Getting to Know the DOC: Who are the Big Players? *MCO, *Pharmacy Providers, *Prescribers and Influencers,
	Understanding the Rx Cycle in the DOC: *Role of Formularies *Ultimate Decision Makers
	Understanding the Corrections MArket
	Key Pharmacoeconomic Concerns in the DOC: *Why Branded is Better!*
	Deapkote corrections Data
	Atypicals Corrections Data

In corrections, the marketing team will carry out brand new programming for 2004 (continued).

	2004 Meeting, Events and Pull Through Tactics for Corrections
Advisory Board Meetings	1-2 National Advisory meetings (one to get a "smart" start out of the gate and one to reassess progress/direction at year-end) 4-8 Regional Advisory Meetings (competitive intelligence has suggested that much of this market functions on a Regional or Localized level. It is therefore necessary to cultivate Regional Advisors who could contribute to the success of this campaign. Two Advisory Meetings in each of 4 Regions would take place.)
National Meeting Symposia	National Committee on Correctional Healthcare: 2 (Spring and Fall Meetings) American Correctional Health Services Association: 2 (Spring and Fall Meetings) American College of Forensic Psychiatry: 1 (Spring)
Meeting Booth Presence	5-6 "National" meetings, booth size medium if Depakote only; Large if coordinated with HIV National Committee on Correctional Healthcare: 2 (Spring and Fall Meetings) American Correctional Health Services Association: 2 (Spring and Fall Meetings) American College of Forensic Psychiatry: 1 (Spring) 14-15 Regional Meetings, booth size small if Depakote only; Medium if coordinated with HIV, Regional Meetings TBD
Regional/District Consulting Meetings	4 Regional/District Consulting Meetings devoted to Corrections
Sales Aid	2 molecule sales aids per year with relevant slim jims, dosing cards and flash cards
Journal Ads	American Journal of Forensic Psychiatry (4-12); Journal of Correctional Health Care (4-12) CorrectCare (4; is a quarterly publication)
Reprints	8-10 dissemination quality reprints
Data Needs	List of MHC/Pharmacy providers servicing DOC: National and Regional List of MDs servicing the DOC market by specialty and with Rxing patterns for Depakote and Competitors (similar to the old "PPP" report) List of key support Organizations for the DOC Contracting performance data

Note: Promotional items would be coordinated with franchise wide activities. Pharmacy counting trays and formulary items would be the only unique LTC additions.

The marketing team will increase its MRDD programming and tailor existing neurology materials.

	2004 Content Development Tactics for MRDD
Care giver/Patient Education Materials (with or without an association tie in)	"Did You Know" patient education pamphlets distributed to families regarding topics in epilepsy, psychiatric conditions and behavioral disturbance Depakote patient education pamphlets: what it is, what it is for, how it is dosed, side effects, etc. *Perhaps in association with ANCOR (American Network of Community Options and Resources) or AAMR (American Association on Mental Retardation)*
CME Programs	"Epilepsy in the mentally retarded / developmentally delayed" "Differential diagnosis: psychiatric and behavioral disturbances in the mentally retarded and developmentally delayed" "The role of anticonvulsants in the treatment of behavioral and psychiatric conditions in the mentally retarded / developmentally delayed population" "Rationalizing treatment regimens for patients on multiple medications" "The role of extended release medications in the treatment of the MRDD patient" Some content development in association with DDRCs (Developmental Disability Research Centers)?
Direct Marketing Programs	Journal subscription program: American Journal of Mental Retardation or Journal of Intellectual Disability Research E-mail blasts featuring news on Depakote in the MRDD population
Market Research Studies	Depakote ER conversion in MRDD facilities Depakote/Depakote ER dosing in MRDD facilities ATU for MRDD prescribers Positioning statement testing: MRDD prescribers and caregivers Sales Aid testing: if new campaign developed with new agency
Investigator Initiated Study Topics/Data Requirements	"The use of divalproex in reducing frequency and severity of agitated / aggressive / impulsive behaviors in MRDD patients with or without seizures."
Training Needs	General training on MRDD: patient types, caregiving environment, special issues in pharmacotherapy for the MRDD population: backgrounder and workshop (sales force) Epilepsy in the MRDD population (sales force) Behavioral disturbance and psychiatric diagnoses in the MRDD population (sales force)

The marketing team will increase its MRDD programming and tailor existing neurology materials (continued.

	2004 Meeting, Events and Pull Through Tactics for MRDD
Advisory Board Meetings	2 annual advisory board meetings
National Meeting Symposia	American Association on Mental Retardation (AAMR) Annual Meeting June 1-4, 2004 (Philadelphia, PA): "Enhancing Quality of Life for the Mentally Retarded and Developmentally Disabled" Developmental Disabilities Nurses Association (DDNA) annual meeting April 24-26, 2004 (Charlotte, NC): "Identifying Seizures in the Developmentally Disabled"
Meeting Booth Presence	**Medium**: American Association on Mental Retardation (AAMR) Annual Meeting June 1-4, 2004 (Philadelphia, PA) **Medium**: Developmental Disabilities Nurses Association (DDNA) annual meeting April 24-26, 2004 (Charlotte, NC)
Regional/District Consulting Meetings	4 Regional Consulting Meetings, 20-25 attendees each
Sales Aid	2 molecule sales aids per year with relevant slim jims, dosing cards and flash cards
Journal Ads	Journal of Intellectual Disability Research American Journal of Mental Retardation More mainstream journals as well: J Clin Psych, e.g.
Reprints	4-6 dissemination quality reprints
Data Needs	List of MRDD facilities with addresses and bed/patient counts List of key prescribers in MRDD with addresses for targeting Industry analyses: State of the States by David Braddock when updated

Note: Promotional items would be coordinated with franchise wide activities. Pharmacy counting trays and formulary items would be the only unique LTC additions.

In 2004, SNF programming will be significantly revised and refocused on more intimate, higher ROI efforts.

	2004 Content Development Tactics for SNFs
Care giver/Patient Education Materials (with or without an association tie in)	Depakote patient education pamphlets: what it is, what it is for, how it is dosed, side effects, etc. Alzheimer's disease education materials in association with Alzheimer's Association Caregiver guide Value added talk: "Planting and Nurturing LTC physicians"
CME Programs	"Differential diagnosis: psychiatric and behavioral disturbances in the elderly" – to include segment on diagnosing bipolar disorder in the older adult "Rationalizing treatment regimens for patients on multiple medications" "The role of extended release medications in the treatment of the elderly patient" Treatment options for older adults with seizures "Neuroprotective properties of divalproex" Neuropsychiatric Issues in Long Term Care CME newsletter – several times a year, CME accredited (like Bipolar Disorder and Impulsive Spectrum Letter in psych) – rep distributed
Direct Marketing Programs	E-mail blasts featuring news on Depakote in the elderly population
Market Research Studies	ATU for SNF prescribers Positioning statement testing: SNF prescribers and caregivers Sales Aid testing: if new campaign developed with new agency Identification of geri-psychs who do not view Depakote favorably; assessment of barriers to support and use
Investigator Initiated Study Topics/Data Requirements	"The use of divalproex as adjunctive treatment in reducing frequency and severity of agitated / aggressive / impulsive behaviors in elderly patients with dementia."
Training Needs	Advanced content training: Differentiating between bipolar disorder, secondary mania, and psychosis in the elderly (sales force) Recognizing epilepsy in the elderly (sales force)

In 2004, SNF programming will be significantly revised and refocused on more intimate, higher ROI efforts (continued).

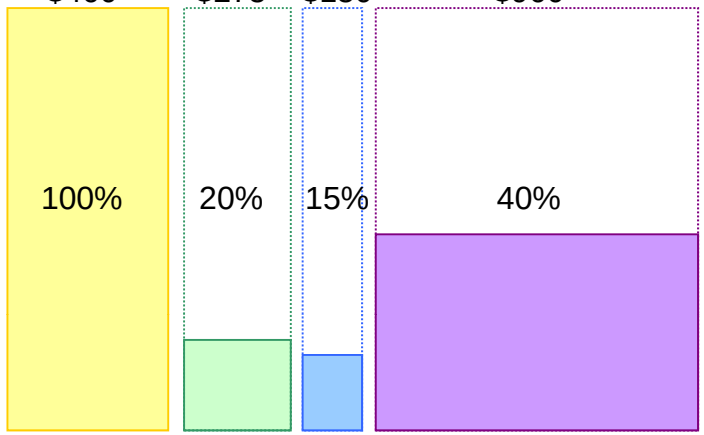
	2004 Meeting, Events and Pull Through Tactics for SNFs
Advisory Board Meetings	2 annual advisory board meetings
National Meeting Symposia	AMDA: March 4-7, Phoenix AZ. "Making the Desert Bloom: Creating Excellence in LTC Medicine" ASCP: At least year-end; potentially mid-year as well Midyear is May 13-15, Scottsdale AZ "Geriatrics '04" AAGP US Geri Congress NADONA or NCGNP
Meeting Booth Presence	Large: AMDA Large: ASCP Large: AAGP Large: US Geri Congress Medium: NADONA or GNP
Regional/District Consulting Meetings	7-14 District Consulting Meetings, 20-25 attendees each
Sales Aid	2 molecule sales aids per year with relevant slim jims, dosing cards and flash cards
Reprints	6-8 dissemination quality reprints
Journal Ads	**American Journal of Geriatric Psychiatry** **More mainstream journals as well: J Clin Psych, e.g.**
Data Needs	Prescriber-level data for all 50 states Facility utilization data for account-based targeting

Note: Promotional items would be coordinated with franchise wide activities. Pharmacy counting trays and formulary items would be the only unique LTC additions.

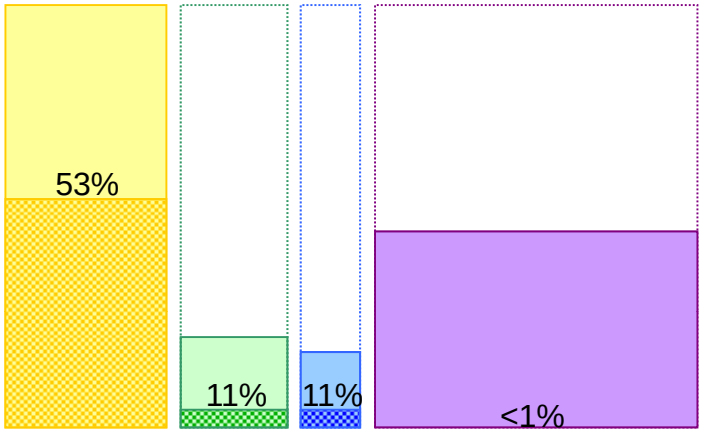
Competitor's Current Contracting Includes Corrections and SNF focused LTCPP's.

Revenue Opportunity - LTC Segments

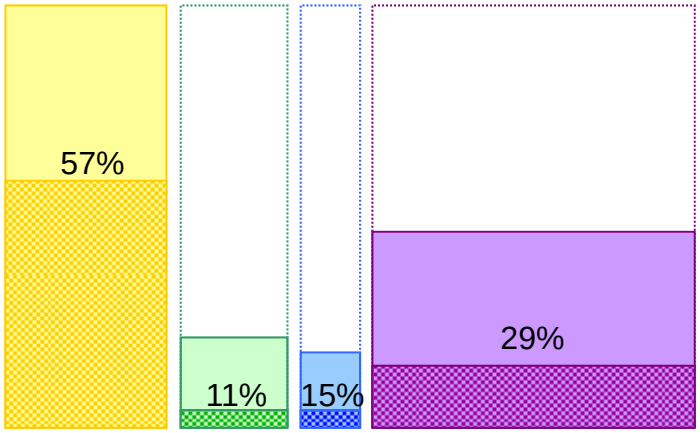
	SNF	ALF	MRDD	CORR
Total Mkt $	$460	$275	$150	$960
% Served by Large or Medium Sized LTCPPs:	100%	20%	15%	40%
"LTC" Mkt $'s Controlled by Large or Medium Sized LTCPPs	**$460**	**$ 55**	**$ 23**	**$384**
% Medicaid (est.)	65-80%	20%	50-65%	0%



Segments Contracted for Depakote
Total Contracts: 7



Segments Contracted for Zyprexa (est)
Total Contracts (est): 12



Source: Abbott analysis.

Contracting with dominant LTC pharmacy providers has been an effective tool for competing in the LTC market.

Zyprexa (REDACTED) & Risperdal (REDACTED)

Contract Driver: Maintaining market share

- **REDACTED's and REDACTED s contracts with LTC pharmacy providers give rebates for maintaining market share for Risperdal and Zyprexa within the atypical market basket**
- **These contracts do not place Depakote in direct competition with atypicals**
- **These contracts are moderately easy to fulfill**
  - Many providers earned several million dollars in rebates last year
  - Abbott's review of the 2002 REDACTED data which we purchase suggests that:
    - » Risperdal received $4 million in rebates on nearly $40 million in sales to REDACTED
    - » Zyprexa received $3 million in rebates on $60 million in sales to REDACTED

Depakote

Contract Driver: Net kilogram growth

- **Abbott contracts with LTC pharmacy providers give rebates for growing kilogram sales**
  - Abbott's current contractees provide pharmacy services for about 54% of SNF beds
- **Contracts also oblige pharmacy providers to participate in Abbott's pull-through programs**
  - Medical education on appropriate use of Depakote
- **Contract structure was altered this year to make contracts more competitive**
  - Earlier contracts required 10% kg growth for 2% rebate and were so difficult to fulfill that LTCPPs did not bother trying
  - Competitive contracts required as a loss-avoidance mechanism:
    - e.g. REDACTED (now owned by REDACTED) instituted a therapeutic interchange program replacing Depakote with generic valproic acid, losing Abbott 24% of its Depakote business; competitive contracts necessary to avoid a repeat occurrence
  - Under new contract terms, most contractees have driven double-digit kilogram growth in 2002 vs. 2001 and are driving ER conversion

Select Contracting Will Further Solidify Influence in LTC

Care Setting	LTCPP Type	Orgs (Beds)	Recom-mendation	Rationale	
				+	-
Skilled Nursing Facilities	Very Large National or Regional LTCPPs	5 (0.81MM)	Continue contracting	• Large numbers of beds tightly controlled by few organizations • Demonstrated performance on Abbott contracts • High strategic fit • High barriers to exit	• Moderate $$ opportunity/bed
	Mid-Sized Independent Pharmacy Providers	6 (42 K)	Do not contract	• Have consultant pharmacists / processes through which to control drug usage • Contracting experience with atypicals	• Moderate $$ opportunity/bed • Moderate number of beds • Moderate to low probability of profitability • Likely acquisition candidates
Corrections	Large LTCPP or MCOs focused on corrections	3 (0.6 MM)	Initiate contracting	• Large numbers of beds tightly controlled by few organizations • High $ opportunity/bed • High probability of profitability • High strategic fit • Synergies with HIV franchise • No Medicaid	• Conversion to VPA already underway
MRDD	Very Large National or Regional LTCPPs	5 (50 K)	Continue contracting	• Same as above • High $ Opportunity/bed	
	Independent PPs focusing on MRDD	5 (12K)	Do not contract	• High opportunity per bed	• Few beds / fragmented • No consultants / poor control

Source: Abbott marketing analysis.

Incremental sales exceed rebates paid under current Depakote LTC contracts…

	Adj Sales Growth 1Q01-1Q02	Incremental Sales	Contract Rebates	Adj Sales Growth 4Q01-4Q02	Incremental Sales	Contract Rebates
REDACTED	12.8%	$955,192	$394,185	17.5%	$1,401,927	$508,544
REDACTED	18.8%	$521,444	$216,023	16.9%	$545,656	$204,674
REDACTED	15.3%	$420,345	$172,933	13.6%	$422,192	$151,477
REDACTED	35.1%	$245,342	$98,121	25.1%	$217,765	$82,139
REDACTED	-6.0%	($50,266)	$0	6.8%	$53,987	$0
REDACTED	28.3%	$143,853	$58,093	27.7%	$180,164	$67,405

Over time, contracts appear to have become more efficient on the *top line*:

In 1Q02, Abbott paid an average of $0.42 for each incremental sales dollar

In 4Q02, Abbott paid an average of $0.36 for each incremental sales dollar

Based on Pricing Department Figures

…But what is the true incremental value of further expanded contracting, relative to the alternative?

Analytic Exercise: Key Steps

- Gather data from contractees (test group)
  - Where possible, dissect test group by bed type
    (test the hypothesis that in some facility types growth is easier to drive)
- Gather data from non-contractees (control group), by bed type where possible
- Compare growth rates for test vs. control group (topline opportunity)
- Compare profitability of test group vs. control group under a contract (pricing assistance)
- Summarize financial opportunity: incremental value of contracting
- Evaluate key non-financial criteria (control, data capabilities, etc.)

Incremental Value of Contracting: Analysis

Example: Skilled Nursing and Assisted Living (Blended)

"Test Group"
Subset of current contractees

Organization	Beds
REDACTED	198,000
REDACTED – REDACTED	24,000
REDACTED – REDACTED	9,100

Source: REDACTED **and** REDACTED **internal records.**

"Control Group"
Subset of potential contractees

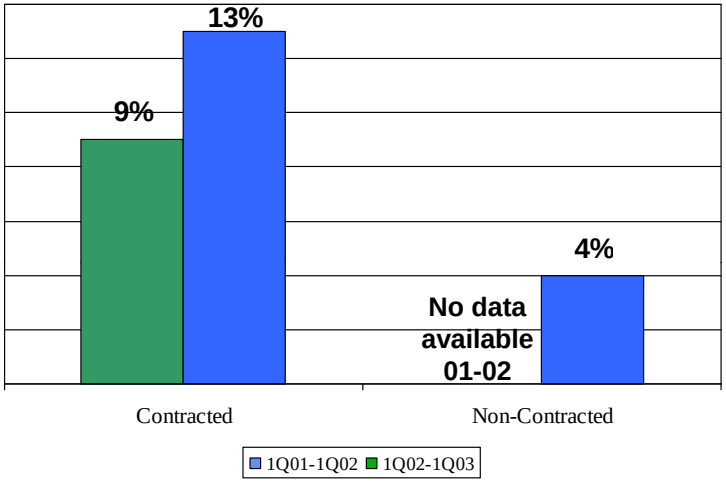
Organization	Beds
REDACTED	7,000
REDACTED	4,200
REDACTED	12,600
REDACTED	1,350

Source: Providers through third-party (REDACTED **survey.**

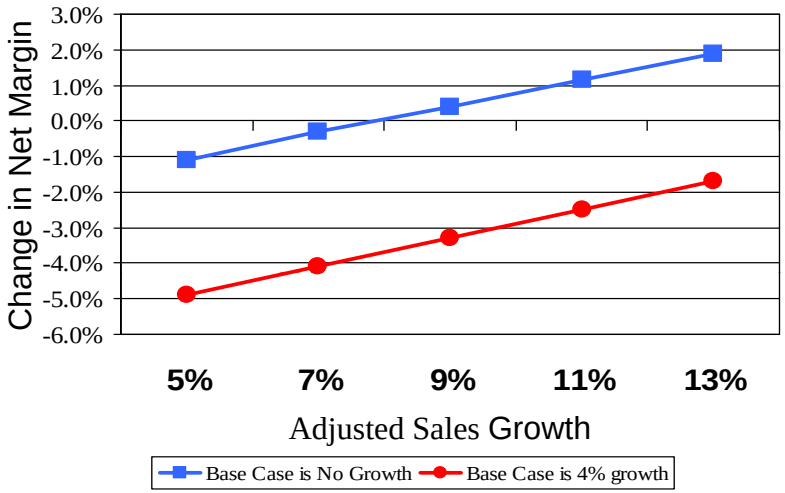
Incremental Value of Contracting: Analysis

Example: Skilled Nursing and Assisted Living (Blended)

Historical:
Adjusted Sales Growth per Bed



New Contract:
Sales Growth vs. Profitability*



- Analysis suggests that if modest growth is occurring without a contract in these SNFs/ALFs, the short-term risk/reward ratio of a contract may be unfavorable.
- A conservative estimate that the regional contractee could achieve half the incremental growth of a national contractee places the expected growth rates under a contract between 7% and 9%, which is only profitable if little to no base case growth is assumed.
- Profitability may be somewhat understated here, however, if ER conversion could be driven higher than the assumed 20% under a contract scenario.

* Assumes that contract drives ER% from 12.5% to 20% (benchmark: REDACTED 18.5%) and that Medicaid % of business = 60%

Incremental Value of Contracting: Comment

MRDD and Corrections Focused Pharmacies

- Data are limited for both "test" and "control" groups for MRDD facilities and correctional facilities. However, assessments may still be made:
- MRDD-Focused Pharmacies:
  - REDACTED (just 421 beds), focusing on MRDD:
    - Kg growth of 9.6% for Q103, over same quarter last year
    - ER% climbed to 25%
  - Preliminary data suggests that for non-contracted accounts, adjusted Depakote use is flat or declining in this market.
  - However, market is too fragmented to make contracting a viable approach
- Correctional facilities:
  - There are no bed-adjusted data on contracted correctional facility beds
  - ***Preliminary*** data suggest that for non-contracted accounts, Depakote use is flat or declining in these markets.
    - Taken together, REDACTED, REDACTED, REDACTED (REDACTED) and REDACTED showed flat Depakote sales (not price adjusted)
    - Limited data on selected smaller non-contractees suggest that Depakote use is declining in their correctional facilities.

Department of Corrections Contracting Makes Sound Economic Sense for Abbott

Corrections Contracting Initiation Rational

- **DOC lives are valuable to Abbott**
  - Dollar value per inmate treated is 2x that of treated SNF residents
  - No Medicaid → high level of profitability
  - Great potential for ER penetration due to med pass reduction

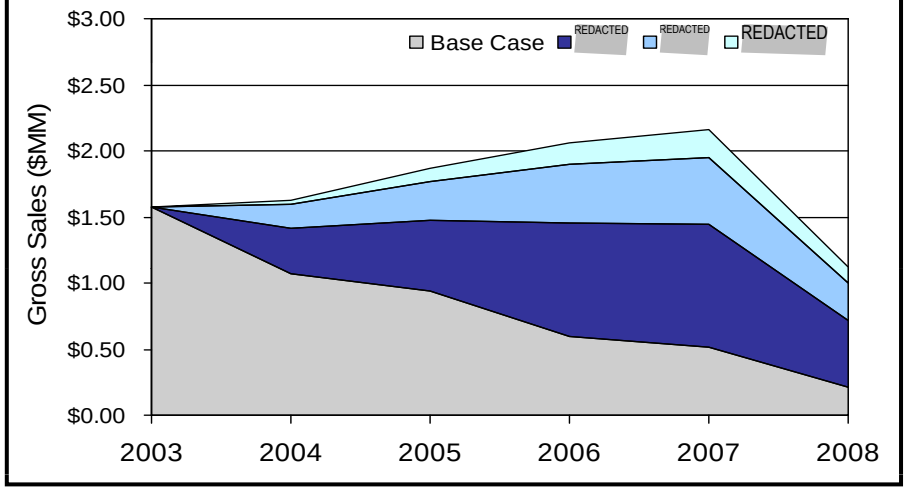
- **Current DOC business is at risk**
  - Major corrections MCOs have begun converting Depakote business to VPA - MATTY Q203 vs. MATLY, VPA purchases grew at 16 times the rate of Depakote/Depakote ER purchases

- **Contracting with 3 major Corrections MCOs and their Pharmacies is a low-cost, low-risk guaranteed return tactic**
  - Contracting with 3 managed care organizations captures over 30% of 2.1 million (est.) DOC lives (REDACTED, REDACTED, REDACTED)
  - HIV is already pursuing contracts with these same three MCOs
  - No additional account management heads are required but additional pull through must be provided by reps
  - Rebate payment is margin positive in every scenario
    - 2004 incremental revenue $0.5 MM in 3 accounts
    - 2005-2008 incremental revenue $5.0 MM in 3 accts
  - Contracting can be further supported by psychotropic appropriate use programming similar to what is currently being done in the state of Massachusetts

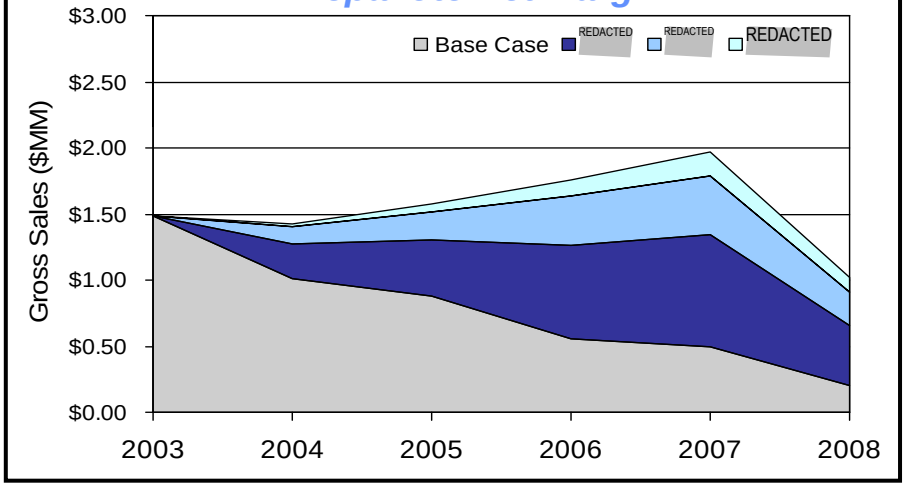
Corrections: Expected Case with Contracting

A contract in combination with an AU program will turn around Depakote declines in these three key accounts.

Depakote Net Sales



Depakote Net Margin

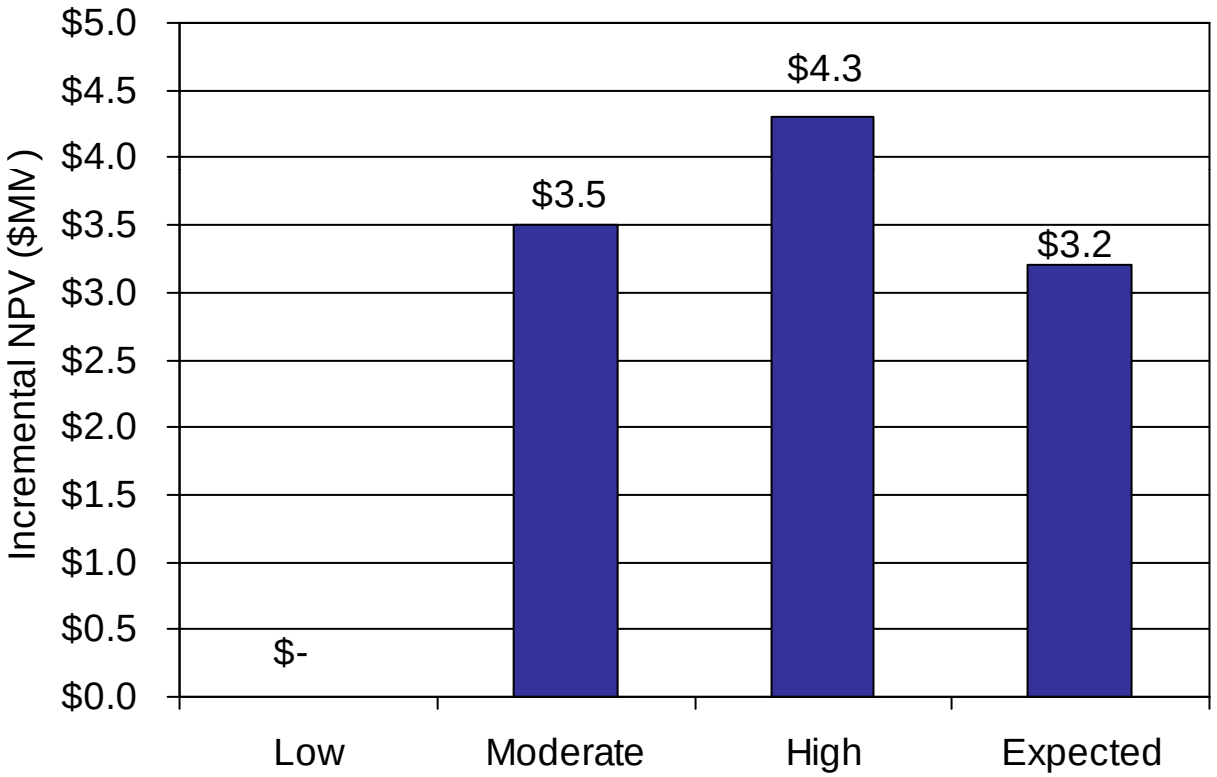


Rationale / Assumptions

- Interviews indicate interest in reducing use of expensive atypicals, particularly Zyprexa
- Combining education with contract rebates will make it more palatable to switch to Depakote and Depakote ER, rather than VPA
  - *Switching from Zyprexa to Depakote ER where appropriate could save accounts approximately $7 per patient per day, estimated to be over $5 million between these three accounts.*
- Recent examples of effective two-pronged strategies:
  - REDACTED *of Kansas City: Overall AIF Rxs declined 10%, while Biaxin market share and volume increased.*
  - REDACTED *of Appleton, WI: Biaxin share grew from 3.8% prior to program launch (4Q97) to 9.3% at the end of the year of launch and 15.2% one year later. Volume more than doubled during this time.*
- REDACTED s generic valproate product may dampen the effects of a contract, but will not preclude growth (as in Cenestin / Premarin case, discussed on p.11)
- Assumes purchasers for the DOC will continue to pay WAC for Depakote and Depakote ER
- Assumes Medicaid will not become a factor in the DOC market in the forecast period.

Corrections: Expected Case with Contracting

Contracting in the DOC NPV is $3.2 MM through 2008
Relative to Base Case



LTC Optimization Resource Needs

Sales Force Optimization

Representative Increase

Management Increases

Key Supports

Marketing Expansion

Marketing Personnel

Marketing Budget

Contracting Expansion

Internal Support Needs

Clinical Data Expansion

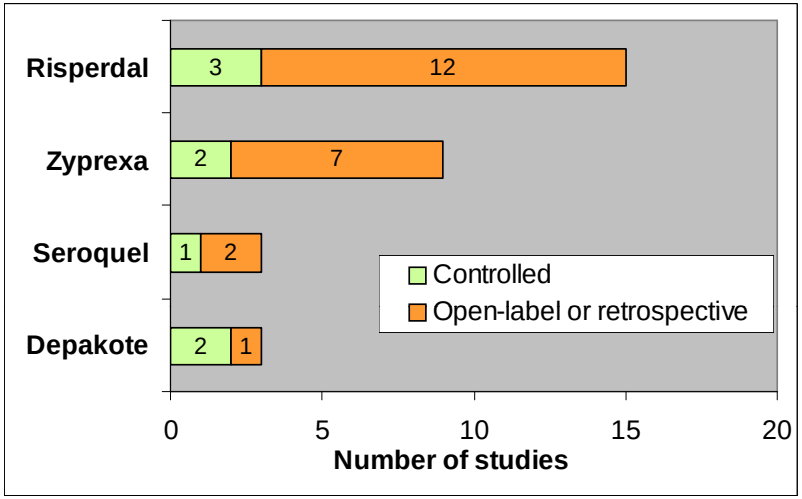
Geriatric IIS

Corrections IIS

MRDD IIS

In SNFs alone, atypicals have much more clinical data than Depakote – especially open label and retrospective studies.

Published dementia studies since 1996



- **This includes all studies** for which abstracts are available on Medline or selected databases, except studies of single cases
  - May include studies that were not sponsored by pharmaceutical companies
  - Each study is counted only once, even if multiple publications have resulted
- **Controlled studies:** blinded and randomized, vs. placebo or comparator
- **Open-label / Retrospective studies:** includes chart reviews

Details of controlled studies:

- **Risperdal studies**
  - n=625 & n=344 vs. placebo; n=58 vs. Haldol
  - Endpoints: psychiatric and behavioral symptoms; extrapyramidal side-effects
- **Zyprexa studies**
  - n=137 & n=206 vs. placebo
  - Endpoints: symptoms of agitation and psychosis
- **Seroquel study**
  - n=378 vs. placebo and Haldol
  - Endpoints: symptoms of agitation and psychosis; tolerability
- **Depakote studies**
  - n=172 vs. placebo, discontinued (M97-738); n=56 vs. placebo
  - Endpoints: symptoms of mania (M97-738); symptoms of agitation (both studies)

Sources: REDACTED REDACTED REDACTED REDACTED

KOLs advise that clinical data specific to each Sector is needed to best impact Depakote business in the DOC and MRDD Markets.

- **For the DOC Sector :**
  - **The DOC represents a unique group of patients with biological and environmental issues contributing to patient condition**
  - **Pharmacological treatment decisions for DOC patients can be different than for those in the general population:**
    - » **Severity of condition can be greater in the DOC environment**
    - » **Patient compliance can be more problematic**
    - » **Consequences of treatment failures more severe**
  - **Studies in the DOC patient population most relevant to practitioners**

- **For the MRDD Sector:**
  - **The MRDD patient population is unique and represents a group that can have severe handicaps**
  - **Identification and appropriate classification of patient conditions is problematic due to the patient's inability to articulate symptoms**
  - **Pharmacologic treatment decisions for MRDD patients can be different due to the nature of the patient's condition**

Source: Abbott Conducted Qualitative Research with Key Opinion Leaders, Summer 2003

Qualitative Opinion Leader Interviews: Assessment of Depakote Study Needs in Correctional and MRDD Settings

Interviews Completed as of 8/19/03:

- Corrections Experts:
  - DR REDACTED
  - DR. REDACTED
  - DR. REDACTED REDACTED REDACTED REDACTED
  - DR. REDACTED
- MRDD Experts:
  - DR REDACTED
  - DR. REDACTED
  - REDACTED, Rph (Chief of REDACTED MRDD program in Illinois, 5000+ beds)
  - REDACTED, RN (Co-Chief of REDACTED MRDD program in Illinois, 5000+ beds)

Influence Clinical Data Would Have on Prescribing Choices:

- Respondents rated the influence of clinical data as a 9 on a ten-point scale (n=6)
  - "On a ten point scale where 10 means extremely influencial to my prescribing choices and 1 means not at all influencial to my prescribing choices , how would you rate clinical data in terms of its influence?"
- Respondents cited peer and Opinion Leader recommendations, articles in peer reviewed journals, and quality CME programs as preferred vehicles to access product information.

Source: Abbott Conducted Qualitative Research with Key Opinion Leaders, Summer 2003

Proposed IIS LTC Study Descriptions in Correctional Facilities

- **Conditions Assessed:**
  - Agitated/Aggressive/Impulsive behaviors with or without head injuries
  - (per REDACTED)Bipolar Disorder with at least one comorbidity (have a laundry list that could include:
    - » Agitated/Aggressive/Impulsive behaviors
    - » MRDD
    - » head injury
    - » substance abuse
    - » ADHD
    - » Others (DR. REDACTED noted that the design could resemble the abulatory study she is currently doing for Psychiatry Team)
- **Type of Study:**
  - Prospective (Note: Informed consent requirements and advocacy oversight may require that any prospective study use two active agents.)
- **Study Setting:**
  - Jails
  - Prisons
  - Probation catchment (DR REDACTED suggested that if getting IRB approved for prison population is a problem, it would be possible to screen probation patients or patients with a prison/jail record)
- **Primary Assessment:**
  - Efficacy
    - » Improvement in Bipolar
    - » Decreased frequency and severity of behaviors; patients “less triggered” by stressors
    - » Decreased frequency and severity of comorbid condition
  - Also measure side effects, safety, tolerability

Source: Abbott Conducted Qualitative Research with Key Opinion Leaders, Summer 2003

Proposed IIS LTC Study Descriptions in Correctional Facilities (continued)

- **Primary endpoints:**
  - YMRS
  - Overt Aggression Scale and others
  - Staff keeps log of frequency of behaviors; measure Vs. staff assessment
    - » Use of restraints
    - » Time in isolation or solitary confinement
    - » Number of medication passes required
  - Seizure measurement scales
  - Other scales relevant to comorbid conditions
  - Cost savings due to better compliance, fewer side effects, fewer relapses etc
- **Time period for study:**
  - Jails: 4 week study
  - Prisons: 4 week study (but could be longer due to inmate length of stay)
  - Probation: 8 week study
- **Patient Inclusion Criteria:**
  - See primary assessment
- **Treatment Arms:**
  - Depakote ER vs placebo or Loading dose Depakote ER vs. Non-Loading Dose DepakoteER (per DR. REDACTED)
  - Depakote ER Vs. valproic acid
  - Depakote ER Vs. an antipsychotic (Zyprexa: could show results and differences in side effect profiles)

Source: Abbott Conducted Qualitative Research with Key Opinion Leaders, Summer 2003

Proposed IIS LTC Clinical Study Descriptions in MRDD

- **Conditions assessed:**
  - Agitated/Aggressive/Impulsive behaviors with or without seizures
- **Type of Study:**
  - Prospective (per MD respondents)
  - Retrospective ok (per REDACTED pharmacist)
- **Primary Assessment:**
  - Efficacy
    - » decrease frequency and severity of behaviors; patients “less triggered” by stressors
    - » decrease frequency and severity of seizures
- **Primary endpoints:**
  - Overt Aggression Scale and others
  - Staff keeps log of frequency of behaviors; measure Vs. staff assessment
  - Seizure measurement scales
- **Time period for study:**
  - 3-6 months (it was noted that there is a seasonal response: patients have more behavioral problems in the Spring/Summer versus Fall/Winter. Therefore a study of 1 yr... or more would eliminate the seasonality)
- **Patient Inclusion Criteria:**
  - Patients are required to have failed behavioral therapy or behavioral therapy must have been ruled out as an option in order to begin pharmacotherapy.
  - It was also suggested that patients could be those who previously failed treatment on a low dose of an antipsychotic
- **Treatment Arms:**
  - Depakote ER Vs. behavioral therapy (double blind)
  - Depakote ER Vs. an antipsychotic (Zyprexa: could show results and differences in side effect profiles)
  - AP therapy Vs. AP plus Depakote ER
  - Depakote ER Vs. another AED

Source: Abbott Conducted Qualitative Research with Key Opinion Leaders, Summer 2003

KOLs also advise that the best development path for Depakote in elderly agitation would be adjunctive studies with atypicals.

- **Two major clinical studies of Depakote monotherapy were discontinued, for reasons unrelated to efficacy:**
  - **M97-738: Depakote in Elderly Mania** – Showed efficacy[1], but discontinued in 1999 because of excessive somnolence
    - » Somnolence was caused by dosing schedule that was too aggressive for an elderly population
  - **M99-082: Behavioral Agitation in Elderly patients with Dementia** – Discontinued in 2001 before any results were available, because recruitment targets could not be met at reasonable cost
    - » Recruitment was very slow because inclusion criteria were too restrictive: in particular, patients on antidepressants were excluded, thus reducing the eligible population by around 50%

- **Key opinion leaders therefore advise an adjunctive study as the best development path for Depakote in BDD:**
  - **Investigators unlikely to be willing to conduct further Depakote monotherapy trials**, because of prior experiences
  - **The adjunctive market is large:** Geriatric psychiatry advisors estimate 50-70% of patients require polypharmacy for management of aggression
  - **Adjunctive Depakote works:** Existing data[2] shows that Depakote + atypical combination is effective in patients unresponsive to monotherapy or taking multiple atypicals
  - **Recruitment will be easier:** The majority of BDD patients are already treated with antipsychotics, so the eligible population will be large
  - **Drop-outs due to adverse events can be minimized:** Availability of ER 250 mg and a better understanding of tolerability issues in the elderly means the side-effects caused M97-738 to be discontinued can be avoided

Sources: (1) Tariot *et al.*, Curr. Therapeutic Res. 2001, 62: 51-67; (2) Narayan & Nelson, J. Clin. Psychiatry, 1997, 58: 351-4; M99-082 Study protocol; Draft FDA submission prepared by Abbott proposing label change to Depakote for indication in elderly agitation; Neuroscience clinical team, strategic review document

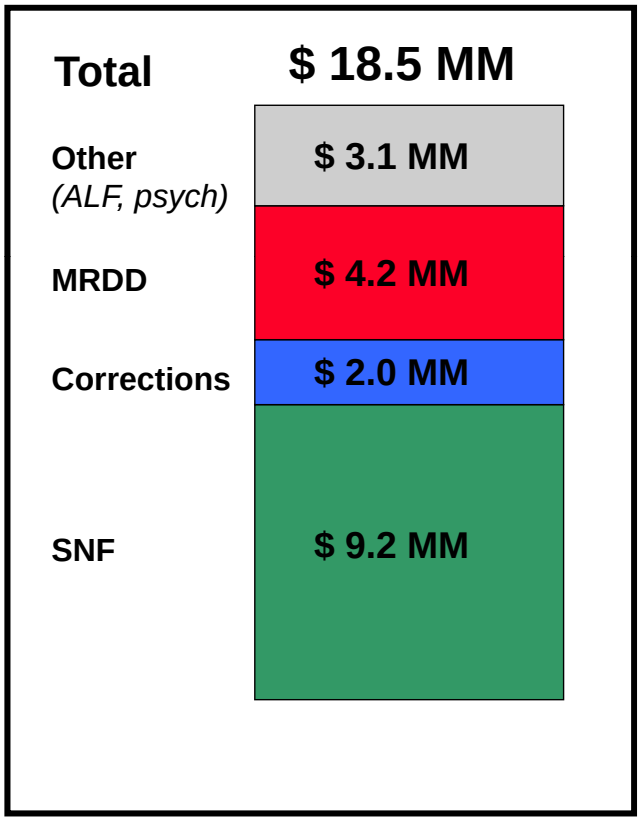
Proposed IIS LTC Clinical Study Descriptions in Elderly Agitation

- **Conditions assessed:**
  - Agitated/Aggressive/Impulsive behaviors with or without seizures
- **Type of Study:**
  - Prospective open label
- **Primary Assessment:**
  - Efficacy as measured by the PANSS Excited Component, which includes measurement of the following:
    - impulse control
    - tension
    - hostility
    - degree of cooperativeness
    - excitement
- **Primary endpoints:**
  - PANSS Excited Component
- **Time period for study:**
  - 12 months
- **Patient Inclusion Criteria:**
  - Probable or possible Alzheimer's
  - Probable or possible vascular dementia
- **Treatment Arms:**
  - Depakote ER and atypical, vs. atypical + atypical , vs. atypical alone; n=30-40 each group

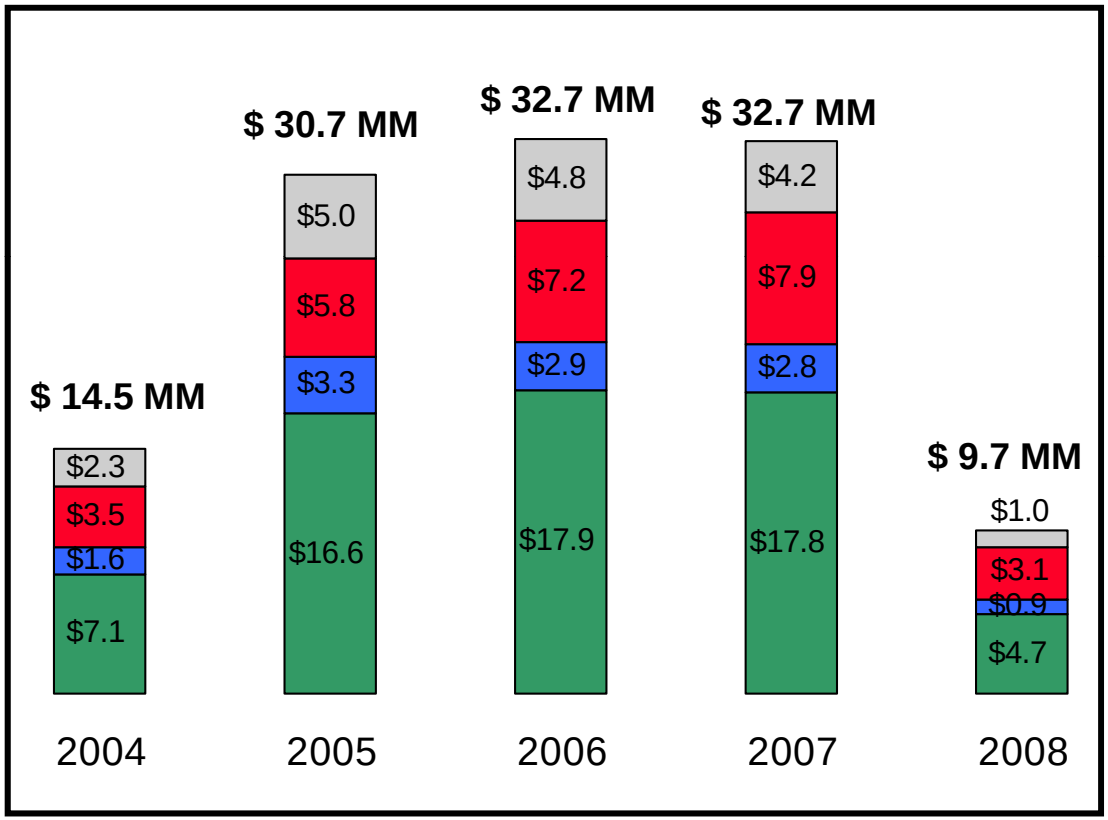
Source: Abbott Conducted Qualitative Research with MLs and Key Opinion Leaders, Fall 2002.

Where does the growth come from?

Change in Revenues
Over 2003 Plan



Change in Revenues
Over 2004 Plan, 2005-2008 LRP*



*Note: The 2005-2008 LRP will be updated in December 2003.

Summary

On June 12, 2002, representatives from the Depakote team met with REDACTED in Boca Raton, FL. Abbott attendees included:

REDACTED Development
REDACTED Development
REDACTED, Regulatory Affairs
REDACTED, Development
REDACTED Development
REDACTED Statistics
REDACTED, Depakote Marketing

Questions, regarding Depakote ER in acute mania and schizophrenia, were forwarded to Dr. REDACTED in advance (see Attachment). The discussion focused on the regulatory issues facing Depakote ER for a claim in acute mania and a claim in schizophrenia. For acute mania, Dr. REDACTED concluded that, given the approval for Depakote DR in mania and a prior negative study in acute mania with Depakote ER, at least one positive acute mania trial with Depakote ER must be submitted to the FDA (in the absence of additional negative trials). The discussion regarding a claim in schizophrenia did not lead to any meaningful conclusions. Notable points regarding schizophrenia included a recommendation to re-open discussions with the FDA regarding the path forward and a recommendation to consider utilizing study 010 within a framework of "acute add-on" or "acute adjunctive" treatment of schizophrenia.

REDACTED Comments

Mania

- FDA will agree that Depakote DR is efficacious for acute mania, because they have already approved it for this indication. The question to be answered is whether the new formulation (ER) maintains the efficacy demonstrated by DR.

- Given the prior negative result for Depakote ER, a subsequent negative trial would raise concerns that the ER formulation is not associated with efficacy; at least one more positive trial (in the absence of another negative trial) should be submitted in order to gain approval. In addition, a proportional dosing strategy is unlikely to succeed given the existing negative trial. A subsequent discussion, related to the question of whether one or two additional trials should be conducted, included the possibility that an active control arm could be included in order to provide more persuasive evidence that a trial failed (not that Depakote ER failed). This discussion was more applicable to the scenario in which two trials are conducted and one is positive and one is negative.

- We will not fully understand why the prior Depakote ER in acute mania trial failed; there is no specific or conclusive evidence as to why Depakote failed to separate from placebo. In addition, the reason for efficacy failure in acute mania (as with unipolar

depression) is usually unknown. REDACTED did cite an example of a unipolar depression submission, which was salvaged from apparently failed studies, due to the efforts of a FDA statistician. In addition, some arguments (especially with regard to dose and VPA level in the failed ER study) may undercut arguments for a mania approval if proportionality data is used to support a mania claim.

- Pivotal studies, especially when a single trial is submitted instead of two, must be robust, meaning that a few centers are not carrying the effect and the same effect size is observed no matter how the study population is stratified.

- Internally, FDA reviewers have been trained never to say that a p-value above a threshold doesn't indicate lack of efficacy; instead, the risk/benefit ratio has been shifted.

- "P-values are purchase-able."

- The pediatric mania study may be supportive of the Depakote ER adult mania NDA, but one must consider the likelihood of success of the pediatric mania study.

- REDACTED is relatively more willing to negotiate than REDACTED (due to roles within FDA).

Schizophrenia

- Study 010 is a positive trial (the effect size is robust). Challenges to this interpretation at the FDA probably arise because the discussion is in the context of a new type of claim.

- What to do with the FDA's decision? The FDA may be warning about a future decision—e.g. what are the long-term safety implications? Abbott could re-submit in future with a fully positive trial, but discussion may focus on safety-efficacy balance.

- Much of REDACTED' arguments regarding the difference of this model with epilepsy (ie the adjunctive framework) are somewhat unclear.

- What is it that would justify the use of adjunctive treatment vs. increasing the dose of an anti-psychotic (AP)?

- Due to uncertainty regarding this claim and the FDA's comments, another meeting with the FDA (with REDACTED, REDACTED and REDACTED is warranted. Including REDACTED is even an option. The proposal for a new meeting might include: "we're having difficulty understanding the FDA's recommendation."

- A lengthy discussion on schizophrenia and the potential motivations of FDA personnel started on a more optimistic note and ended more pessimistically. Specifics of the conversation aside, REDACTED stated that he began the conversation with

the belief that Depakote's use in schizophrenia was already well-recognized and study 010 served to reflect existing practice beliefs (similar to the bipolar pivotals for Depakote DR). He ended the conversation with the perspective that study 010 served to create, for the first time, a new use for Depakote (generating excitement in the community, but not necessarily reflecting an existing entrenched practice). The former perspective led REDACTED to cite a 25% likelihood of negotiating a strategy in which a single additional study (for some type of "acute add-on" claim) might be successful, while the latter perspective led REDACTED to cite a 10% likelihood of success.

- Comments under the earlier perspective (that Depakote in schizophrenia, as demonstrated by study 010, is already established practice) included:
  - Build buy-in from opinion leaders in support of new discussions with FDA (REDACTED).
  - The arguments provided by REDACTED are not consistent with his logic historically.
  - The division, however, "jealously guards the protocol-specified primary."
  - Definitions of onset have been historically problematic (REDACTED has never liked the definitions of onset as recommended by REDACTED, REDACTED et al).
  - While we have agreed with the FDA that study 010 does not support combination use (as defined strictly the combination being superior to each agent alone), we could still argue for study 010's applicability to add-on (including the idea that, although patients may have undergone a pharmacokinetic washout, there was not an effective pharamacodynamic washout and Study 010, therefore, was an add-on study).
  - One option is to repeat study 010, conduct it anyway we wish (including AUC endpoints, no washout) and submit an NDA for "acute add-on." If the NDA is not accepted, go up the FDA ladder. This proposal should be adequate for efficacy, but safety (especially safety-efficacy balance) will be the contentious issue.
  - An inside-FDA political issue may relate to the dynamics between REDACTED and REDACTED. In this case, REDACTED may be deferring to REDACTED, who may not be flexible.

- REDACTED had raised several questions regarding how Depakote should be used in schizophrenia (when would one choose to increase the dose of an atypical vs. adding Depakote, which patient types, which atypicals, what is the definition of being maximized on an atypical, etc), none of which could be adequately answered at this time.

- Durability of treatment could be addressed with discontinuation designs (randomized withdrawal of responders).

- An "adjunctive" claim begs the question of what kinds of patients should be treated with Depakote and where in the course of their treatment should they receive Depakote?

- Strictly speaking, "combination" refers to fixed combination studies (21CFR300.5), and is a concept being stretched to fit the current proposal. In this situation, one's

goal is only to show that Depakote alone is not active. With respect to the inclusion of a placebo arm, placebo should be non-controversial in a study of non-responders (if a combination or add-on study were to include such patients).

Minutes written by REDACTED June 25, 2002.

Attachment

Questions: Bipolar Program

1. What is the smallest package of data to obtain an approval of Depakote ER in mania? What is the likelihood of success?
2. Given that the M97-696 study of Depakote ER in the treatment of mania was a negative trial, would one additional adequate and well-controlled study be sufficient for obtaining an indication label for ER in the treatment of mania? Estimate the probability of success, in obtaining a label for ER in the treatment of mania, with one more study. Given rates of failed trials in psychiatry would you recommend doing 1 or 2 trials in mania?
3. Given the results of M97-696, does the newly proposed study, M01-346, address the potential shortcomings of the original trial design and adequately control for potential placebo response? Are there any other design features that could be added to the current proposed trial to enhance recruitment and minimize a placebo response?
4. Could the indication for Depakote ER in bipolar be obtained with a PK argument?
5. Will a positive pediatric study with Depakote ER (as proposed in the PPSR) provide support of a label in mania?

Questions: Schizophrenia Program

1. What is the smallest package of data needed to obtain an indication of adjunctive Depakote ER in the treatment of schizophrenia?
2. Under what circumstances would one trial be adequate for approval?
3. Which treatment paradigm would be a more successful strategy in pursuing an indication:
   - a combination approach (simultaneous initiation of Depakote with an antipsychotic agent in patients in an acute exacerbation of schizophrenia)
   - add-on approach (Depakote added on to an existing antipsychotic agent in partially responding patients), or
   - one combination trial and one add-on trial?
4. If two trials are required for a combination indication, must a Depakote/placebo group be required for both trials?
5. Given what the FDA has already stated in the minutes of the March 4, 2002 meeting, do you think that the agency would require a study with a placebo/placebo group?
6. Do you think that approval in this indication would be accompanied by a phase IV commitment (e.g., pediatric, safety, maintenance)?
7. Do you think the agency will require PK data? If so, what might they require?

August 9, 2001

EnERgize the Excellence

010 Communication Plan

Consultant, PI Advisory Mtngs

PI/MPD Meeting
10/1, Chicago

"CATs" (250)
9/24, 10 Teleconferences

Rep Access

Poster to Advisors
7/27, via MLs

Posters to Advisors
8/15, via MLs

Slides to Advisors
10/1, via MLs

Press Release
7/27, via D. Casey

Medical Information Letter
8/1, World Cong Poster

June | July | August | September | October | November | December

CENE Monograph
9/1, Impulsivity/Aggression

CENE Symposia (100+)
6/23 Chicago

CENE Dinner Meetings (25+)
20 Cities

CENE Symposia (100+)
9/9 Atlanta
9/15 Dallas
9/23 San Francisco

CENE Symposia (100+)
10/5 New York
10/19 LA

Bipolar Newletter
10/30 (PsychTimes)

JCP Visuals Communicator
9/10, AEDs in Psychosis

Clinical, Peer Mtngs

World Congress
ACNP-Poster
Poster

IPS-Poster
10/13, Orlando

Psych Congress
Symposia & Poster

REDACTED

From: REDACTED
REDACTED com>
To: REDACTED @abbott.com>;
REDACTED @abbott.com>; REDACTED @abbott.com>
Cc: REDACTED @abbott.com>;
< REDACTED @abbott.com>; < REDACTED @abbott.com>;
REDACTED REDACTED .com
Bcc:
Subject: Depakote Psychosis Speaker/Faculty Development Meeting
Date: Thu Feb 21 2002 16:51:47 EST
Attachments: D211 Tentative Agenda.doc
d211 invite.dot

REDACTED, REDACTED, and REDACTED

On behalf of the Abbott Neuroscience Franchise, I would like to invite you to attend a Depakote Psychosis Speaker/Faculty Development Meeting. This meeting will include the review of a recently completed, double blind, randomized placebo controlled trial assessing divalproex efficacy as adjunctive treatment for schizophrenia.

The meeting will be held on Saturday, March 23, 2002 at the Ritz Carlton in Marina del Rey, California.

There will be a Welcome Reception on Friday evening and the meeting will be held on Saturday from 8:00 am to 12:00 pm. There will also be an optional lunch from 12:00 pm to 1:00 pm.

Attached, for your information, is a copy of the invitation and tentative agenda sent to physicians asking them to attend this program.

Upon confirmation of your attendance, further information will be forthcoming. If you have any questions or concerns, please feel free to contact me at REDACTED

Sincerely,

REDAC
REDACTED
Manager, Program Planning
REDACTED

- d211 invite.dot - D211 Tentative Agenda.doc

ABBOTT LABORATORIES

Depakote Psychosis Speaker/Faculty Development

Tentative Meeting Agenda

Friday, March 22

5:00 pm	Arrivals
6:00 – 8:00 pm	Welcome Reception and Dinner

Saturday, March 23

7:30 – 8:00 am	Breakfast
8:00 - 8:15 am	Introduction and Meeting Objectives…… REDACTED /*Abbott Park*
8:15 - 8:30 am	Abbott Laboratories and Neuroscience Update…… REDACTED /*Abbott Park*
8:30 - 10:00 am	**Depakote Adjunctive Treatment in Schizophrenia** …… REDACTED *MD* - M99-010 Slide Review
10:00 - 10:15 am	Break
10:15 - 11:30 am	**Depakote Adjunctive Treatment in Schizophrenia (cont'd)**… REDACTED *MD* - M99-010 Slide Review
11:30 – 12:00 pm	**Closing Remarks** ……..…… REDACTED /*Abbott Park*
12:00 – 1:00 pm	Optional Lunch/Adjourn

Tuesday, February 12, 2002

«Contact»
«Company»
«Address_1»
«Address_2»
«Address_3»
«City», «State» «Zip»

Fax: «Fax»
1 page including this sheet

Subject: Depakote Psychosis Speaker/Faculty Development Meeting

Dear «Salutation»:

On behalf of the Abbott Neuroscience Franchise, we would like to invite you to participate in a Depakote Psychosis Speaker/Faculty Development Meeting. This meeting will include the review of a recently completed, double blind, randomized placebo controlled trial assessing divalproex efficacy as adjunctive treatment for schizophrenia. After participation in the meeting, you may be asked to present this data at various medical education programs in 2002.

The meeting will be held on **Saturday, March 23, 2002** at the Ritz Carlton in Marina Del Rey, California.

There will be a Welcome Reception on Friday evening and the meeting will be held on Saturday from 8:00 am to 12:00 pm. There will be a lunch from 12:00 to 1:00 pm (attendance at the lunch is optional).

You will be provided one roundtrip coach class airfare, one-night hotel accommodations on Friday, planned meals and an honorarium in the amount of $2,500.

Please take a moment to indicate your interest and/or availability to attend, and return to REDACTED ***, via facsimile, to*** REDACTED ***by Monday, February 18, 2002.***

☐ Yes, I am available ☐ No, I am not available

☐ I am not interested in participating in a Faculty Development Meeting

REDACTED will be handling the logistics for this meeting. If you have any questions or concerns, please call at REDACTED ext. REDACTED Thank you for taking the time to respond to this fax and we look forward to hearing from you.

Sincerely,

REDACTED

REDACTED
Product Manager, Psychiatry

From: REDACTED lake/ppd/abbott;nsf; REDACTED @abbott.com;smtp

To: REDACTED lake/ppd/abbott@abbott; REDACTED /lake/ppd/abbott@abbott

Cc: REDACTED /lake/ppd/abbott@abbott; REDACTED /lake/pprd/abbott@abbott; REDACTED /lake/ppd/abbott@abbott; REDACTED /lake/ppd/abbott@abbott; REDACTED /lake/ppd/abbott@abbott; REDACTED lake/ppd/abbott@abbott; REDACTED lake/ppd/abbott@abbott; REDACTED /lake/ppd/abbott@abbott; REDACTED lake/ppd/abbott@abbott; REDACTED /lake/ppd/abbott@abbott; REDACTED lake/ppd/abbott@abbott; REDACTED /lake/ppd/abbott@abbott; REDACTED lake/ppd/abbott@abbott; REDACTED /lake/ppd/abbott@abbott; REDACTED lake/ppd/abbott@abbott; REDACTED /lake/ppd/abbott@abbott; REDACTED lake/ppd/abbott@abbott; REDACTED /lake/ppd/abbott@abbott; REDACTED lake/ppd/abbott@abbott

Bcc:

Subject: REP AWARENESS: Depakote Schizophrenia Trial
Date: Mon Aug 14 2006 18:17:43 EDT

REDACTED and REDACTED, please forward this on to NSR and SAE sales management.

Representative Awareness Literature

The attached literature is being provided to you to keep you aware of professional and consumer literature recently appearing in the public domain. This communication is intended to keep you up to date with literature in the public domain having relevance to our business.

The information in this communication has not been reviewed to confirm the accuracy of its content. Neither does it mean that Abbott agrees with statements, positions, opinions, or conclusions in the publication. This literature may not be discussed with, distributed to, or shown to our customers, or used for the promotion of our products.

Talk to your manager if you have questions about the use of this information.

Results from Abbott study M02-547 (Title: A Randomized, Double-Blind Study of the Safety and Efficacy of Depakote® ER plus an Atypical Antipsychotic vs. an Atypical Antipsychotic Alone in the

Treatment of Schizophrenia) were posted on the clinicalstudyresults.org website on August 11, 2006.

The study was a Phase II, placebo-controlled, double-blind, randomized, parallel-group, multicenter study designed to assess the safety and efficacy of Depakote ER in combination with either olanzapine or risperidone vs. antipsychotic monotherapy with olanzapine or risperidone for the treatment of schizophrenia. In this study the combination of Depakote ER with olanzapine or risperidone did not result in statistically significant clinical efficacy benefits beyond those observed with antipsychotic monotherapy. Depakote ER in combination with atypical antipsychotic therapy was as well tolerated as therapy with risperidone or olanzapine alone.

Depakote ER and Depakote are not FDA approved as treatments for schizophrenia in any age group. Results from the current trial were not intended to support a regulatory submission for an indication for Depakote ER in schizophrenia.

Depakote ER is FDA approved as a treatment for acute manic and mixed episodes associated with bipolar disorder, with or without psychotic features, in adults aged 18 years and older.

Abbott is committed to disclosing all results in company-sponsored clinical trials and to advancing scientific understanding of its products. As such, results from this trial will also be submitted in manuscript form for publication consideration by an appropriate peer-reviewed journal.

Any inquiries or questions from healthcare providers regarding this trial should be directed to Medical Information.

- REDACTED

REDACTED
Marketing Director
Abbott Neuroscience
Neuroscience Marketing
Abbott
REDACTED
200 Abbott Park Road
Abbott Park, IL 60064
Office REDACTED
Fax REDACTED
REDACTED@abbott.com

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IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
ABINGDON DIVISION

UNITED STATES	:	
	:	
v.	:	**Criminal No.** 1:12CR26
	:	
ABBOTT LABORATORIES	:	

AGREED ORDER OF FORFEITURE

IT IS HEREBY ORDERED THAT:

1. As the result of the guilty plea to the Information, the defendant shall forfeit to the United States quantities of Depakote, Depakote ER and Depakote Sprinkle that were misbranded when introduced into interstate commerce, pursuant to 21 U.S.C. § 334 and 28 U.S.C. § 2461

2. Pursuant to the defendant's plea agreement, the defendant shall forfeit $198,500,000.00 (one hundred ninety-eight million five hundred thousand dollars), in the form of certified funds made payable to the U.S. Treasury Department, or as otherwise directed by the United States, as a substitute asset pursuant to 21 U.S.C. § 853(p).

3. The Court shall retain jurisdiction to enforce this Order, and to amend it as necessary, pursuant to Fed. R. Crim. P. 32.2(e). Payment shall be made within three days of entry of the defendant's guilty plea. As payment is voluntarily being remitted to the United States, notice and publication are not required.

4. Pursuant to Fed. R. Crim. P. 32.2(b)(4), this Order of Forfeiture shall become final as to the defendant upon entry, and shall be made a part of the sentence and included in the judgment.

5. The Clerk of this Court shall certify copies of this Order to counsel of record and shall certify copies to the United States Attorney's Office, Asset Forfeiture Section, P.O. Box 1709, Roanoke, Virginia 24008.

6. ENTERED this 7th day of May, 2012.

Hon. Samuel G. Wilson
United States District Judge

SETTLEMENT AGREEMENT

I. PARTIES

This Settlement Agreement ("Agreement") is entered into among the United States of America, acting through the United States Department of Justice, and on behalf of the Office of Inspector General of the Department of Health and Human Services ("OIG-HHS"), the TRICARE Management Activity ("TMA"), the United States Office of Personnel Management ("OPM"), the United States Department of Veterans Affairs ("VA"), and the Office of Workers Compensation Programs of the United States Department of Labor ("DOL-OWCP") (collectively the "United States"); Meredith McCoyd, Susan Mulcahy, Doreen Merriam, Sondra Knowles, Tamara Dietzler, Thomas J. Spetter, Jr. (collectively, "Relators"); and Abbott Laboratories ("Abbott"), through its authorized representatives. Collectively, all of the above will be referred to as "the Parties."

II. RECITALS

A. Abbott is an Illinois corporation headquartered in Abbott Park, Illinois. At all relevant times, Abbott distributed, marketed, and sold pharmaceutical products in the United States, including a drug sold under the trade names Depakote DR, Depakote ER, and Depakote Sprinkle (collectively, "Depakote").

B. Relators have filed the following qui tam actions against Abbott (collectively, the "Civil Actions"):

i. *United States, et al., ex rel. Meredith McCoyd v. Abbott Labs., et al.,* Civil Action No. 1:07-cv-00081 (W.D. Va.);

ii. *United States ex rel. Susan Mulcahy, Doreen Merriam, and Sondra Knowles v. Abbott Labs., et al.*, Civil Action No. 1:08-cv-00054 (W.D. Va.);

iii. *United States of America, et al., ex rel. Tamara Dietzler v. Abbott Labs.*, Civil Action No. 1:09-cv-00051 (W.D. Va.);

iv. *United States, et al., ex rel. Thomas J. Spetter, Jr. v. Abbott Labs., Inc., et al.*, Civil Action No. 1:10-cv-00006 (W.D. Va.).

C. The United States of America intervened in the Civil Actions on February 1, 2011.

D. On such date as may be determined by the Court, Abbott will plead guilty pursuant to Fed. R. Crim. P. 11 to an Information to be filed by the United States in *United States v Abbott Labs.*, Criminal Action No. [to be assigned] (W.D. Va.) (the "Criminal Action") that will allege a violation of 21 U.S.C. §§ 331(a) and 333(a)(1), 352(a) and 352(f)(1), namely, the introduction into interstate commerce of a misbranded drug, Depakote, in violation of the Food, Drug and Cosmetic Act.

E. Abbott has entered or will be entering into separate settlement agreements, described in Paragraph III.1(b) below (the "Medicaid State Settlement Agreements") with certain states and the District of Columbia in settlement of the Covered Conduct, defined below. States with which Abbott executes a Medicaid State Settlement Agreement in the form to which Abbott and the National Association of Medicaid Fraud Control Units ("NAMFCU") have agreed, or in a form otherwise agreed to by Abbott and an individual State, shall be defined as "Medicaid Participating States."

F. The United States alleges that Abbott caused claims for payment for Depakote to be submitted to the Medicaid Program, Title XIX of the Social Security Act, 42 U.S.C. §§ 1396-1396v ("Medicaid") and the Medicare Program, Title XVIII of the Social Security Act, 42 U.S.C. §§ 1395-1395kkk-1 ("Medicare"). The United States further alleges that Abbott caused claims for payment for Depakote to be submitted to the TRICARE program, 10 U.S.C. §§ 1071-1109 ("TRICARE"); the Federal Employees Health Benefits Program, 5 U.S.C. §§ 8901-8914 ("FEHBP"); and the following DOL-OWCP programs: the Federal Employees' Compensation Act, 5 U.S.C. § 8101 et seq. ("FECA"), the Energy Employees Occupational

Illness Compensation Program Act, 42 U.S.C. § 7384 et seq. ("EEOICPA"), and the Black Lung Benefits Act, 30 U.S.C. § 901 et seq. ("BLBA"); and that Abbott caused purchases of Depakote by the VA, 38 U.S.C. §§ 1701-1743 (collectively, the "Other Federal Healthcare Programs").

G. The United States contends that it and the Medicaid Participating States have certain civil claims against Abbott, as specified in Paragraph III.2 below, for engaging in the following conduct concerning the marketing, promotion and sale of Depakote between January 1998 and December 31, 2008 (hereinafter referred to as the "Covered Conduct"):

Abbott illegally marketed Depakote by:

(a) knowingly promoting the sale and use of Depakote for uses that were not approved by the Food and Drug Administration as safe and effective ("unapproved uses"), including behavioral disturbances in dementia patients, psychiatric conditions in children and adolescents, schizophrenia, depression, anxiety, conduct disorders, obsessive-compulsive disorder, post-traumatic stress disorder, alcohol and drug withdrawal, attention deficit disorder, autism, and other psychiatric conditions. Some of these unapproved uses were not medically accepted indications for which the United States and state Medicaid programs provided coverage for Depakote. This promotion included, in part:

(i) making false and misleading statements about the safety, efficacy, dosing, and cost-effectiveness of Depakote for some of these unapproved uses;

(ii) marketing Depakote to health care professionals to control behavioral disturbances in dementia patients in nursing homes by claiming that Depakote was not subject to certain requirements of the Omnibus Budget Reconciliation Act of 1987 (OBRA) designed to prevent the use of unnecessary drugs in nursing homes and that this use of Depakote would help nursing homes avoid the administrative burdens and costs of complying with OBRA regulatory restrictions applicable to antipsychotics.

(b) offering and paying illegal remuneration to health care professionals and long term care pharmacy providers to induce them to promote and/or prescribe Depakote and to improperly and unduly influence the content of company sponsored Continuing Medical Education programs, in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b).

As a result of the foregoing conduct, the United States alleges that Abbott knowingly caused false and/or fraudulent claims for Depakote to be submitted to, or caused purchases by, Medicare, Medicaid and the Other Federal Healthcare Programs.

H. The United States also contends that it has certain administrative claims against Abbott as specified in Paragraphs III.4 through III.7, below, for engaging in the Covered Conduct.

I. This Agreement is made in compromise of disputed claims. This Agreement is not an admission of facts or liability by Abbott, nor a concession by the United States that its claims are not well-founded. Abbott expressly denies the allegations of the United States and Relators as set forth herein and in the Civil Actions and denies that it engaged in any wrongful conduct in connection with the Covered Conduct, with the exception of such admissions that are made in connection with any guilty plea by Abbott in connection with the Criminal Action and the following:

(1) A substantial percentage of nursing home residents with dementia were beneficiaries of federal healthcare programs, including Medicare and Medicaid. Promotion of Depakote to healthcare providers in nursing homes for the control of the agitation and aggression of dementia patients caused the submission of certain claims to federal healthcare programs for that use. These programs paid hundreds of millions of dollars for claims resulting from the use of Depakote for the control of the agitation and aggression of dementia patients.

(2) A substantial percentage of individuals suffering from schizophrenia were beneficiaries of federal healthcare programs, including Medicare and Medicaid. Promotion of Depakote to healthcare providers for the treatment of schizophrenia caused the submission of certain claims to federal healthcare programs for

that use. These programs paid millions of dollars for claims resulting from the use of Depakote to treat schizophrenia.

Neither this Agreement or its execution, nor the performance of any obligation arising under it, including any payment, nor the fact of settlement, is intended to be, or shall be understood as, an admission of liability or wrongdoing, or other expression reflecting on the merits of the dispute by any party to this Agreement.

J. Relators claim entitlement under 31 U.S.C. § 3730(d) to a share of the proceeds of this Agreement and to Relators' reasonable expenses, attorneys' fees, and costs.

K. To avoid the delay, expense, inconvenience, and uncertainty of protracted litigation of the above claims, and in consideration of the mutual promises and obligations of this Agreement, the parties agree and covenant as follows:

III. TERMS AND CONDITIONS

1. Abbott shall pay to the United States and the Medicaid Participating States, collectively, the sum of Eight Hundred Million Dollars ($800,000,000.00), plus accrued interest in an amount of 2.5% per annum from September 16, 2011 and continuing until and including the day of payment (the "Settlement Amount"). The Settlement Amount shall constitute a debt immediately due and owing to the United States and the Medicaid Participating States on the Effective Date of this Agreement. This debt shall be discharged by payments to the United States and the Medicaid Participating States, under the following terms and conditions:

(a) Abbott shall pay to the United States the sum of $560,851,357, plus accrued interest as set forth above ("Federal Settlement Amount"). The Federal Settlement Amount shall be paid by electronic funds transfer pursuant to written instructions from the United States no later than seven (7) business days after (i) this Agreement is fully executed by the Parties and delivered to Abbott's attorneys; or (ii) the Court accepts a Fed. R. Crim. P. 11(c)(1)(C) guilty plea as described in Preamble Paragraph II.D in connection with the Criminal Action and imposes the agreed upon sentence, whichever occurs later.

(b) Abbott shall deposit the sum of $239,148,643, plus accrued interest as set forth above ("Medicaid State Settlement Amount") into one or more interest-bearing money market or bank accounts that are held in the name of Abbott, but segregated from other Abbott accounts (the "State Settlement Accounts"), and make payment from the State Settlement Accounts to the Medicaid Participating States pursuant to written instructions from the NAMFCU Negotiating Team and under the terms and conditions of the Medicaid State Settlement Agreements that Abbott will enter into with the Medicaid Participating States.

(c) Contingent upon the United States receiving the Federal Settlement Amount from Abbott, the United States agrees to pay, as soon as feasible upon receipt, to Relator Meredith

McCoyd, the sum of $84,127,704, plus 15 percent of the actual accrued interest paid to the United States by Abbott, as set forth in Paragraph III.1(a), above ("Relators' Share") as Relators' share of the proceeds pursuant to 31 U.S.C. § 3730(d). No other relator payments shall be made by the United States with respect to the matters covered by this Agreement. All Relators represent that they will abide by the terms of any separate agreements that they may have reached with one or more of the other Relators concerning the allocation of the Relators' Share among themselves.

(d) If Abbott's agreed-upon guilty plea pursuant to Fed. R. Crim. P. 11(c)(1)(C) in the Criminal Action described in Preamble Paragraph II.D is not accepted by the Court or the Court does not impose the agreed-upon sentence for whatever reason, this Agreement shall be null and void at the option of either the United States or Abbott. If either the United States or Abbott exercises this option, which option shall be exercised by notifying all Parties, through counsel, in writing within five (5) business days of the Court's decision, the Parties will not object and this Agreement will be rescinded. If this Agreement is rescinded, Abbott will not plead, argue or otherwise raise any defenses under the theories of statute of limitations, laches, estoppel or similar theories, to any civil or administrative claims, actions or proceedings arising from the Covered Conduct that are brought by the United States within 90 calendar days of rescission, except to the extent such defenses were available on the day on which the qui tam complaints listed in Preamble Paragraph II.B, above, were filed.

2. Subject to the exceptions in Paragraph III.9 below (concerning excluded claims) and conditioned upon Abbott's full payment of the Settlement Amount, the United States (on behalf of itself, its officers, agents, servants, agencies, and departments) releases Abbott, together with its current and former parent corporations, direct and indirect subsidiaries, brother or sister corporations, divisions, current or former owners, and their current and former directors, officers,

and employees, and the predecessors, successors, and assigns of any of them (the "Released Parties") from any civil or administrative monetary claim the United States has or may have for the Covered Conduct under the False Claims Act, 31 U.S.C. §§ 3729-3733; the Civil Monetary Penalties Law, 42 U.S.C. § 1320a-7a; the Program Fraud Civil Remedies Act, 31 U.S.C. §§ 3801-3812; any statutory provision creating a cause of action for civil damages or civil penalties which the Civil Division of the Department of Justice has actual or present authority to assert and compromise pursuant to 28 C.F.R. Pt. 0, Subpart I, 0.45(d); or the common law theories of payment by mistake, unjust enrichment, fraud, disgorgement, and, if applicable, breach of contract.

3. Subject to the exceptions in Paragraph III.9 below (concerning excluded claims) and Paragraph III.20 below (concerning Relators' Share and reasonable fees, expenses, and costs), and conditioned upon Abbott's full payment of the Settlement Amount, Relators, for themselves and for their heirs, successors, attorneys, agents, and assigns, fully and finally release, waive and forever discharge Abbott together with its current and former parent corporations, direct and indirect subsidiaries, brother or sister corporations, divisions, transferees, and the predecessors, successors, and assigns of any of them and their current or former owners, directors, officers and employees, representatives, servants, agents, consultants and attorneys, individually and collectively, from any civil monetary claim the United States has or may have for the Covered Conduct under the False Claims Act, 31 U.S.C. §§ 3729-3733, and any claims, allegations, demands, actions or causes of action whatsoever, known or unknown, fixed or contingent, in law or in equity, in contract or in tort, under any federal or state statute or regulation, or under common law, that they, their heirs, successors, attorneys, agents and assigns otherwise would have standing to bring, including, without limitation, any claim that the Relators asserted or could have asserted in the Civil Actions.

4. In consideration of the obligations of Abbott in this Agreement and the Corporate Integrity Agreement ("CIA") entered into between OIG-HHS and Abbott, and conditioned upon Abbott's full payment of the Settlement Amount, OIG-HHS agrees to release and refrain from instituting, directing, or maintaining any administrative action seeking exclusion from the Medicare, Medicaid, and other Federal health care programs (as defined in 42 U.S.C. § 1320a-7b(f)) against Abbott under 42 U.S.C. § 1320a-7a (Civil Monetary Penalties Law) or 42 U.S.C. § 1320a-7(b)(7) (permissive exclusion for fraud, kickbacks or other prohibited activities) for the Covered Conduct, or against Abbott under 42 U.S.C. § 1320a-7(b)(1) based on Abbott's agreement to plead guilty to the charge in the Criminal Action referenced above in Preamble Paragraph II.D, except as reserved in Paragraph III.9 (concerning excluded claims), below, and as reserved in this Paragraph. The OIG-HHS expressly reserves all rights to comply with any statutory obligations to exclude Abbott from the Medicare, Medicaid, or other Federal health care programs under 42 U.S.C. § 1320a-7(a) (mandatory exclusion) based upon the Covered Conduct. Nothing in this Section precludes the OIG-HHS from taking action against entities or persons, or for conduct and practices, for which claims have been reserved in Paragraph III.9, below.

5. In consideration of the obligations of Abbott set forth in this Agreement, conditioned upon Abbott's full payment of the Settlement Amount, TMA agrees to release and refrain from instituting, directing, or maintaining any administrative action seeking exclusion from the TRICARE Program against Abbott, its predecessors, and its current and former divisions, parents, affiliates, subsidiaries, successors, and assigns, and their current and former directors, officers, and employees under 32 C.F.R. § 199.9 for the Covered Conduct, except as reserved in Paragraph III.9 (concerning excluded claims) below, and as reserved in this Paragraph. TMA expressly reserves its authority to exclude Abbott under 32 C.F.R. §

199.9(f)(1)(i)(A), (f)(1)(i)(B), and (f)(1)(iii), based upon the Covered Conduct. Nothing in this Paragraph precludes TMA or the TRICARE Program from taking action against entities or persons, or for conduct and practices, for which claims have been reserved in Paragraph III.9, below.

6. In consideration of the obligations of Abbott set forth in this Agreement, and conditioned upon Abbott's full payment of the Settlement Amount, OPM agrees to release and refrain from instituting, directing, or maintaining any administrative action against Abbott, its predecessors, and its current and former divisions, parents, affiliates, subsidiaries, successors, and assigns, and their current and former directors, officers, and employees under 5 U.S.C. § 8902a(b) or 5 C.F.R. Part 919 for the Covered Conduct, except as reserved in Paragraph III.9 (concerning excluded claims) below, and except if excluded by the OIG-HHS pursuant to 42 U.S.C. § 1320a-7(a). Nothing in this Paragraph precludes OPM from taking action against entities or persons, or for conduct and practices, for which claims have been reserved in Paragraph III.9, below.

7. In consideration of the obligations of Abbott in this Agreement, and conditioned upon Abbott's full payment of the Settlement Amount, DOL-OWCP agrees to release and refrain from instituting, directing, or maintaining any administrative action seeking exclusion and debarment from the FECA, EEOICPA and BLBA programs against Abbott, its predecessors, and its current and former divisions, parents, affiliates, subsidiaries, successors and assigns, and their current and former directors, officers, and employees under 20 C.F.R. §§ 10.815, 30.715 and 702.431 for the Covered Conduct, except as reserved in Paragraph III.9 (concerning excluded claims), below and except if excluded by the OIG-HHS pursuant to 42 U.S.C. § 1320a-7(a). Nothing in this Paragraph precludes the OWCP of the DOL from taking action against entities or

persons, or for conduct and practices, for which claims have been reserved in Paragraph III.9, below.

8. Abbott has publicly announced that it plans to separate into two publicly traded companies, one a diversified medical products company, which may retain the Abbott name, ("Diversified Company") and the other a research-based pharmaceutical company ("Pharmaceutical Company') which will not be a subsidiary or corporate affiliate of Abbott (this separation is hereinafter referred to as the "Transaction" and the "Effective Time" shall be the date and time that the Transaction becomes effective). In the event the Transaction occurs, and as of the Effective Time, the foregoing releases in Paragraphs III.2 through III.3 and III.5 through III.7 that run to the benefit of Abbott will continue to apply fully to Abbott, the Diversified Company, the Pharmaceutical Company, and their subsidiaries and the foregoing release in Paragraph III.4 will apply fully to Abbott, the Diversified Company, and the Pharmaceutical Company.

9. Notwithstanding the releases given in Paragraphs III.2 through III.8 of this Agreement, or any other term of this Agreement, the following claims of the United States are specifically reserved and are not released:

(a) Any liability arising under Title 26, United States Code (Internal Revenue Code);

(b) Any criminal liability;

(c) Except as explicitly stated in this Agreement, any administrative liability, including mandatory exclusion from Federal health care programs;

(d) Any liability to the United States (or its agencies) for any conduct other than the Covered Conduct;

(e) Any liability based upon such obligations as are created by this Agreement;

(f) Any liability for express or implied warranty claims or other claims for defective or deficient products and services, including quality of goods and services;

(g) Any liability for personal injury or property damage or for other consequential damages arising from the Covered Conduct;

(h) Any liability for failure to deliver goods or services due; and

(i) Any liability of individuals (including current or former directors, officers, employees, agents, or shareholders of Abbott) who receive written notification that they are the target of a criminal investigation (as defined in the United States Attorneys' Manual), are indicted or charged, or enter into a plea agreement.

10. Relators and their heirs, successors, attorneys, agents, and assigns shall not object to this Agreement but agree and confirm that this Agreement is fair, adequate, and reasonable under all the circumstances, pursuant to 31 U.S.C. § 3730(c)(2)(B). Conditioned upon the payment of the Relators' Share described in Paragraph 1(c), Relators and their heirs, successors, attorneys, agents, and assigns fully and finally release, waive, and forever discharge the United States, its agencies, officers, agents, employees, and servants, from any claims arising from the filing of the Civil Actions or under 31 U.S.C. § 3730, and from any claims to a share of the proceeds of this Agreement and/or the Civil Actions.

11. Abbott waives and shall not assert any defenses Abbott may have to any criminal prosecution or administrative action relating to the Covered Conduct that may be based in whole or in part on a contention that, under the Double Jeopardy Clause in the Fifth Amendment of the Constitution, or under the Excessive Fines Clause in the Eighth Amendment of the Constitution, this Agreement bars a remedy sought in such criminal prosecution or administrative action.

Nothing in this paragraph or any other provision of this Agreement constitutes an agreement by the United States concerning the characterization of the Settlement Amount for purposes of the Internal Revenue laws, Title 26 of the United States Code.

12. Abbott fully and finally releases the United States, its agencies, officers, agents, employees, and servants, from any claims (including attorney's fees, costs, and expenses of every kind and however denominated) that Abbott has asserted, could have asserted, or may assert in the future against the United States, and its agencies, officers, agents, employees, and servants, related to the Covered Conduct and the United States' investigation and prosecution thereof.

13. Conditioned on Relators' compliance with their obligations under this Agreement, Abbott together with its current and former parent corporations, direct and indirect subsidiaries, brother or sister corporations, divisions, transferees, and the predecessors, successors, and assigns of any of them and their current or former owners, directors, officers and employees, representatives, servants, agents, consultants and attorneys, individually and collectively, fully and finally release, waive and forever discharge Relators and their heirs, successors, attorneys, agents, and assigns, from any claims, allegations, demands, actions or causes of action whatsoever, known or unknown, fixed or contingent, in law or in equity, in contract or in tort, under any federal or state statute or regulation, or under common law, that they otherwise would have standing to bring, including, without limitation, any claim that Abbott asserted or could have asserted in the Civil Actions, except to the extent related to: (i) Relators' claims for a Relators' Share of the Medicaid State Settlement Amount under the Medicaid State Settlement Agreements; (ii) Relators' claims arising under the *qui tam* provisions of any State with which Abbott does not execute a Medicaid State Settlement Agreement pursuant to the terms of this

Agreement; or (iii) Relators' claims for reasonable attorneys' fees, expenses, and costs pursuant to 31 U.S.C. § 3730(d)(1).

14. The Settlement Amount shall not be decreased as a result of the denial of claims for payment now being withheld from payment by any Medicare carrier or intermediary or any other state or Federal payer, related to the Covered Conduct; and Abbott agrees not to resubmit to any Medicare carrier or intermediary or any other state or Federal payer any previously denied claims related to the Covered Conduct, and agrees not to appeal any such denials of claims.

15. Abbott agrees to the following:

(a) Unallowable Costs Defined. All costs (as defined in the Federal Acquisition Regulation, 48 C.F.R. § 31.205-47 and in Titles XVIII and XIX of the Social Security Act, 42 U.S.C. §§ 1395-1395kkk-1 and 1396-1396w-5, and the regulations and official program directives promulgated thereunder) incurred by or on behalf of Abbott, its present or former officers, directors, employees, shareholders, and agents in connection with the following are "Unallowable Costs" for government contracting purposes and under Medicare, Medicaid, TRICARE, and FEHBP:

(i) the matters covered by this Agreement and the plea agreement referenced in Preamble Paragraph II.D;

(ii) the United States' audit(s) and civil and criminal investigation(s) of the matters covered by this Agreement;

(iii) Abbott's investigation, defense, and corrective actions undertaken in response to the United States' audit(s) and civil and criminal investigation(s) in connection with the matters covered by this Agreement (including attorneys' fees);

(iv) the negotiation and performance of this Agreement, the Plea Agreement, and the Medicaid State Settlement Agreements;

(v) the payments Abbott makes to the United States or any State pursuant to this Agreement, the Plea Agreement, or the Medicaid State Settlement Agreements, and any payments that Abbott may make to Relators (including costs and attorneys' fees); and

(vi) the negotiation of, and obligations undertaken pursuant to the CIA to: (a) retain an independent review organization to perform annual reviews as described in Section III of the CIA; and (b) prepare and submit reports to OIG-HHS. However, nothing in this Paragraph III.15(a)(vi) that may apply to the obligations undertaken pursuant to the CIA affects the status of costs that are not allowable based on any other authority applicable to Abbott.

(b) Future Treatment of Unallowable Costs. Unallowable Costs shall be separately estimated and accounted for by Abbott, and Abbott shall not charge such Unallowable Costs directly or indirectly to any contracts with the United States or any State Medicaid program, or seek payment for such Unallowable Costs through any cost report, cost statement, information statement, or payment request submitted by Abbott or any of its subsidiaries or affiliates to the Medicare, Medicaid, TRICARE, or FEHBP Programs.

(c) Treatment of Unallowable Costs Previously Submitted for Payment. Abbott further agrees that within 90 days of the Effective Date of this Agreement, it shall identify to applicable Medicare and TRICARE fiscal intermediaries, carders, and/or contractors, and Medicaid and FEHBP fiscal agents, any Unallowable Costs (as defined in this Paragraph) included in payments previously sought from the United States, or any State Medicaid Program,

including, but not limited to, payments sought in any cost reports, cost statements, information reports, or payment requests already submitted by Abbott or any of its subsidiaries or affiliates, and shall request, and agree, that such cost reports, cost statements, information reports, or payment requests, even if already settled, be adjusted to account for the effect of the inclusion of the Unallowable Costs. Abbott agrees that the United States, at a minimum, shall be entitled to recoup from Abbott any overpayment, plus applicable interest and penalties, as a result of the inclusion of such Unallowable Costs on previously-submitted cost reports, information reports, cost statements, or requests for payment. Any payments due after the adjustments have been made shall be paid to the United States pursuant to the direction of the Department of Justice and/or the affected agencies. The United States reserves its rights to disagree with any calculations submitted by Abbott, or any of its subsidiaries or affiliates on the effect of inclusion of Unallowable Costs on Abbott's or any of its subsidiaries' or affiliates' cost reports, cost statements, or information reports.

(d) Nothing in this Agreement shall constitute a waiver of the rights of the United States to audit, examine, or re-examine Abbott's books and records to determine that no Unallowable Costs have been claimed in accordance with the provisions of this Paragraph.

16. Abbott agrees to cooperate fully and truthfully with the United States' investigation of individuals and entities not released in this Agreement. Upon reasonable notice, Abbott shall encourage, and agrees not to impair, the cooperation of its directors, officers, and employees, and shall use its best efforts to make available, and encourage, the cooperation of former directors, officers, and employees for interviews and testimony, consistent with the rights and privileges of such individuals.

17. This Agreement is intended to be for the benefit of the Parties only. The Parties do not release any claims against any other person or entity, except to the extent provided for in Paragraphs III.8 and III.18 (waiver for beneficiaries paragraph), below.

18. Abbott agrees that it waives and shall not seek payment for any of the healthcare billings covered by this Agreement from any health care beneficiaries or their parents, sponsors, legally responsible individuals, or third party payors based upon the claims defined as Covered Conduct.

19. Abbott warrants that it has reviewed its financial situation and that it currently is solvent within the meaning of 11 U.S.C. §§ 547(b)(3) and 548(a)(1)(B)(ii)(I), and shall remain solvent following payment of the Settlement Amount. Further, the Parties warrant that, in evaluating whether to execute this Agreement, they (a) have intended that the mutual promises, covenants, and obligations set forth herein constitute a contemporaneous exchange for new value given to Abbott, within the meaning of 11 U.S.C. § 547(c)(1); and (b) have concluded that these mutual promises, covenants, and obligations do, in fact, constitute such a contemporaneous exchange. Further, the Parties warrant that the mutual promises, covenants, and obligations set forth herein are intended to and do, in fact, represent a reasonably equivalent exchange of value that is not intended to hinder, delay, or defraud any entity that Abbott was or became indebted to on or after the date of this transfer, within the meaning of 11 U.S.C. § 548(a)(I).

20. Upon receipt of the payments described in Paragraph 1, above, the United States and Relators shall file a Joint Stipulation of Dismissal as to the Released Parties in each of the Civil Actions pursuant to Rule 41(a)(1). Each stipulation of dismissal shall be (a) with prejudice as to the United States' and Relators' claims as to the Covered Conduct pursuant to and consistent with the terms and conditions of this Agreement; (b) without prejudice as to the United States and with prejudice as to Relators as to all other claims; (c) provided, however, that

the following claims shall not be dismissed until they are settled, adjudicated, or otherwise resolved, and the Court is so informed: (i) Relators' claims for a Relators' Share of the Medicaid State Settlement Amount under the Medicaid State Settlement Agreements; (ii) Relators' claims arising under the *qui tam* provisions of any State or political subdivision with which Abbott does not execute a Medicaid State Settlement Agreement pursuant to the terms of this Agreement; or (iii) Relators' claims for reasonable attorneys' fees, expenses, and costs pursuant to 31 U.S.C. § 3730(d)(1).

21. Except as expressly provided to the contrary in this Agreement, each Party shall bear its own legal and other costs incurred in connection with this matter, including the preparation and performance of this Agreement.

22. Each party and signatory to this Agreement represents that it freely and voluntarily enters into this Agreement without any degree of duress or compulsion.

23. This Agreement is governed by the laws of the United States. The exclusive jurisdiction and venue for any dispute relating to this Agreement is the United States District Court for the Western District of Virginia, except that disputes arising under the CIA shall be resolved exclusively through the dispute resolution provisions set forth in the CIA. For purposes of construing this Agreement, this Agreement shall be deemed to have been drafted by all Parties to this Agreement and shall not, therefore, be construed against any Party for that reason in any subsequent dispute.

24. This Agreement constitutes the complete agreement between the Parties with respect to the issues covered by this Agreement. This Agreement may not be amended except by written consent of the Parties.

25. The undersigned counsel represent and warrant that they are authorized to execute this Agreement on behalf of the persons and entities indicated below.

26. This Agreement may be executed in counterparts, each of which constitutes an original and all of which constitute one and the same Agreement.

27. This Agreement is binding on Abbott's successors, transferees, heirs, and assigns.

28. This Agreement is binding on Relators' successors, transferees, heirs, and assigns.

29. All Parties consent to the United States' disclosure of this Agreement, and information about this Agreement, to the public.

30. This Agreement is effective on the date of signature of the last signatory to the Agreement (the "Effective Date"). Facsimiles of signatures shall constitute acceptable binding signatures for purposes of this Agreement.

THE UNITED STATES OF AMERICA

By: _____ Dated: 5/7/12
TIMOTHY J. HEAPHY
United States Attorney
United States Attorney's Office
Western District of Virginia

By: _____ Dated: 5/7/12
RICK A. MOUNTCASTLE
Chief, Civil Division
United States Attorney's Office
Western District of Virginia

By: _____ Dated: _____
BRIAN McCABE
Trial Attorney
Commercial Litigation Branch
Civil Division
United States Department of Justice

By: _____ Dated: _____
EDWARD C. CROOKE
Trial Attorney
Commercial Litigation Branch
Civil Division
United States Department of Justice

THE UNITED STATES OF AMERICA

By: _____ Dated: _____

TIMOTHY J. HEAPHY
United States Attorney
United States Attorney's Office
Western District of Virginia

By: _____ Dated: _____

RICK A. MOUNTCASTLE
Chief, Civil Division
United States Attorney's Office
Western District of Virginia

By: Brian J. McCabe Dated: 5/7/12

BRIAN McCABE
Trial Attorney
Commercial Litigation Branch
Civil Division
United States Department of Justice

By: Edward Crooke Dated: 5/7/12

EDWARD C. CROOKE
Trial Attorney
Commercial Litigation Branch
Civil Division
United States Department of Justice

By: _____ Dated: 5/6/12

GREGORY E. DEMSKE
Chief Counsel to the Inspector General
Office of Counsel to the Inspector General
United States Department of Health and Human Service

By: _____ Dated: _____

PAUL J. HUTTER
General Counsel
TRICARE Management Activity
United States Department of Defense

By: _____ Dated: _____

SHIRLEY R. PATTERSON
Assistant Director for Federal Employee Insurance Operations
United States Office of Personnel Management

By: _____ Dated: _____

DAVID COPE
Debarring Official
Office of the Assistant Inspector General for Legal Affairs
United States Office of Personnel Management

By: _____ Dated: _____

CECILY A. RAYBURN
Director, Division of Planning, Policy and Standards
Office of Workers' Compensation Programs
United States Department of Labor

By: _____ Dated: _____
GREGORY E. DEMSKE
Assistant Inspector General for Legal Affairs
Office of Counsel to the Inspector General
United States Department of Health and Human Service

By: _____ Dated: 4/30/12
PAUL J. HUTTER
General Counsel
TRICARE Management Activity
United States Department of Defense

By: _____ Dated: _____
SHIRLEY R. PATTERSON
Assistant Director for Federal Employee Insurance Operations
United States Office of Personnel Management

By: _____ Dated: _____
DAVID COPE
Debarring Official
Office of the Assistant Inspector General for Legal Affairs
United States Office of Personnel Management

By: _____ Dated: _____
CECILY A. RAYBURN
Director, Division of Planning, Policy and Standards
Office of Workers' Compensation Programs
United States Department of Labor

By: _____ Dated: _____
GREGORY E. DEMSKE
Assistant Inspector General for Legal Affairs
Office of Counsel to the Inspector General
United States Department of Health and Human Service

By: _____ Dated: _____
PAUL J. HUTTER
General Counsel
TRICARE Management Activity
United States Department of Defense

By: Shirley R Patterson Dated: 5/1/12
SHIRLEY R. PATTERSON
Assistant Director for Federal Employee Insurance Operations
United States Office of Personnel Management

By: _____ Dated: 5/1/2012
DAVID COPE
Debarring Official
Office of the Assistant Inspector General for Legal Affairs
United States Office of Personnel Management

By: _____ Dated: _____
CECILY A. RAYBURN
Director, Division of Planning, Policy and Standards
Office of Workers' Compensation Programs
United States Department of Labor

By: _____ Dated: _____
GREGORY E. DEMSKE
Assistant Inspector General for Legal Affairs
Office of Counsel to the Inspector General
United States Department of Health and Human Service

By: _____ Dated: _____
PAUL J. HUTTER
General Counsel
TRICARE Management Activity
United States Department of Defense

By: _____ Dated: _____
SHIRLEY R. PATTERSON
Assistant Director for Federal Employee Insurance Operations
United States Office of Personnel Management

By: _____ Dated: _____
DAVID COPE
Debarring Official
Office of the Assistant Inspector General for Legal Affairs
United States Office of Personnel Management

By: _____ Dated: 4/27/12
CECILY A. RAYBURN
Director, Division of Planning, Policy and Standards
Office of Workers' Compensation Programs
United States Department of Labor

DEFENDANT ABBOTT LABORATORIES

By: _____ Dated: _____
LAURA J. SCHUMACHER
Executive Vice-President, General Counsel, and Secretary
of Abbott Laboratories
Authorized Corporate Officer

By: _____ Dated: _____
THEODORE V. WELLS, JR., ESQ.
Counsel for Abbott Laboratories

By: _____ Dated: _____
MARK FILIP, ESQ.
Counsel for Abbott Laboratories

RELATOR MEREDITH McCOYD

By: _____ Dated: 5/3/2012
MEREDITH McCOYD
Relator

By: _____ Dated: 5/3/2012
REUBEN A. GUTTMAN, ESQ.
Counsel for Relator McCoyd

RELATORS SUSAN MULCAHY, DOREEN MERRIAM, SONDRA KNOWLES

By: Susan Mulcahy
SUSAN MULCAHY
Relator

Dated: May 3, 2012

By: _____
DOREEN MERRIAM
Relator

Dated: _____

By: _____
SONDRA KNOWLES
Relator

Dated: _____

By: _____
JAMES A. BACKSTROM, ESQ.
Counsel for Relators Mulcahy, Merriam, and Knowles

Dated: May 3, 2012

RELATORS SUSAN MULCAHY, DOREEN MERRIAM, SONDRA KNOWLES

By: _____ Dated: _____
SUSAN MULCAHY
Relator

By: Doreen Merriam Dated: May 3, 2012
DOREEN MERRIAM
Relator

By: _____ Dated: _____
SONDRA KNOWLES
Relator

By: _____ Dated: May 3, 2012
JAMES A. BACKSTROM, ESQ.
Counsel for Relators Mulcahy, Merriam, and Knowles

RELATORS SUSAN MULCAHY, DOREEN MERRIAM, SONDRA KNOWLES

By: _____ Dated: _____
SUSAN MULCAHY
Relator

By: _____ Dated: _____
DOREEN MERRIAM
Relator

By: Sondra Knowles Dated: May 3, 2012
SONDRA KNOWLES
Relator

By: _____ Dated: May 3, 2012.
JAMES A. BACKSTROM, ESQ.
Counsel for Relators Mulcahy, Merriam, and Knowles

RELATOR TAMARA DIETZLER

By: _____ Dated: 5/2/12
TAMARA DIETZLER
Relator

By: _____ Dated: _____
SUSAN M. COLER, ESQ.
Counsel for Relator Dietzler

By: _____ Dated: _____
STEVEN M. SPRENGER
Counsel for Tamara Dietzler

RELATOR TAMARA DIETZLER

By: _____ Dated: _____
TAMARA DIETZLER
Relator

By: _____ Dated: 5/3/2012
SUSAN M. COLER, ESQ.
Counsel for Relator Dietzler

By: _____ Dated: _____
STEVEN M. SPRENGER
Counsel for Tamara Dietzler

RELATOR TAMARA DIETZLER

By: _____ Dated: _____
TAMARA DIETZLER
Relator

By: _____ Dated: _____
SUSAN M. COLER, ESQ.
Counsel for Relator Dietzler

By: _____ Dated: 5-4-12
STEVEN M. SPRENGER
Counsel for Tamara Dietzler

RELATOR THOMAS J. SPETTER, JR.

By: Thomas J. Spetter Jr. Dated: 5-3-12
THOMAS J. SPETTER, JR.
Relator

By: W. Scott Simmer Dated: May 3, 2012
W. SCOTT SIMMER, ESQ.
Counsel for Relator Spetter

CERTIFICATE

I, John A. Berry, do hereby certify that I am a duly appointed and qualified Assistant Secretary of Abbott Laboratories and acting as such; that Abbott Laboratories is a corporation duly organized and validly existing under the laws of the State of Illinois with its principal office at 100 Abbott Park Road, Abbott Park, Lake County. Illinois; that I am a keeper of its books and records and its corporate seal; that the following resolution is a true, complete and correct copy of the resolution adopted at a regular meeting of its Board of Directors on April 27, 2012; that said meeting was duly called, a quorum was present there at; and that that such resolution is still in effect:

RESOLVED, that the Executive Vice President, General Counsel and Secretary is hereby authorized to enter or cause to be entered on behalf of this Corporation: the Plea Agreement, civil settlement agreements with the federal government and the coordinating states, a Corporate Integrity Agreement with the HHS Office of Inspector General, and all other documents necessary or appropriate to effectuate the settlement of all aspects of the investigation of the Corporation's sales and marketing practices for Depakote from 1998 to 2008 by the United States Department of Justice at any time on or after the date of this meeting.

IN WITNESS WHEREOF, I have affixed my name as Assistant Secretary and have caused the corporate seal of Abbott Laboratories to be hereunto affixed as of this 30th day of April, 2012.

John A. Berry
Assistant Secretary



SETTLEMENT AGREEMENT

I. PARTIES

This Settlement Agreement ("Agreement") is entered into among the United States of America, acting through the United States Department of Justice, and on behalf of the Office of Inspector General of the Department of Health and Human Services ("OIG-HHS"), the TRICARE Management Activity ("TMA"), the United States Office of Personnel Management ("OPM"), the United States Department of Veterans Affairs ("VA"), and the Office of Workers Compensation Programs of the United States Department of Labor ("DOL-OWCP") (collectively the "United States"); Meredith McCoyd, Susan Mulcahy, Doreen Merriam, Sondra Knowles, Tamara Dietzler, Thomas J. Spetter, Jr. (collectively, "Relators"); and Abbott Laboratories ("Abbott"), through its authorized representatives. Collectively, all of the above will be referred to as "the Parties."

II. RECITALS

A. Abbott is an Illinois corporation headquartered in Abbott Park, Illinois. At all relevant times, Abbott distributed, marketed, and sold pharmaceutical products in the United States, including a drug sold under the trade names Depakote DR, Depakote ER, and Depakote Sprinkle (collectively, "Depakote").

B. Relators have filed the following qui tam actions against Abbott (collectively, the "Civil Actions"):

i. *United States, et al., ex rel. Meredith McCoyd v. Abbott Labs., et al.,* Civil Action No. 1:07-cv-00081 (W.D. Va.);

ii. *United States ex rel. Susan Mulcahy, Doreen Merriam, and Sondra Knowles v. Abbott Labs., et al.*, Civil Action No. 1:08-cv-00054 (W.D. Va.);

iii. *United States of America, et al., ex rel. Tamara Dietzler v. Abbott Labs.*, Civil Action No. 1:09-cv-00051 (W.D. Va.);

iv. *United States, et al., ex rel. Thomas J. Spetter, Jr. v. Abbott Labs., Inc., et al.*, Civil Action No. 1:10-cv-00006 (W.D. Va.).

C. The United States of America intervened in the Civil Actions on February 1, 2011.

D. On such date as may be determined by the Court, Abbott will plead guilty pursuant to Fed. R. Crim. P. 11 to an Information to be filed by the United States in *United States v Abbott Labs.*, Criminal Action No. [to be assigned] (W.D. Va.) (the "Criminal Action") that will allege a violation of 21 U.S.C. §§ 331(a) and 333(a)(1), 352(a) and 352(f)(1), namely, the introduction into interstate commerce of a misbranded drug, Depakote, in violation of the Food, Drug and Cosmetic Act.

E. Abbott has entered or will be entering into separate settlement agreements, described in Paragraph III.1(b) below (the "Medicaid State Settlement Agreements") with certain states and the District of Columbia in settlement of the Covered Conduct, defined below. States with which Abbott executes a Medicaid State Settlement Agreement in the form to which Abbott and the National Association of Medicaid Fraud Control Units ("NAMFCU") have agreed, or in a form otherwise agreed to by Abbott and an individual State, shall be defined as "Medicaid Participating States."

F. The United States alleges that Abbott caused claims for payment for Depakote to be submitted to the Medicaid Program, Title XIX of the Social Security Act, 42 U.S.C. §§ 1396-1396v ("Medicaid") and the Medicare Program, Title XVIII of the Social Security Act, 42 U.S.C. §§ 1395-1395kkk-1 ("Medicare"). The United States further alleges that Abbott caused claims for payment for Depakote to be submitted to the TRICARE program, 10 U.S.C. §§ 1071-1109 ("TRICARE"); the Federal Employees Health Benefits Program, 5 U.S.C. §§ 8901-8914 ("FEHBP"); and the following DOL-OWCP programs: the Federal Employees' Compensation Act, 5 U.S.C. § 8101 et seq. ("FECA"), the Energy Employees Occupational

Illness Compensation Program Act, 42 U.S.C. § 7384 et seq. ("EEOICPA"), and the Black Lung Benefits Act, 30 U.S.C. § 901 et seq. ("BLBA"); and that Abbott caused purchases of Depakote by the VA, 38 U.S.C. §§ 1701-1743 (collectively, the "Other Federal Healthcare Programs").

G. The United States contends that it and the Medicaid Participating States have certain civil claims against Abbott, as specified in Paragraph III.2 below, for engaging in the following conduct concerning the marketing, promotion and sale of Depakote between January 1998 and December 31, 2008 (hereinafter referred to as the "Covered Conduct"):

Abbott illegally marketed Depakote by:

(a) knowingly promoting the sale and use of Depakote for uses that were not approved by the Food and Drug Administration as safe and effective ("unapproved uses"), including behavioral disturbances in dementia patients, psychiatric conditions in children and adolescents, schizophrenia, depression, anxiety, conduct disorders, obsessive-compulsive disorder, post-traumatic stress disorder, alcohol and drug withdrawal, attention deficit disorder, autism, and other psychiatric conditions. Some of these unapproved uses were not medically accepted indications for which the United States and state Medicaid programs provided coverage for Depakote. This promotion included, in part:

(i) making false and misleading statements about the safety, efficacy, dosing, and cost-effectiveness of Depakote for some of these unapproved uses;

(ii) marketing Depakote to health care professionals to control behavioral disturbances in dementia patients in nursing homes by claiming that Depakote was not subject to certain requirements of the Omnibus Budget Reconciliation Act of 1987 (OBRA) designed to prevent the use of unnecessary drugs in nursing homes and that this use of Depakote would help nursing homes avoid the administrative burdens and costs of complying with OBRA regulatory restrictions applicable to antipsychotics.

(b) offering and paying illegal remuneration to health care professionals and long term care pharmacy providers to induce them to promote and/or prescribe Depakote and to improperly and unduly influence the content of company sponsored Continuing Medical Education programs, in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b).

As a result of the foregoing conduct, the United States alleges that Abbott knowingly caused false and/or fraudulent claims for Depakote to be submitted to, or caused purchases by, Medicare, Medicaid and the Other Federal Healthcare Programs.

H. The United States also contends that it has certain administrative claims against Abbott as specified in Paragraphs III.4 through III.7, below, for engaging in the Covered Conduct.

I. This Agreement is made in compromise of disputed claims. This Agreement is not an admission of facts or liability by Abbott, nor a concession by the United States that its claims are not well-founded. Abbott expressly denies the allegations of the United States and Relators as set forth herein and in the Civil Actions and denies that it engaged in any wrongful conduct in connection with the Covered Conduct, with the exception of such admissions that are made in connection with any guilty plea by Abbott in connection with the Criminal Action and the following:

(1) A substantial percentage of nursing home residents with dementia were beneficiaries of federal healthcare programs, including Medicare and Medicaid. Promotion of Depakote to healthcare providers in nursing homes for the control of the agitation and aggression of dementia patients caused the submission of certain claims to federal healthcare programs for that use. These programs paid hundreds of millions of dollars for claims resulting from the use of Depakote for the control of the agitation and aggression of dementia patients.

(2) A substantial percentage of individuals suffering from schizophrenia were beneficiaries of federal healthcare programs, including Medicare and Medicaid. Promotion of Depakote to healthcare providers for the treatment of schizophrenia caused the submission of certain claims to federal healthcare programs for

that use. These programs paid millions of dollars for claims resulting from the use of Depakote to treat schizophrenia.

Neither this Agreement or its execution, nor the performance of any obligation arising under it, including any payment, nor the fact of settlement, is intended to be, or shall be understood as, an admission of liability or wrongdoing, or other expression reflecting on the merits of the dispute by any party to this Agreement.

J. Relators claim entitlement under 31 U.S.C. § 3730(d) to a share of the proceeds of this Agreement and to Relators' reasonable expenses, attorneys' fees, and costs.

K. To avoid the delay, expense, inconvenience, and uncertainty of protracted litigation of the above claims, and in consideration of the mutual promises and obligations of this Agreement, the parties agree and covenant as follows:

III. TERMS AND CONDITIONS

1. Abbott shall pay to the United States and the Medicaid Participating States, collectively, the sum of Eight Hundred Million Dollars ($800,000,000.00), plus accrued interest in an amount of 2.5% per annum from September 16, 2011 and continuing until and including the day of payment (the "Settlement Amount"). The Settlement Amount shall constitute a debt immediately due and owing to the United States and the Medicaid Participating States on the Effective Date of this Agreement. This debt shall be discharged by payments to the United States and the Medicaid Participating States, under the following terms and conditions:

(a) Abbott shall pay to the United States the sum of $560,851,357, plus accrued interest as set forth above ("Federal Settlement Amount"). The Federal Settlement Amount shall be paid by electronic funds transfer pursuant to written instructions from the United States no later than seven (7) business days after (i) this Agreement is fully executed by the Parties and delivered to Abbott's attorneys; or (ii) the Court accepts a Fed. R. Crim. P. 11(c)(1)(C) guilty plea as described in Preamble Paragraph II.D in connection with the Criminal Action and imposes the agreed upon sentence, whichever occurs later.

(b) Abbott shall deposit the sum of $239,148,643, plus accrued interest as set forth above ("Medicaid State Settlement Amount") into one or more interest-bearing money market or bank accounts that are held in the name of Abbott, but segregated from other Abbott accounts (the "State Settlement Accounts"), and make payment from the State Settlement Accounts to the Medicaid Participating States pursuant to written instructions from the NAMFCU Negotiating Team and under the terms and conditions of the Medicaid State Settlement Agreements that Abbott will enter into with the Medicaid Participating States.

(c) Contingent upon the United States receiving the Federal Settlement Amount from Abbott, the United States agrees to pay, as soon as feasible upon receipt, to Relator Meredith

McCoyd, the sum of $84,127,704, plus 15 percent of the actual accrued interest paid to the United States by Abbott, as set forth in Paragraph III.1(a), above ("Relators' Share") as Relators' share of the proceeds pursuant to 31 U.S.C. § 3730(d). No other relator payments shall be made by the United States with respect to the matters covered by this Agreement. All Relators represent that they will abide by the terms of any separate agreements that they may have reached with one or more of the other Relators concerning the allocation of the Relators' Share among themselves.

(d) If Abbott's agreed-upon guilty plea pursuant to Fed. R. Crim. P. 11(c)(1)(C) in the Criminal Action described in Preamble Paragraph II.D is not accepted by the Court or the Court does not impose the agreed-upon sentence for whatever reason, this Agreement shall be null and void at the option of either the United States or Abbott. If either the United States or Abbott exercises this option, which option shall be exercised by notifying all Parties, through counsel, in writing within five (5) business days of the Court's decision, the Parties will not object and this Agreement will be rescinded. If this Agreement is rescinded, Abbott will not plead, argue or otherwise raise any defenses under the theories of statute of limitations, laches, estoppel or similar theories, to any civil or administrative claims, actions or proceedings arising from the Covered Conduct that are brought by the United States within 90 calendar days of rescission, except to the extent such defenses were available on the day on which the qui tam complaints listed in Preamble Paragraph II.B, above, were filed.

2. Subject to the exceptions in Paragraph III.9 below (concerning excluded claims) and conditioned upon Abbott's full payment of the Settlement Amount, the United States (on behalf of itself, its officers, agents, servants, agencies, and departments) releases Abbott, together with its current and former parent corporations, direct and indirect subsidiaries, brother or sister corporations, divisions, current or former owners, and their current and former directors, officers,

and employees, and the predecessors, successors, and assigns of any of them (the "Released Parties") from any civil or administrative monetary claim the United States has or may have for the Covered Conduct under the False Claims Act, 31 U.S.C. §§ 3729-3733; the Civil Monetary Penalties Law, 42 U.S.C. § 1320a-7a; the Program Fraud Civil Remedies Act, 31 U.S.C. §§ 3801-3812; any statutory provision creating a cause of action for civil damages or civil penalties which the Civil Division of the Department of Justice has actual or present authority to assert and compromise pursuant to 28 C.F.R. Pt. 0, Subpart I, 0.45(d); or the common law theories of payment by mistake, unjust enrichment, fraud, disgorgement, and, if applicable, breach of contract.

3. Subject to the exceptions in Paragraph III.9 below (concerning excluded claims) and Paragraph III.20 below (concerning Relators' Share and reasonable fees, expenses, and costs), and conditioned upon Abbott's full payment of the Settlement Amount, Relators, for themselves and for their heirs, successors, attorneys, agents, and assigns, fully and finally release, waive and forever discharge Abbott together with its current and former parent corporations, direct and indirect subsidiaries, brother or sister corporations, divisions, transferees, and the predecessors, successors, and assigns of any of them and their current or former owners, directors, officers and employees, representatives, servants, agents, consultants and attorneys, individually and collectively, from any civil monetary claim the United States has or may have for the Covered Conduct under the False Claims Act, 31 U.S.C. §§ 3729-3733, and any claims, allegations, demands, actions or causes of action whatsoever, known or unknown, fixed or contingent, in law or in equity, in contract or in tort, under any federal or state statute or regulation, or under common law, that they, their heirs, successors, attorneys, agents and assigns otherwise would have standing to bring, including, without limitation, any claim that the Relators asserted or could have asserted in the Civil Actions.

4. In consideration of the obligations of Abbott in this Agreement and the Corporate Integrity Agreement ("CIA") entered into between OIG-HHS and Abbott, and conditioned upon Abbott's full payment of the Settlement Amount, OIG-HHS agrees to release and refrain from instituting, directing, or maintaining any administrative action seeking exclusion from the Medicare, Medicaid, and other Federal health care programs (as defined in 42 U.S.C. § 1320a-7b(f)) against Abbott under 42 U.S.C. § 1320a-7a (Civil Monetary Penalties Law) or 42 U.S.C. § 1320a-7(b)(7) (permissive exclusion for fraud, kickbacks or other prohibited activities) for the Covered Conduct, or against Abbott under 42 U.S.C. § 1320a-7(b)(1) based on Abbott's agreement to plead guilty to the charge in the Criminal Action referenced above in Preamble Paragraph II.D, except as reserved in Paragraph III.9 (concerning excluded claims), below, and as reserved in this Paragraph. The OIG-HHS expressly reserves all rights to comply with any statutory obligations to exclude Abbott from the Medicare, Medicaid, or other Federal health care programs under 42 U.S.C. § 1320a-7(a) (mandatory exclusion) based upon the Covered Conduct. Nothing in this Section precludes the OIG-HHS from taking action against entities or persons, or for conduct and practices, for which claims have been reserved in Paragraph III.9, below.

5. In consideration of the obligations of Abbott set forth in this Agreement, conditioned upon Abbott's full payment of the Settlement Amount, TMA agrees to release and refrain from instituting, directing, or maintaining any administrative action seeking exclusion from the TRICARE Program against Abbott, its predecessors, and its current and former divisions, parents, affiliates, subsidiaries, successors, and assigns, and their current and former directors, officers, and employees under 32 C.F.R. § 199.9 for the Covered Conduct, except as reserved in Paragraph III.9 (concerning excluded claims) below, and as reserved in this Paragraph. TMA expressly reserves its authority to exclude Abbott under 32 C.F.R. §

199.9(f)(1)(i)(A), (f)(1)(i)(B), and (f)(1)(iii), based upon the Covered Conduct. Nothing in this Paragraph precludes TMA or the TRICARE Program from taking action against entities or persons, or for conduct and practices, for which claims have been reserved in Paragraph III.9, below.

6. In consideration of the obligations of Abbott set forth in this Agreement, and conditioned upon Abbott's full payment of the Settlement Amount, OPM agrees to release and refrain from instituting, directing, or maintaining any administrative action against Abbott, its predecessors, and its current and former divisions, parents, affiliates, subsidiaries, successors, and assigns, and their current and former directors, officers, and employees under 5 U.S.C. § 8902a(b) or 5 C.F.R. Part 919 for the Covered Conduct, except as reserved in Paragraph III.9 (concerning excluded claims) below, and except if excluded by the OIG-HHS pursuant to 42 U.S.C. § 1320a-7(a). Nothing in this Paragraph precludes OPM from taking action against entities or persons, or for conduct and practices, for which claims have been reserved in Paragraph III.9, below.

7. In consideration of the obligations of Abbott in this Agreement, and conditioned upon Abbott's full payment of the Settlement Amount, DOL-OWCP agrees to release and refrain from instituting, directing, or maintaining any administrative action seeking exclusion and debarment from the FECA, EEOICPA and BLBA programs against Abbott, its predecessors, and its current and former divisions, parents, affiliates, subsidiaries, successors and assigns, and their current and former directors, officers, and employees under 20 C.F.R. §§ 10.815, 30.715 and 702.431 for the Covered Conduct, except as reserved in Paragraph III.9 (concerning excluded claims), below and except if excluded by the OIG-HHS pursuant to 42 U.S.C. § 1320a-7(a). Nothing in this Paragraph precludes the OWCP of the DOL from taking action against entities or

persons, or for conduct and practices, for which claims have been reserved in Paragraph III.9, below.

8. Abbott has publicly announced that it plans to separate into two publicly traded companies, one a diversified medical products company, which may retain the Abbott name, ("Diversified Company") and the other a research-based pharmaceutical company ("Pharmaceutical Company') which will not be a subsidiary or corporate affiliate of Abbott (this separation is hereinafter referred to as the "Transaction" and the "Effective Time" shall be the date and time that the Transaction becomes effective). In the event the Transaction occurs, and as of the Effective Time, the foregoing releases in Paragraphs III.2 through III.3 and III.5 through III.7 that run to the benefit of Abbott will continue to apply fully to Abbott, the Diversified Company, the Pharmaceutical Company, and their subsidiaries and the foregoing release in Paragraph III.4 will apply fully to Abbott, the Diversified Company, and the Pharmaceutical Company.

9. Notwithstanding the releases given in Paragraphs III.2 through III.8 of this Agreement, or any other term of this Agreement, the following claims of the United States are specifically reserved and are not released:

(a) Any liability arising under Title 26, United States Code (Internal Revenue Code);

(b) Any criminal liability;

(c) Except as explicitly stated in this Agreement, any administrative liability, including mandatory exclusion from Federal health care programs;

(d) Any liability to the United States (or its agencies) for any conduct other than the Covered Conduct;

(e) Any liability based upon such obligations as are created by this Agreement;

(f) Any liability for express or implied warranty claims or other claims for defective or deficient products and services, including quality of goods and services;

(g) Any liability for personal injury or property damage or for other consequential damages arising from the Covered Conduct;

(h) Any liability for failure to deliver goods or services due; and

(i) Any liability of individuals (including current or former directors, officers, employees, agents, or shareholders of Abbott) who receive written notification that they are the target of a criminal investigation (as defined in the United States Attorneys' Manual), are indicted or charged, or enter into a plea agreement.

10. Relators and their heirs, successors, attorneys, agents, and assigns shall not object to this Agreement but agree and confirm that this Agreement is fair, adequate, and reasonable under all the circumstances, pursuant to 31 U.S.C. § 3730(c)(2)(B). Conditioned upon the payment of the Relators' Share described in Paragraph 1(c), Relators and their heirs, successors, attorneys, agents, and assigns fully and finally release, waive, and forever discharge the United States, its agencies, officers, agents, employees, and servants, from any claims arising from the filing of the Civil Actions or under 31 U.S.C. § 3730, and from any claims to a share of the proceeds of this Agreement and/or the Civil Actions.

11. Abbott waives and shall not assert any defenses Abbott may have to any criminal prosecution or administrative action relating to the Covered Conduct that may be based in whole or in part on a contention that, under the Double Jeopardy Clause in the Fifth Amendment of the Constitution, or under the Excessive Fines Clause in the Eighth Amendment of the Constitution, this Agreement bars a remedy sought in such criminal prosecution or administrative action.

Nothing in this paragraph or any other provision of this Agreement constitutes an agreement by the United States concerning the characterization of the Settlement Amount for purposes of the Internal Revenue laws, Title 26 of the United States Code.

12. Abbott fully and finally releases the United States, its agencies, officers, agents, employees, and servants, from any claims (including attorney's fees, costs, and expenses of every kind and however denominated) that Abbott has asserted, could have asserted, or may assert in the future against the United States, and its agencies, officers, agents, employees, and servants, related to the Covered Conduct and the United States' investigation and prosecution thereof.

13. Conditioned on Relators' compliance with their obligations under this Agreement, Abbott together with its current and former parent corporations, direct and indirect subsidiaries, brother or sister corporations, divisions, transferees, and the predecessors, successors, and assigns of any of them and their current or former owners, directors, officers and employees, representatives, servants, agents, consultants and attorneys, individually and collectively, fully and finally release, waive and forever discharge Relators and their heirs, successors, attorneys, agents, and assigns, from any claims, allegations, demands, actions or causes of action whatsoever, known or unknown, fixed or contingent, in law or in equity, in contract or in tort, under any federal or state statute or regulation, or under common law, that they otherwise would have standing to bring, including, without limitation, any claim that Abbott asserted or could have asserted in the Civil Actions, except to the extent related to: (i) Relators' claims for a Relators' Share of the Medicaid State Settlement Amount under the Medicaid State Settlement Agreements; (ii) Relators' claims arising under the *qui tam* provisions of any State with which Abbott does not execute a Medicaid State Settlement Agreement pursuant to the terms of this

Agreement; or (iii) Relators' claims for reasonable attorneys' fees, expenses, and costs pursuant to 31 U.S.C. § 3730(d)(1).

14. The Settlement Amount shall not be decreased as a result of the denial of claims for payment now being withheld from payment by any Medicare carrier or intermediary or any other state or Federal payer, related to the Covered Conduct; and Abbott agrees not to resubmit to any Medicare carrier or intermediary or any other state or Federal payer any previously denied claims related to the Covered Conduct, and agrees not to appeal any such denials of claims.

15. Abbott agrees to the following:

(a) Unallowable Costs Defined. All costs (as defined in the Federal Acquisition Regulation, 48 C.F.R. § 31.205-47 and in Titles XVIII and XIX of the Social Security Act, 42 U.S.C. §§ 1395-1395kkk-1 and 1396-1396w-5, and the regulations and official program directives promulgated thereunder) incurred by or on behalf of Abbott, its present or former officers, directors, employees, shareholders, and agents in connection with the following are "Unallowable Costs" for government contracting purposes and under Medicare, Medicaid, TRICARE, and FEHBP:

(i) the matters covered by this Agreement and the plea agreement referenced in Preamble Paragraph II.D;

(ii) the United States' audit(s) and civil and criminal investigation(s) of the matters covered by this Agreement;

(iii) Abbott's investigation, defense, and corrective actions undertaken in response to the United States' audit(s) and civil and criminal investigation(s) in connection with the matters covered by this Agreement (including attorneys' fees);

(iv) the negotiation and performance of this Agreement, the Plea Agreement, and the Medicaid State Settlement Agreements;

(v) the payments Abbott makes to the United States or any State pursuant to this Agreement, the Plea Agreement, or the Medicaid State Settlement Agreements, and any payments that Abbott may make to Relators (including costs and attorneys' fees); and

(vi) the negotiation of, and obligations undertaken pursuant to the CIA to: (a) retain an independent review organization to perform annual reviews as described in Section III of the CIA; and (b) prepare and submit reports to OIG-HHS. However, nothing in this Paragraph III.15(a)(vi) that may apply to the obligations undertaken pursuant to the CIA affects the status of costs that are not allowable based on any other authority applicable to Abbott.

(b) Future Treatment of Unallowable Costs. Unallowable Costs shall be separately estimated and accounted for by Abbott, and Abbott shall not charge such Unallowable Costs directly or indirectly to any contracts with the United States or any State Medicaid program, or seek payment for such Unallowable Costs through any cost report, cost statement, information statement, or payment request submitted by Abbott or any of its subsidiaries or affiliates to the Medicare, Medicaid, TRICARE, or FEHBP Programs.

(c) Treatment of Unallowable Costs Previously Submitted for Payment. Abbott further agrees that within 90 days of the Effective Date of this Agreement, it shall identify to applicable Medicare and TRICARE fiscal intermediaries, carders, and/or contractors, and Medicaid and FEHBP fiscal agents, any Unallowable Costs (as defined in this Paragraph) included in payments previously sought from the United States, or any State Medicaid Program,

including, but not limited to, payments sought in any cost reports, cost statements, information reports, or payment requests already submitted by Abbott or any of its subsidiaries or affiliates, and shall request, and agree, that such cost reports, cost statements, information reports, or payment requests, even if already settled, be adjusted to account for the effect of the inclusion of the Unallowable Costs. Abbott agrees that the United States, at a minimum, shall be entitled to recoup from Abbott any overpayment, plus applicable interest and penalties, as a result of the inclusion of such Unallowable Costs on previously-submitted cost reports, information reports, cost statements, or requests for payment. Any payments due after the adjustments have been made shall be paid to the United States pursuant to the direction of the Department of Justice and/or the affected agencies. The United States reserves its rights to disagree with any calculations submitted by Abbott, or any of its subsidiaries or affiliates on the effect of inclusion of Unallowable Costs on Abbott's or any of its subsidiaries' or affiliates' cost reports, cost statements, or information reports.

(d) Nothing in this Agreement shall constitute a waiver of the rights of the United States to audit, examine, or re-examine Abbott's books and records to determine that no Unallowable Costs have been claimed in accordance with the provisions of this Paragraph.

16. Abbott agrees to cooperate fully and truthfully with the United States' investigation of individuals and entities not released in this Agreement. Upon reasonable notice, Abbott shall encourage, and agrees not to impair, the cooperation of its directors, officers, and employees, and shall use its best efforts to make available, and encourage, the cooperation of former directors, officers, and employees for interviews and testimony, consistent with the rights and privileges of such individuals.

17. This Agreement is intended to be for the benefit of the Parties only. The Parties do not release any claims against any other person or entity, except to the extent provided for in Paragraphs III.8 and III.18 (waiver for beneficiaries paragraph), below.

18. Abbott agrees that it waives and shall not seek payment for any of the healthcare billings covered by this Agreement from any health care beneficiaries or their parents, sponsors, legally responsible individuals, or third party payors based upon the claims defined as Covered Conduct.

19. Abbott warrants that it has reviewed its financial situation and that it currently is solvent within the meaning of 11 U.S.C. §§ 547(b)(3) and 548(a)(1)(B)(ii)(I), and shall remain solvent following payment of the Settlement Amount. Further, the Parties warrant that, in evaluating whether to execute this Agreement, they (a) have intended that the mutual promises, covenants, and obligations set forth herein constitute a contemporaneous exchange for new value given to Abbott, within the meaning of 11 U.S.C. § 547(c)(1); and (b) have concluded that these mutual promises, covenants, and obligations do, in fact, constitute such a contemporaneous exchange. Further, the Parties warrant that the mutual promises, covenants, and obligations set forth herein are intended to and do, in fact, represent a reasonably equivalent exchange of value that is not intended to hinder, delay, or defraud any entity that Abbott was or became indebted to on or after the date of this transfer, within the meaning of 11 U.S.C. § 548(a)(I).

20. Upon receipt of the payments described in Paragraph 1, above, the United States and Relators shall file a Joint Stipulation of Dismissal as to the Released Parties in each of the Civil Actions pursuant to Rule 41(a)(1). Each stipulation of dismissal shall be (a) with prejudice as to the United States' and Relators' claims as to the Covered Conduct pursuant to and consistent with the terms and conditions of this Agreement; (b) without prejudice as to the United States and with prejudice as to Relators as to all other claims; (c) provided, however, that

the following claims shall not be dismissed until they are settled, adjudicated, or otherwise resolved, and the Court is so informed: (i) Relators' claims for a Relators' Share of the Medicaid State Settlement Amount under the Medicaid State Settlement Agreements; (ii) Relators' claims arising under the *qui tam* provisions of any State or political subdivision with which Abbott does not execute a Medicaid State Settlement Agreement pursuant to the terms of this Agreement; or (iii) Relators' claims for reasonable attorneys' fees, expenses, and costs pursuant to 31 U.S.C. § 3730(d)(1).

21. Except as expressly provided to the contrary in this Agreement, each Party shall bear its own legal and other costs incurred in connection with this matter, including the preparation and performance of this Agreement.

22. Each party and signatory to this Agreement represents that it freely and voluntarily enters into this Agreement without any degree of duress or compulsion.

23. This Agreement is governed by the laws of the United States. The exclusive jurisdiction and venue for any dispute relating to this Agreement is the United States District Court for the Western District of Virginia, except that disputes arising under the CIA shall be resolved exclusively through the dispute resolution provisions set forth in the CIA. For purposes of construing this Agreement, this Agreement shall be deemed to have been drafted by all Parties to this Agreement and shall not, therefore, be construed against any Party for that reason in any subsequent dispute.

24. This Agreement constitutes the complete agreement between the Parties with respect to the issues covered by this Agreement. This Agreement may not be amended except by written consent of the Parties.

25. The undersigned counsel represent and warrant that they are authorized to execute this Agreement on behalf of the persons and entities indicated below.

26. This Agreement may be executed in counterparts, each of which constitutes an original and all of which constitute one and the same Agreement.

27. This Agreement is binding on Abbott's successors, transferees, heirs, and assigns.

28. This Agreement is binding on Relators' successors, transferees, heirs, and assigns.

29. All Parties consent to the United States' disclosure of this Agreement, and information about this Agreement, to the public.

30. This Agreement is effective on the date of signature of the last signatory to the Agreement (the "Effective Date"). Facsimiles of signatures shall constitute acceptable binding signatures for purposes of this Agreement.

THE UNITED STATES OF AMERICA

By: _____ Dated: 5/7/12
TIMOTHY J. HEAPHY
United States Attorney
United States Attorney's Office
Western District of Virginia

By: _____ Dated: _____
RICK A. MOUNTCASTLE
Chief, Civil Division
United States Attorney's Office
Western District of Virginia

By: _____ Dated: _____
BRIAN McCABE
Trial Attorney
Commercial Litigation Branch
Civil Division
United States Department of Justice

By: _____ Dated: _____
EDWARD C. CROOKE
Trial Attorney
Commercial Litigation Branch
Civil Division
United States Department of Justice

THE UNITED STATES OF AMERICA

By: _____ Dated: _____
TIMOTHY J. HEAPHY
United States Attorney
United States Attorney's Office
Western District of Virginia

By: _____ Dated: _____
RICK A. MOUNTCASTLE
Chief, Civil Division
United States Attorney's Office
Western District of Virginia

By: Brian J. McCabe Dated: 5/7/12
BRIAN McCABE
Trial Attorney
Commercial Litigation Branch
Civil Division
United States Department of Justice

By: Edward Crooke Dated: 5/7/12
EDWARD C. CROOKE
Trial Attorney
Commercial Litigation Branch
Civil Division
United States Department of Justice

By: _____ Dated: 5/6/12

GREGORY E. DEMSKE
Chief Counsel to the Inspector General
Office of Counsel to the Inspector General
United States Department of Health and Human Service

By: _____ Dated: _____

PAUL J. HUTTER
General Counsel
TRICARE Management Activity
United States Department of Defense

By: _____ Dated: _____

SHIRLEY R. PATTERSON
Assistant Director for Federal Employee Insurance Operations
United States Office of Personnel Management

By: _____ Dated: _____

DAVID COPE
Debarring Official
Office of the Assistant Inspector General for Legal Affairs
United States Office of Personnel Management

By: _____ Dated: _____

CECILY A. RAYBURN
Director, Division of Planning, Policy and Standards
Office of Workers' Compensation Programs
United States Department of Labor

By: _____ Dated: _____
GREGORY E. DEMSKE
Assistant Inspector General for Legal Affairs
Office of Counsel to the Inspector General
United States Department of Health and Human Service

By: _____ Dated: 4/30/12
PAUL J. HUTTER
General Counsel
TRICARE Management Activity
United States Department of Defense

By: _____ Dated: _____
SHIRLEY R. PATTERSON
Assistant Director for Federal Employee Insurance Operations
United States Office of Personnel Management

By: _____ Dated: _____
DAVID COPE
Debarring Official
Office of the Assistant Inspector General for Legal Affairs
United States Office of Personnel Management

By: _____ Dated: _____
CECILY A. RAYBURN
Director, Division of Planning, Policy and Standards
Office of Workers' Compensation Programs
United States Department of Labor

By: _____ Dated: _____
GREGORY E. DEMSKE
Assistant Inspector General for Legal Affairs
Office of Counsel to the Inspector General
United States Department of Health and Human Service

By: _____ Dated: _____
PAUL J. HUTTER
General Counsel
TRICARE Management Activity
United States Department of Defense

By: Shirley R Patterson Dated: 5/1/12
SHIRLEY R. PATTERSON
Assistant Director for Federal Employee Insurance Operations
United States Office of Personnel Management

By: _____ Dated: 5/1/2012
DAVID COPE
Debarring Official
Office of the Assistant Inspector General for Legal Affairs
United States Office of Personnel Management

By: _____ Dated: _____
CECILY A. RAYBURN
Director, Division of Planning, Policy and Standards
Office of Workers' Compensation Programs
United States Department of Labor

By: _____ Dated: _____
GREGORY E. DEMSKE
Assistant Inspector General for Legal Affairs
Office of Counsel to the Inspector General
United States Department of Health and Human Service

By: _____ Dated: _____
PAUL J. HUTTER
General Counsel
TRICARE Management Activity
United States Department of Defense

By: _____ Dated: _____
SHIRLEY R. PATTERSON
Assistant Director for Federal Employee Insurance Operations
United States Office of Personnel Management

By: _____ Dated: _____
DAVID COPE
Debarring Official
Office of the Assistant Inspector General for Legal Affairs
United States Office of Personnel Management

By: _____ Dated: 4/27/12
CECILY A. RAYBURN
Director, Division of Planning, Policy and Standards
Office of Workers' Compensation Programs
United States Department of Labor

DEFENDANT ABBOTT LABORATORIES

By: _____ Dated: 5/7/12
LAURA J. SCHUMACHER
Executive Vice-President, General Counsel, and Secretary
of Abbott Laboratories
Authorized Corporate Officer

By: _____ Dated: 5-7-12
THEODORE V. WELLS, JR., ESQ.
Counsel for Abbott Laboratories

By: _____ Dated: 5/1/12
MARK FILIP, ESQ.
Counsel for Abbott Laboratories

RELATOR MEREDITH McCOYD

By: _____ Dated: 5/3/2012
MEREDITH McCOYD
Relator

By: _____ Dated: 5/7/2012
REUBEN A. GUTTMAN, ESQ.
Counsel for Relator McCoyd

RELATORS SUSAN MULCAHY, DOREEN MERRIAM, SONDRA KNOWLES

By: Susan Mulcahy
SUSAN MULCAHY
Relator

Dated: May 3, 2012

By: _____
DOREEN MERRIAM
Relator

Dated: _____

By: _____
SONDRA KNOWLES
Relator

Dated: _____

By: _____
JAMES A. BACKSTROM, ESQ.
Counsel for Relators Mulcahy, Merriam, and Knowles

Dated: May 3, 2012.

RELATORS SUSAN MULCAHY, DOREEN MERRIAM, SONDRA KNOWLES

By: _____ Dated: _____
SUSAN MULCAHY
Relator

By: Doreen Merriam Dated: May 3, 2012
DOREEN MERRIAM
Relator

By: _____ Dated: _____
SONDRA KNOWLES
Relator

By: _____ Dated: May 3, 2012
JAMES A. BACKSTROM, ESQ.
Counsel for Relators Mulcahy, Merriam, and Knowles

RELATORS SUSAN MULCAHY, DOREEN MERRIAM, SONDRA KNOWLES

By: _____ Dated: _____
SUSAN MULCAHY
Relator

By: _____ Dated: _____
DOREEN MERRIAM
Relator

By: Sondra Knowles Dated: May 3, 2012
SONDRA KNOWLES
Relator

By: _____ Dated: May 3, 2012.
JAMES A. BACKSTROM, ESQ.
Counsel for Relators Mulcahy, Merriam, and Knowles

RELATOR TAMARA DIETZLER

By: _____ Dated: 5/2/12
TAMARA DIETZLER
Relator

By: _____ Dated: _____
SUSAN M. COLER, ESQ.
Counsel for Relator Dietzler

By: _____ Dated: _____
STEVEN M. SPRENGER
Counsel for Tamara Dietzler

RELATOR TAMARA DIETZLER

By: _____ Dated: _____
TAMARA DIETZLER
Relator

By: _____ Dated: 5/3/2012
SUSAN M. COLER, ESQ.
Counsel for Relator Dietzler

By: _____ Dated: _____
STEVEN M. SPRENGER
Counsel for Tamara Dietzler

RELATOR TAMARA DIETZLER

By: _____ Dated: _____
TAMARA DIETZLER
Relator

By: _____ Dated: _____
SUSAN M. COLER, ESQ.
Counsel for Relator Dietzler

By: _____ Dated: 5-4-12
STEVEN M. SPRENGER
Counsel for Tamara Dietzler

RELATOR THOMAS J. SPETTER, JR.

By: Thomas J Spetter Jr. Dated: 5-3-12

THOMAS J. SPETTER, JR.
Relator

By: W. Scott Simmer Dated: May 3, 2012

W. SCOTT SIMMER, ESQ.
Counsel for Relator Spetter

CORPORATE INTEGRITY AGREEMENT
BETWEEN THE
OFFICE OF INSPECTOR GENERAL
OF THE
DEPARTMENT OF HEALTH AND HUMAN SERVICES
AND
ABBOTT LABORATORIES

I. PREAMBLE

Abbott Laboratories (Abbott) hereby enters into this Corporate Integrity Agreement (CIA) with the Office of Inspector General (OIG) of the United States Department of Health and Human Services (HHS) to promote compliance with the statutes, regulations, and written directives of Medicare, Medicaid, and all other Federal health care programs (as defined in 42 U.S.C. § 1320a-7b(f)) (Federal health care program requirements) and with the statutes, regulations, and written directives of the Food and Drug Administration (FDA requirements).

Contemporaneously with this CIA, Abbott is entering into a Settlement Agreement and a Plea Agreement with the United States. Abbott will also enter into settlement agreements with various States (State Settlement Agreement) and Abbott's agreement to this CIA is a condition precedent to those agreements.

Among other services, Abbott currently markets, promotes and sells human pharmaceutical products that are reimbursed by Federal health care programs in the United States through its U.S. Pharmaceutical Products Group (PPG). Abbott has publicly announced and represented to the OIG that it plans to separate into two, publicly-traded companies: one a diversified medical products company, which may retain the Abbott name (Diversified Company); and the other a research-based human pharmaceuticals company (Pharmaceutical Company), which will not be a subsidiary or corporate affiliate of Abbott. This separation is hereinafter referred to as the "Transaction." Abbott also has represented to the OIG that at the effective date and time of the Transaction (Effective Time), the assets of Abbott's research-based human pharmaceuticals products business will be transferred, conveyed and/or assigned by Abbott to the Pharmaceutical Company and that the Diversified Company shall no longer be involved in the marketing or promotion of research-based human pharmaceutical products in the United States.

Abbott shall keep the OIG apprised of the status of the Transaction until it is completed. Assuming that the Transaction is completed in accordance with the terms described above, Abbott shall include in a contract or agreement with the Pharmaceutical Company relating to the transfer, conveyance or assignment of the assets of the research-based human pharmaceutical products business to the Pharmaceutical Company a provision stating that the Pharmaceutical Company agrees that the terms and obligations of the CIA will become fully binding on the Pharmaceutical Company as of the Effective Time of the Transaction. In the event the Transaction takes place as set forth above, the Pharmaceutical Company will be deemed to be Abbott's successor-in-interest for purposes of this CIA. As of the Effective Time of the Transaction, this CIA shall transfer in its entirety to and be fully binding on the Pharmaceutical Company, which shall assume sole responsibility for the terms and obligations of the CIA. As of the Effective Time, the Pharmaceutical Company's business units and locations and all Covered Persons at each business unit and location shall be subject to the applicable requirements of this CIA; Abbott and the Diversified Company shall no longer be a party to or have any obligations under this CIA.

Prior to the Effective Date of this CIA (as defined below), Abbott established a voluntary compliance program applicable to all officers, managers, and employees of PPG (Compliance Program). The Compliance Program includes a Chief Ethics and Compliance Officer, an Office of Ethics and Compliance, and a U.S. Pharmaceutical Compliance Committee. The Compliance Program also includes a code of conduct, written policies and procedures, educational and training initiatives, a disclosure program, investigation of potential compliance violations, disciplinary procedures, screening measures for ineligible persons, and regular internal auditing procedures.

Abbott shall continue its Compliance Program throughout the term of this CIA and shall do so in accordance with the terms set forth below. Abbott may modify its Compliance Program as appropriate, but, at a minimum, Abbott shall ensure that during the term of this CIA, it shall comply with the obligations set forth herein.

II. TERM AND SCOPE OF THE CIA

A. The period of the compliance obligations assumed by Abbott under this CIA shall be five years from the effective date of this CIA, unless otherwise specified. The "Effective Date" shall be the date on which Abbott is obligated to pay the Settlement Amount as set forth in the Settlement Agreement between Abbott and the United States. Each one-year period, beginning with the one-year period following the Effective Date, shall be referred to as a "Reporting Period."

B. Sections VII, X, and XI shall expire no later than 120 days after OIG's receipt of: (1) Abbott's final Annual Report; or (2) any additional materials submitted by Abbott pursuant to OIG's request, whichever is later.

C. The scope of this CIA shall be governed by the following definitions:

1. "Covered Persons" includes:

a. all owners of Abbott who are natural persons (other than shareholders who: (1) have an ownership interest of less than 5% and (2) acquired the ownership interest through public trading) and all directors of Abbott;

b. all officers and employees of PPG who are engaged in or who have responsibilities relating to any of the Covered Functions (as defined below in Section II.C.7); and

c. all contractors, subcontractors, agents, and other persons who perform any of the Covered Functions on behalf of PPG, including, but not limited to third party vendors who provide services relating to the Covered Functions (e.g., for speaker programs or medical education programs.)

Notwithstanding the above, the term Covered Persons does not include: (1) part-time or per diem employees, contractors, subcontractors, agents, and other persons who are not reasonably expected to work more than 160 hours per year on behalf of PPG, except that any such individuals shall become "Covered Persons" at the point when they work more than 160 hours during the calendar year; or (2) employees, contractors, subcontractors, agents or other personnel of Abbott's Animal Health, Diagnostics (including Abbott Diagnostics Division, Abbott Molecular, Abbott Point of Care, STARLIMS, and IBIS), Nutritional Products, and Medical Devices Divisions (including Abbott Vascular, Abbott Diabetes Care, and Abbott Medical Optics), so long as they do not have responsibilities relating to any of the Covered Functions.

2. "Relevant Covered Persons" includes all Covered Persons whose job responsibilities relate to any of the Covered Functions.

3. "Government Reimbursed Products" refers to all Abbott human pharmaceutical products that are marketed or sold by PPG in the United States or pursuant to contracts with the United States that are reimbursed by Federal health care programs.

4. The term "Promotional Functions" includes: (a) the selling, detailing, marketing, advertising, promoting, or branding of Government Reimbursed Products; and (b) the preparation or external dissemination of promotional materials or information about, or the provision of promotional services relating to, Government Reimbursed Products, including those functions relating to any applicable review committees.

5. The term "Product Related Functions" includes: (a) the preparation or external dissemination of non-promotional materials that are governed by Federal healthcare program and/or FDA requirements and distributed to healthcare professionals (HCPs) and healthcare institutions (HCIs) about Government Reimbursed Products, including those functions relating to any applicable review committees and to PPG's Global Medical Affairs department (GMA) and Global Medical Information department (GMI); (b) contracting with HCPs licensed in the United States to conduct post-marketing clinical trials, investigator-initiated studies, and post-marketing observational studies relating to Government Reimbursed Products; (c) authorship, publication, and disclosure of articles or study results relating to Government Reimbursed Products; and (d) activities related to the submission of information about Government Reimbursed Products to government-listed compendia (such as DrugDex or other compendia of information about Government Reimbursed Products.)

6. The term "Managed Healthcare Related Functions" refers to Promotional Functions and Product Related Functions as they relate to interactions between Abbott and: (a) government payors, pharmacy benefit managers (PBMs), or other individuals or entities under contract with or acting on behalf of government payors; and (b) institutional purchasers or providers, long-term care or specialty pharmacies, or other

individuals or entities under contract with or acting on behalf of institutional purchasers or providers and who are in a position to influence the use of Government Reimbursed Products in the institution. Managed Healthcare Related Functions includes functions undertaken by the Integrated Managed Healthcare Group as well as Clinical Executives in the Clinical Evidence and Outcomes group.

7. The term "Covered Functions" refers to "Promotional Functions" and "Product Related Functions" which include "Managed Healthcare Related Functions", as defined above.

8. The term "Third Party Personnel" shall mean personnel who perform Covered Functions who are employees of entities with whom Abbott has entered or may in the future (during the term of this CIA) enter into agreements to promote or co-promote a Government Reimbursed Product in the United States or to engage in joint promotional activities in the United States relating to such a product. Abbott has represented that: (1) Third Party Personnel are employed by entities other than Abbott; (2) Abbott does not control Third Party Personnel; and (2) it would be commercially impractical to compel the compliance of Third Party Personnel with the requirements set forth in this CIA. Abbott agrees to promote compliance by Third Party Personnel with Federal health care program and FDA requirements by complying with the provisions set forth below in Sections III.B.2, V.A.8 and V.B.5. Provided that Abbott complies with the requirements of Sections III.B.2., V.A.8., and V.B.5, Abbott shall not be required to fulfill the other CIA obligations that would otherwise apply to Third Party Personnel who meet the definitions of Covered Persons.

9. The term "Third Party Educational Activity" shall mean any continuing medical education (CME), disease awareness, or other scientific, educational, or professional program, meeting, or event governed by Federal health care programs and/or FDA requirements and supported by PPG, including but not limited to, sponsorship of symposia at medical conferences.

III. CORPORATE INTEGRITY OBLIGATIONS

Abbott shall establish and maintain a Compliance Program that includes the following elements:

A. Compliance Responsibilities of Certain Abbott Employees and the Board of Directors.

1. *Compliance Officer.* Prior to the Effective Date, Abbott appointed an individual to serve as its chief compliance officer (known as its Chief Ethics and Compliance Officer or CECO) and Abbott shall maintain a CECO for the term of the CIA. The CECO is, and shall continue to be, responsible for developing and implementing policies, procedures, and practices designed to ensure compliance with the requirements set forth in this CIA and with Federal health care program and FDA requirements. The CECO shall be a member of senior management of Abbott, shall report directly to the Chief Executive Officer of Abbott, shall make periodic (at least four times per year) reports regarding compliance matters directly to the Board of Directors of Abbott or a designated Committee of the Board (Board Committee), and shall be authorized to report on such matters to the Board of Directors or Board Committee at any time. Within 90 days after the Effective Date, Abbott shall ensure that the CECO shall not be, or be subordinate to, the General Counsel or Chief Financial Officer. The CECO shall be responsible for monitoring the day-to-day compliance activities engaged in by Abbott as well as for any reporting obligations created under this CIA. Any noncompliance job responsibilities of the CECO shall be limited and must not interfere with the CECO's ability to perform the duties outlined in this CIA.

Abbott shall report to OIG, in writing, any change in the identity of the CECO, or any actions or changes that would affect the CECO's ability to perform the duties necessary to meet the obligations in this CIA, within five days after such a change.

2. *Compliance Committee.* Prior to the Effective Date, Abbott appointed a compliance committee (known as the U.S. Pharmaceutical Compliance Committee) which, in conjunction with the CECO assists in the implementation and enhancement of the Compliance Program. Abbott shall continue the U.S. Pharmaceutical Compliance Committee during the term of this CIA. The U.S. Pharmaceutical Compliance Committee shall, at a minimum, include the CECO and other members of senior management necessary to meet the requirements of this CIA (e.g., senior executives of relevant departments, such as legal, regulatory affairs, sales, marketing, human resources, audit, research and development, and finance. The CECO shall chair the U.S. Pharmaceutical Compliance Committee and the U.S. Pharmaceutical Compliance Committee shall

support the CECO in fulfilling his/her responsibilities with regard to the Compliance Program (e.g., shall assist in the analysis of PPG's risk areas relating to Covered Functions and shall oversee monitoring of internal and external audits and investigations). The U.S. Pharmaceutical Compliance Committee shall meet at least four times per year.

Abbott shall report to OIG, in writing, any changes in the composition of the U.S. Pharmaceutical Compliance Committee, or any actions or changes that would affect the U.S. Pharmaceutical Compliance Committee's ability to perform the duties necessary to meet the obligations in this CIA, within 15 days after such a change.

3. *Board of Directors Compliance Obligations*. The Abbott Board of Directors (Board) or an authorized subcommittee thereof (Board Committee) shall be responsible for the review and oversight of matters related to compliance with Federal health care program requirements, FDA requirements, and the obligations of this CIA. The Board or Board Committee shall, at a minimum, be responsible for the following:

a. The Board or Board Committee shall meet at least four times per year to review and oversee Abbott's Compliance Program as it relates to the Covered Functions undertaken by PPG, which includes receiving updates about the activities of the CECO, the U.S. Pharmaceutical Compliance Committee, and the Compliance Program. The Board or Board Committee shall also receive updates about adoption and implementation of policies, procedures and practices designed to ensure compliance with the requirements set forth in this CIA and with Federal health care program and FDA requirements, and shall evaluate the effectiveness of the Compliance Program.

b. For each Reporting Period of the CIA, the Board or Board Committee shall adopt a resolution, signed by each individual member of the Board or Board Committee, summarizing its review and oversight of PPG's compliance with Federal health care program requirements, FDA requirements, and the obligations of this CIA.

At minimum, the resolution shall include the following language:

"The Board of Directors (or authorized subcommittee thereof) has made a reasonable inquiry into the operations of Abbott's Compliance Program as it relates to the Covered Functions undertaken by PPG during the preceding twelve-month period, which included receiving updates and reports by the CECO and/or a representative from the U.S. Pharmaceutical Compliance Committee about the effectiveness of the Compliance

Program and the activities of the CECO and the U.S. Pharmaceutical Compliance Committee. Based on its inquiry and review, the Board has concluded that, to the best of its knowledge, Abbott has implemented an effective Compliance Program to meet Federal health care program requirements, FDA requirements, and the obligations of the CIA."

If the Board or Board Committee is unable to provide such a conclusion in the resolution, the Board or Board Committee shall include in the resolution a written explanation of the reasons why it is unable to provide the conclusion and the steps it is taking to implement an effective Compliance Program at Abbott.

Abbott shall report to OIG, in writing, any changes in the composition of the Board or Board Committee, or any actions or changes that would affect the Board's or Board Committee's ability to perform the duties necessary to meet the obligations in this CIA, within 15 days after such a change.

4. *Management Accountability and Certifications*: In addition to the responsibilities set forth in this CIA for all Covered Persons, certain Abbott officers or employees (Certifying Employees) are specifically expected to monitor and oversee activities within their areas of authority and shall annually certify that their applicable business unit is compliant with applicable Federal health care program and FDA requirements and with the obligations of this CIA. These Certifying Employees shall include, at a minimum, the following: Executive Vice President, Pharmaceutical Products Group; Senior Vice President, Proprietary Pharmaceutical Products, Global Commercial Operations; Senior Vice President, Pharmaceuticals Research and Development; Senior Vice President, Global Strategic Marketing and Services, Pharmaceutical Products Group; Vice President, Regulatory Affairs; Vice President, Proprietary Pharmaceuticals United States; Vice President, Pharmaceuticals, Manufacturing and Supply, and, to the extent that a PPG business unit performs Covered Functions and is not covered by the certifications of one of the above-listed individuals, such other PPG executives, vice-presidents, or leader/heads of business units as would be necessary to ensure that there is a Certifying Employee from each such business unit.

For each Reporting Period, each Certifying Employee shall sign a certification that states:

"I have been trained on and understand the compliance requirements and responsibilities as they relate to [department or functional area], an area under my supervision. My job responsibilities include ensuring compliance with regard to the

_____ [insert name of the department or functional area] with all applicable Federal health care program requirements, FDA requirements, obligations of the Corporate Integrity Agreement, and Abbott policies, and I have taken steps to promote such compliance. In the event that I have identified potential issues of noncompliance with these requirements, I have referred all such issues consistent with Abbott processes for reporting potential misconduct for further review and follow up. Apart from those referred issues, I am not currently aware in [insert department name] of any violations of applicable Federal health care program requirements, FDA requirements, or the obligations of the CIA. I understand that this certification is being provided to and relied upon by the United States."

Abbott has represented that the position of Executive Vice President, PPG, will cease to exist as of the Effective Time of the Transaction. Following the Transaction, a copy of the certification from the CEO of the Pharmaceutical Company as required by Section 14 of the Plea Agreement shall be submitted to the OIG pursuant to this Section III.A.4 in lieu of the certification from the Executive Vice President, PPG. After the Effective Time of the Transaction and through the remaining term of the CIA, Abbott shall continue to submit to the OIG certifications from the individuals occupying the other positions outlined above in accordance with the requirements of this Section III.A.4.

If any Certifying Employee is unable to provide such a conclusion in the certification, the Certifying Employee shall provide a written explanation of the reasons why he or she is unable to provide the certification outlined above and the steps being taken to address the issue(s) identified in the certification.

B. Written Standards.

1. *Code of Conduct.* Prior to the Effective Date, Abbott developed, implemented, and distributed a written or electronic code of conduct to all Covered Persons who are Abbott employees. This code is known as Abbott's Code of Business Conduct. Abbott makes, and shall continue to make, adherence to the Code of Business Conduct an element in evaluating the performance of all employees who are Covered Persons. Abbott's Code of Business Conduct includes, or within 120 days after the Effective Date, shall be revised to address or include the following:

a. Abbott's commitment to full compliance with all Federal health care program requirements and FDA requirements, including its

commitment to comply with all requirements relating to the Covered Functions;

b. Abbott's requirement that all of its Covered Persons shall be expected to comply with all applicable Federal health care program requirements, FDA Requirements, and with Abbott's own Policies and Procedures;

c. Abbott's requirement that all of its Covered Persons shall be expected to report to the CECO, or other appropriate individual designated by Abbott, suspected violations of any Federal health care program requirements, FDA requirements, or of Abbott's own Policies and Procedures;

d. the personal obligations of each Covered Person to comply with Federal health care program requirements, FDA requirements, and Abbott's Policies and Procedures; and

e. the right of all individuals to use the Disclosure Program described in Section III.F, and Abbott's commitment to nonretaliation and to maintain, as appropriate, confidentiality and anonymity with respect to such disclosures.

To the extent not already accomplished, within 120 days after the Effective Date, each Covered Person shall certify, in writing or electronically, that he or she has received, read, understood, and shall abide by Abbott's Code of Business Conduct. New Covered Persons shall receive the Code of Business Conduct and shall complete the required certification within 30 days after becoming a Covered Person or within 120 days after the Effective Date, whichever is later.

Abbott shall periodically review the Code of Business Conduct to determine if revisions are appropriate and shall make any necessary revisions based on such review. Any revised Code of Business Conduct shall be distributed within 30 days after any revisions are finalized. Each Covered Person shall certify, in writing or electronically, that he or she has received, read, understood, and shall abide by the revised Code of Business Conduct within 30 days after the distribution of the revised Code of Business Conduct.

2. *Third Party Personnel.* Within 120 days after the Effective Date, and annually thereafter by the anniversary of the Effective Date, Abbott shall send a letter to each entity employing Third Party Personnel. The letter shall outline Abbott's obligations under the CIA and its commitment to full compliance with all Federal health care program and FDA requirements. The letter shall include a description of Abbott's Compliance Program. Abbott shall attach a copy of its Code of Conduct to the letter and shall request the entity employing Third Party Personnel to either: (a) make a copy of Abbott's Code of Conduct and a description of Abbott's Compliance Program available to its Third Party Personnel; or (b) represent to Abbott that it has and enforces a substantially comparable code of conduct and compliance program for its Third Party Personnel.

3. *Policies and Procedures.* To the extent not already accomplished, Abbott shall implement written policies and procedures regarding the operation of the Compliance Program and compliance with Federal health care program and FDA requirements (Policies and Procedures). At a minimum, the Policies and Procedures must address the following with respect to Covered Functions and/or Government Reimbursed Products:

a. the subjects relating to the Code of Business Conduct identified in Section III.B.1;

b. appropriate ways to conduct Promotional Functions (including those relating to Managed Healthcare Related Functions) in compliance with all applicable Federal healthcare program requirements, including, but not limited to the Federal anti-kickback statute (codified at 42 U.S.C. § 1320a-7b(b)), and the False Claims Act (codified at 31 U.S.C. §§ 3729-3733) and in compliance with all applicable FDA requirements;

c. appropriate ways to conduct Product Related Functions (including those relating to Managed Healthcare Related Functions) in compliance with all applicable Federal healthcare program requirements, including, but not limited to the Federal anti-kickback statute (codified at 42 U.S.C. § 1320a-7b(b)), and the False Claims Act (codified at 31 U.S.C. §§ 3729-3733) and in compliance with all applicable FDA requirements;

d. the materials and information that may be distributed by Abbott sales representatives about Government Reimbursed Products and the manner in which sales representatives respond to requests for information about non-FDA approved (or "off-label") uses of Government Reimbursed Products. These Policies and Procedures shall require that Abbott sales representatives not prompt requests for information about non-FDA approved ("off-label") uses of Government Reimbursed Products but that, if HCPs make such inquiries, all such requests shall be referred to GMI;

e. the materials and information that may be distributed by GMI and the mechanisms through, and manner in which, GMI receives and responds to requests for information from an HCP or another individual or entity about off-label uses of Abbott's Government Reimbursed Products that have been submitted or referred by a sales representative; the form and content of information disseminated by GMI in response to such requests; and the internal review process for the information disseminated. The Policies and Procedures shall require responses to such requests (often called "medical information letters") to be accurate and unbiased.

The Policies and Procedures shall include a requirement that GMI develop a database ("Inquiries Database") to track all requests for information about Government Reimbursed Products. The Inquiries Database shall include the following items of information for each unique inquiry (Inquiry) received for information about PPG's products: 1) date of Inquiry; 2) form of Inquiry (e.g., fax, phone, etc.); 3) name of the requesting HCP, health care institution (HCI), or other individual or entity in accordance with applicable privacy laws; 4) nature and topic of request (including exact language of the Inquiry if made in writing); 5) nature/form of the response from Abbott (including a record of the materials provided to the HCP or HCI in response to the request); and 6) the name of the Abbott representative who called on or interacted with the HCP, customer, or HCI, if known;

f. the manner and circumstances under which medical personnel from GMA interact with or participate in meetings or events with HCPs or HCIs (either alone or with sales representatives or account executives) and the role of the medical personnel at such meetings or events, as well as how they handle responses to unsolicited requests about off-label indications of Government Reimbursed Products;

g. the development, implementation, and review of call plans for sales representatives who promote and sell Government Reimbursed Products. For each Government Reimbursed Product, the Policies and Procedures shall require that Abbott review the call plans for the product and the bases upon, and circumstances under which HCPs and HCIs belonging to specified medical specialties or types of clinical practice are included in, or excluded from, the call plans. The Policies and Procedures shall also require that Abbott modify the call plans as necessary to ensure that Abbott is promoting Government Reimbursed Products in a manner that complies with all applicable Federal health care program and FDA requirements. The call plan reviews shall occur at least annually and shall also occur each time when the FDA approves a new or additional indication for a Government Reimbursed Product;

h. the development, implementation, and review of plans for the distribution of samples of Government Reimbursed Products (Sample Distribution Plans). This shall include a review of the bases upon, and circumstances under, which HCPs and HCIs belonging to specified medical specialties or types of clinical practice may receive such samples from Abbott. The Policies and Procedures shall also require that Abbott modify the Sample Distribution Plans as necessary to ensure that Abbott is promoting Government Reimbursed Products in a manner that complies with all applicable Federal health care program and FDA requirements;

i. consultant or other fee-for-service arrangements entered into with HCPs or HCIs (including, but not limited to speaker programs, speaker training programs, presentations, consultant task force meetings, advisory boards, and ad hoc advisory activities, and any other financial engagement or arrangement with an HCP or HCI) and all events and expenses relating to such engagements or arrangements. These Policies and Procedures shall be designed to ensure that the arrangements and related events are used for legitimate and lawful purposes in accordance with applicable Federal health care program and FDA requirements. The Policies and Procedures shall include requirements about the content and circumstances of such arrangements and events;

j. programs to educate sales representatives, including but not limited to presentations by HCPs at sales meetings, preceptorships, tutorials, and experience-based learning activities, if any. These Policies and Procedures shall be designed to ensure that the programs are used for legitimate and lawful purposes in accordance with applicable Federal health care program and FDA requirements. The Policies shall include requirements about the content and circumstances of such arrangements and events;

k. sponsorship or funding of grants (including educational grants) or charitable contributions. These Policies and Procedures shall be designed to ensure that PPG's funding and/or sponsorship complies with all applicable Federal health care program and FDA requirements;

l. funding of, or participation in, any Third Party Educational Activity as defined in Section II.C.9 above. These Policies and Procedures shall be designed to ensure that PPG's funding and/or sponsorship of such programs satisfies all applicable Federal health care program and FDA requirements. The Policies and Procedures shall require CME grant-making decisions to be approved by Abbott's financial or other organizations separate from sales and marketing and that financial support shall be provided only to programs that foster increased understanding of scientific, clinical or healthcare issues.

The Policies and Procedures shall require that: 1) Abbott disclose its financial support of the Third Party Educational Activity and, to the extent feasible consistent with subsection III.B.3.1.4 below, any financial relationships with faculty, speakers, or organizers at such Activity; 2) as a condition of funding, the third party shall agree to disclose Abbott's financial support of the Third Party Educational Activity and to require faculty, speakers, or organizers at such Activity to disclose any financial relationship with Abbott; 3) the Third Party Educational Activity have an educational focus; 4) the content, organization, and operation of the Third Party Educational Activity (including the faculty, educational methods, materials, and venue) be independent of Abbott's control; 5) Abbott support only Third Party Educational Activity that is non-promotional in tone/nature; and 6) Abbott's support of a Third Party Educational Activity shall be contingent on the provider's commitment to provide information at the Third Party Educational Activity that is fair, balanced, accurate and not misleading;

m. review of promotional materials and information about Government Reimbursed Products intended to be disseminated outside Abbott by appropriate qualified personnel (such as regulatory, medical, and/or legal personnel) in a manner designed to ensure that legal, regulatory, and medical concerns are properly addressed during the review and approval process and are elevated when appropriate. Abbott currently uses a process for the review and approval of all promotional pieces directed to HCPs or customers that have product claims or disease awareness educational information. Abbott shall continue to use the current process or a substantively equivalent process during the term of the CIA. The Policies and Procedures shall be designed to ensure that such materials and information comply with all applicable Federal health care program and FDA requirements. The Policies and Procedures shall require that: 1) applicable review committees review all promotional materials prior to the distribution or use of such materials; and 2) deviations from the standard review committee practices and protocols (including

timetables for the submission of materials for review) shall be documented and referred for appropriate follow-up;

n. sponsorship, funding of, and disclosures relating to Product Related Functions. These Policies and Procedures shall be designed to ensure that Abbott's funding, sponsorship, and disclosure complies with all applicable Federal health care program and FDA requirements;

o. compensation (including through salaries, bonuses, contests or other means) for Relevant Covered Persons who are sales representatives promoting a Government Reimbursed Product. These Policies and Procedures shall: 1) be designed to ensure that financial incentives do not inappropriately motivate such individuals to engage in improper (including off-label) promotion, sales, and marketing of Government Reimbursed Products; and 2) include mechanisms, where appropriate, to exclude from incentive compensation sales that may indicate off-label promotion of Government Reimbursed Products;

p. the submission of information about any Government Reimbursed Product to any compendia such as Drugdex or other published source of information used in connection with the determination of coverage by a Federal health care program for the product (hereafter "Compendia"). This includes any initial submission of information to any Compendia and the submission of any additional, updated, supplemental, or changed information (e.g., any changes based on Abbott's discovery of erroneous or scientifically unsound information or data associated with the information in the Compendia.) The Policies and Procedures shall include a requirement that Abbott conduct an annual review of all arrangements, processing fees, or other payments or financial support (if any) provided by PPG to any Compendia. Abbott U.S. compliance personnel shall be involved in this review;

q. sponsorship of post-marketing clinical trials, investigator-initiated studies (IISs) (sometimes also called investigator-

sponsored studies or (ISSs)), and post-marketing observational studies (collectively "Research") by PPG, including the decision to provide financial or other support for such Research; the manner in which Research support is provided; and support for the publication of information about the Research, including the publication of information about the Research outcomes and results; and uses made of publications relating to Research;

r. authorship of journal articles or other publications about Government Reimbursed Products or about therapeutic areas or disease states that may be treated with Government Reimbursed Products, including, but not limited to, the disclosure of any and all relationships between the author and Abbott, the identification of all authors or contributors (including professional writers) associated with a given publication, and the scope and breadth of research results made available to each author or contributor; and

s. disciplinary policies and procedures for violations of Abbott's Policies and Procedures, including policies relating to Federal health care program and FDA requirements.

To the extent not already accomplished, within 120 days after the Effective Date, the Policies and Procedures shall be made available to all Covered Persons. Appropriate and knowledgeable staff shall be available to explain the Policies and Procedures.

At least annually (and more frequently, if appropriate), Abbott shall assess and update, as necessary, the Policies and Procedures. Within 30 days after the effective date of any revisions, any such revised Policies and Procedures shall be made available to all Covered Persons.

C. Training and Education.

1. *General Training.* Within 120 days after the Effective Date, Abbott shall provide at least one hour of General Training to each Covered Person. This training, at a minimum, shall explain Abbott's:

a. CIA requirements; and

b. Compliance Program (including the Code of Business Conduct).

New Covered Persons shall receive the General Training described above within 30 days after becoming a Covered Person or within 120 days after the Effective Date, whichever is later. After receiving the initial General Training described above, each Covered Person shall receive at least one hour of General Training in each subsequent Reporting Period.

2. *Specific Training*. Abbott shall provide annual training to each Relevant Covered Person relating to his or her specific job responsibilities. This training shall be known as Specific Training.

Within 120 days after the Effective Date, each Relevant Covered Person engaged in Promotional Functions or Product Related Functions shall receive at least three hours of Specific Training in addition to the General Training required above.

This Specific Training shall include a discussion of:

a. all applicable Federal health care program requirements relating to Promotional Functions and to Product Related Functions;

b. all applicable FDA requirements relating to Promotional Functions and to Product Related Functions;

c. all Abbott Policies and Procedures and other requirements applicable to Promotional Functions and Product Related Functions;

d. the personal obligation of each individual involved in Promotional Functions and Product Related Functions to comply with all applicable Federal health care program and FDA requirements and all other applicable legal requirements;

e. the legal sanctions for violations of the applicable Federal health care program and FDA requirements; and

f. examples of proper and improper practices related to Promotional Functions and Product Related Functions.

Within 120 days after the Effective Date, each Relevant Covered Person engaged in Managed Healthcare Related Functions shall receive at least three hours of Specific Training in addition to the General Training required above.

This Specific Training shall include a discussion of:

g. all applicable Federal health care program requirements and FDA requirements relating to Managed Healthcare Related Functions;

h. Abbott's systems and processes applicable to Managed Healthcare Related Functions;

i. all Abbott Policies and Procedures and other requirements applicable to Promotional Functions and Product Related Functions;

j. the personal obligation of each individual involved in Managed Healthcare Related Functions to ensure that all information provided or reported to Government Payors (or to PBMs or other individuals or entities under contract with or acting on behalf of the payors) or to institutional payors is complete, accurate and not misleading;

k. the legal sanctions for violations of the applicable Federal health care program and FDA requirements; and

l. examples of proper and improper practices relating to Managed Healthcare Related Functions.

New Relevant Covered Persons shall receive their Specific Training within 30 days after the beginning of their employment or becoming Relevant Covered Persons, or within 120 days after the Effective Date, whichever is later. An Abbott employee who has completed the Specific Training shall review a new Relevant Covered Person's work, to the extent that the work relates to any of the Covered Functions, until such time as the new Relevant Covered Person completes his or her Specific Training.

After receiving the initial Specific Training described in this Section, each Relevant Covered Person shall receive at least three hours of Specific Training in each subsequent Reporting Period.

3. *Board Member Training.* Within 120 days after the Effective Time, Abbott shall provide simultaneously to each member of the Board of Directors three hours of training covering the topics set forth in Section III.C.1 above and addressing the responsibilities of board members and corporate governance.

New members of the Board of Directors shall receive the Board Member Training described above within 30 days after becoming a board member or within 120 days after the Effective Time, whichever is later.

4. Certification. Each Covered Person who is required to complete training shall certify, in writing or in electronic form, if applicable, that he or she has received such training. The certification shall specify the type of training received and the date received. The CECO (or designee) shall retain these certifications, along with all course materials. These shall be made available to OIG, upon request.

5. *Qualifications of Trainer.* Persons responsible for providing the General and Specific Training shall be knowledgeable about the subject area of the training, including about applicable Federal health care program and FDA requirements.

6. *Update of Training.* Abbott shall review its training annually, and, where appropriate, shall update the training to reflect changes in Federal health care program requirements, FDA requirements, any issues discovered during internal audits or the IRO Reviews or the Risk Process Reviews and any other relevant information.

7. *Computer-based Training.* Abbott may provide the training required under this CIA through appropriate computer-based training approaches. If Abbott chooses to provide computer-based training, it shall make available appropriately qualified and knowledgeable staff or trainers to answer questions or provide additional information to the individuals receiving such training. In addition, if Abbott chooses to provide computer-based General or Specific Training, all applicable requirements to provide a number of "hours" of training in this Section III.C may be met with respect to computer-based training by providing the required number of "normative" hours as that term is used in the computer-based training industry.

D. Risk Assessment and Mitigation Process. Abbott has represented that prior to the Effective Date, Abbott implemented certain standardized risk assessment and mitigation standards, processes, and practices for Government Reimbursed Products, including in the areas of sales, marketing, and promotion (including the risk of off-label promotion) and product safety. These processes are described in more detail in Appendix B and shall be referred to as Abbott's Risk Assessment and Mitigation Processes (Risk Assessment and Mitigation Processes). These Risk Assessment and Mitigation Processes consist of the development and maintenance of standardized and centrally managed regulatory history documents for currently promoted Government Reimbursed Products and the following centralized, cross-functional review processes: PPD Material Review Board; PPD Management Review; and PPG Safety Review Board and Safety Council meetings. Based on the outcomes of these Risk Assessment and Mitigation Processes, PPG develops and implements actions designed to mitigate any identified risks, Abbott shall maintain these or equivalent standards, processes, and practices throughout the term of the CIA.

E. Review Procedures.

1. *General Description.*

a. *Engagement of Independent Review Organization.* Within 120 days after the Effective Date, Abbott shall engage an entity (or entities), such as an accounting, auditing, or consulting firm (or firms) (hereinafter "Independent Review Organization(s)" or "IRO(s)"), to perform reviews to assist Abbott in assessing and evaluating its Covered Functions. More specifically, the IRO(s) shall conduct reviews that assess Abbott's systems, processes, policies, procedures, and practices relating to the Covered Functions (including Research and publication activities associated with such Research) (defined below in Section III.L.2 and Section III.L.3, and collectively referred to as "Research and Publication Activities"), and Risk Assessment and Mitigation Processes (IRO Reviews).

The applicable requirements relating to the IRO are outlined in Appendix A to this CIA, which is incorporated by reference. Each IRO engaged by Abbott shall have expertise in applicable Federal health care program and FDA requirements relating to the Covered Functions as may be appropriate to the Review for which

the IRO is retained, including expertise in the pharmaceutical industry with respect to Research and Publication Activities and FDA requirements relating to marketing and promotion of products. Each IRO shall assess, along with Abbott, whether it can perform the engagement in a professionally independent and objective fashion, as appropriate to the nature of the review, taking into account any other business relationships or other engagements that may exist.

b. *Frequency and Brief Description of Reviews.*

(i) System, Transaction, and Additional Items Reviews. As set forth more fully in Appendix B, the IRO reviews shall consist of two components: Systems Reviews and Transactions Reviews relating to the Covered Functions. The Systems Reviews shall assess Abbott's systems, processes, policies, and procedures relating to the Covered Functions and Risk Assessment and Mitigation Processes. If there are no material changes in Abbott's relevant systems, processes, policies, and procedures, the Systems Review shall be performed for the periods covering the first and fourth Reporting Periods. If Abbott materially changes its relevant systems, processes, policies, and procedures, the IRO shall perform a Systems Review for the Reporting Period in which such changes were made in addition to conducting the Systems Review for the first and fourth Reporting Periods, as set forth more fully in Appendix B.

The Transactions Review shall be performed annually and shall cover each of the five Reporting Periods. The IRO(s) shall perform all components of each annual Transaction Review. As set forth more fully in Appendix B, the Transactions Review shall include several components.

In addition, each Transactions Review shall also include a review of up to three additional areas or practices of Abbott identified by the OIG in its discretion (hereafter "Additional Items"). For purposes of identifying the Additional Items to be included in the Transactions Review for a particular Reporting Period, the OIG will consult with Abbott and may consider internal audit work conducted by Abbott, the Government Reimbursed Product portfolio, the nature and scope

of PPG's promotional practices and arrangements with HCPs and HCIs, and other information known to it.

As set forth more fully in Appendix B, Abbott may propose to the OIG that its internal audit(s) be partially substituted for one or more of the Additional Items that would otherwise be reviewed by the IRO as part of the Transactions Review. The OIG retains sole discretion over whether, and in what manner, to allow Abbott's internal audit work to be substituted for a portion of the Additional Items review conducted by the IRO.

The OIG shall notify Abbott of the nature and scope of the IRO review for each of the Additional Items not later than 150 days prior to the end of each Reporting Period. Prior to undertaking the review of the Additional Items, the IRO and/or Abbott shall submit an audit work plan to the OIG for approval and the IRO shall conduct the review of the Additional Items based on a work plan approved by the OIG.

c. *Retention of Records*. The IRO and Abbott shall retain and make available to OIG, upon request, all work papers, supporting documentation, correspondence, and draft reports (those exchanged between the IRO and Abbott) related to the IRO Reviews.

2. *IRO Review Reports*. The IRO shall prepare a report based upon each IRO Review performed (IRO Review Report). Information to be included in the IRO Review Report is described in Appendices A and B.

3. *Validation Review*. In the event OIG has reason to believe that: (a) any of Abbott's IRO Reviews fails to conform to the requirements of this CIA; or (b) the IRO's findings or Review results are inaccurate, OIG may, at its sole discretion, conduct its own review to determine whether the applicable IRO Review complied with the requirements of the CIA and/or the findings or Review results are inaccurate (Validation Review). Abbott shall pay for the reasonable cost of any such review performed by OIG or any of its designated agents. Any Validation Review of Reports submitted as part of Abbott's final Annual Report shall be initiated no later than one year after Abbott's final submission (as described in Section II) is received by OIG.

Prior to initiating a Validation Review, OIG shall notify Abbott of its intent to do so and provide a written explanation of why OIG believes such a review is necessary. To resolve any concerns raised by OIG, Abbott may request a meeting with OIG to: (a) discuss the results of any IRO Review submissions or findings; (b) present any additional information to clarify the results of the IRO Review or to correct the inaccuracy of the IRO Review; and/or (c) propose alternatives to the proposed Validation Review. Abbott agrees to provide any additional information as may be requested by OIG under this Section III.E.3 in an expedited manner. OIG will attempt in good faith to resolve any IRO Review issues with Abbott prior to conducting a Validation Review. However, the final determination as to whether or not to proceed with a Validation Review shall be made at the sole discretion of OIG.

4. *Independence and Objectivity Certification.* The IRO shall include in its report(s) to Abbott a certification that the IRO has: (a) evaluated its professional independence and objectivity with respect to the reviews conducted under this Section III.E; and (b) concluded that it is, in fact, independent and objective in accordance with the requirements specified in Appendix A.

F. Disclosure Program.

Prior to the Effective Date, Abbott established a Disclosure Program that includes a mechanism (the toll free Ethics and Compliance Helpline) to enable individuals to disclose, to the CECO or some other person who is not in the disclosing individual's chain of command, any identified issues or questions associated with Abbott's policies, conduct, practices, or procedures with respect to a Federal health care program or an FDA requirement believed by the individual to be a potential violation of criminal, civil, or administrative law. Abbott publicizes, and shall continue to appropriately publicize, the existence of the Disclosure Program and the Ethics and Compliance Helpline (e.g., via periodic e-mails to employees, by posting the information in prominent common areas, or through references in the Code of Business Conduct and during training.)

The Disclosure Program shall emphasize a nonretribution, non-retaliation policy and shall include a reporting mechanism for anonymous communications for which appropriate confidentiality shall be maintained. Upon receipt of a disclosure, the CECO (or designee) shall gather all relevant information from the disclosing individual. The CECO (or designee) shall make a preliminary, good faith inquiry into the allegations set forth in every disclosure to ensure that it obtains all necessary information to determine whether a further review should be conducted. For any disclosure that is sufficiently specific so that it reasonably: (1) permits a determination of the appropriateness of the

alleged improper practice; and (2) provides an opportunity for taking corrective action, Abbott shall conduct an internal review of the allegations set forth in the disclosure and ensure that proper follow-up is conducted.

Abbott shall maintain, a disclosure log, which includes a record and summary of each disclosure received (whether anonymous or not), the status of the respective internal reviews, and any corrective action taken in response to the internal reviews. The disclosure log for PPG shall be made available to OIG upon request.

G. Ineligible Persons.

1. *Definitions.* For purposes of this CIA:

a. an "Ineligible Person" shall include an individual or entity who:

i. is currently excluded, debarred, suspended, or otherwise ineligible to participate in the Federal health care programs or in Federal procurement or nonprocurement programs; or

ii. has been convicted of a criminal offense that falls within the scope of 42 U.S.C. § 1320a-7(a), but has not yet been excluded, debarred, suspended, or otherwise declared ineligible.

b. "Exclusion Lists" include:

i. the HHS/OIG List of Excluded Individuals/Entities (available through the Internet at http://www.oig.hhs.gov); and

ii. the General Services Administration's List of Parties Excluded from Federal Programs (available through the Internet at http://www.epls.gov).

2. *Screening Requirements.* Abbott shall ensure that all prospective and current Covered Persons are not Ineligible Persons, by implementing the following screening requirements.

a. as part of the hiring or contracting process, Abbott shall require all prospective and current Covered Persons to disclose whether they are Ineligible Persons and shall screen potential Covered Persons against the Exclusion Lists prior to engaging their services.

b. Abbott shall screen all Covered Persons against the Exclusion Lists within 90 days after the Effective Date and on an annual basis thereafter.

c. Abbott shall maintain a policy requiring all Covered Persons to disclose immediately any debarment, exclusion, suspension, or other event that makes that person an Ineligible Person.

Nothing in this Section III.G affects Abbott's responsibility to refrain from (and liability for) billing Federal health care programs for items or services furnished, ordered, or prescribed by excluded persons. Abbott understands that items or services furnished by excluded persons are not payable by Federal health care programs and that Abbott may be liable for overpayments and/or criminal, civil, and administrative sanctions for employing or contracting with an excluded person regardless of whether Abbott meets the requirements of Section III.G.

3. *Removal Requirement.* If Abbott has actual notice that a Covered Person has become an Ineligible Person, Abbott shall remove such Covered Person from responsibility for, or involvement with, Abbott's business operations related to the Federal health care programs and shall remove such Covered Person from any position for which the Covered Person's compensation or the items or services furnished, ordered, or prescribed by the Covered Person are paid in whole or part, directly or indirectly, by Federal health care programs or otherwise with Federal funds at least until such time as the Covered Person is reinstated into participation in the Federal health care programs.

4. *Pending Charges and Proposed Exclusions.* If Abbott has actual notice that a Covered Person is charged with a criminal offense that falls within the scope of 42 U.S.C. §§ 1320a-7(a), 1320a-7(b)(1)-(3), or is proposed for exclusion during the Covered Person's employment or contract term, Abbott shall take all appropriate actions to ensure that the responsibilities of that Covered Person have not and shall not adversely affect the quality of care rendered to any beneficiary, patient, or resident, or the accuracy of any claims submitted to any Federal health care program.

H. Notification of Government Investigation or Legal Proceedings.

Within 30 days after discovery, Abbott shall notify OIG, in writing, of any ongoing investigation or legal proceeding known to Abbott conducted or brought by a U.S.-based governmental entity or its agents involving an allegation that Abbott has committed a crime or has engaged in fraudulent activities. This notification shall include a description of the allegation, the identity of the investigating or prosecuting agency, and the status of such investigation or legal proceeding. Abbott shall also provide written notice to OIG within 30 days after the resolution of the matter, and shall provide OIG with a description of the findings and/or results of the investigation or proceedings, if any.

I. Reportable Events.

1. *Definition of Reportable Event.* For purposes of this CIA, a "Reportable Event" means anything that involves:

a. a matter that a reasonable person would consider a probable violation of criminal, civil, or administrative laws applicable to any Federal health care program for which penalties or exclusion may be authorized;

b. a matter that a reasonable person would consider a probable violation of criminal, civil, or administrative laws applicable to any FDA requirements relating to the promotion of Government Reimbursed Products (including an FDA Warning Letter issued to Abbott);

c. the employment of or contracting with a Covered Person who is an Ineligible Person as defined by Section III.G.1.a; or

d. the filing of a bankruptcy petition by Abbott.

A Reportable Event may be the result of an isolated event or a series of occurrences.

2. *Reporting of Reportable Events.* If Abbott determines (after a reasonable opportunity to conduct an appropriate review or investigation of the allegations) through any means that there is a Reportable Event, Abbott shall notify OIG,

in writing, within 30 days after making the determination that the Reportable Event exists.

3. *Reportable Events under Sections III.I.1.a-c.* For Reportable Events under Sections III.I.1.a-c, the report to OIG shall include:

a. a complete description of the Reportable Event, including the relevant facts, persons involved, and legal and Federal health care program or FDA authorities implicated;

b. a description of Abbott's actions taken to correct the Reportable Event; and

c. any further steps Abbott plans to take to address the Reportable Event and prevent it from recurring.

4. *Reportable Events under Section III.I.1.d.* For Reportable Events under Section III.I.1.d, the report to the OIG shall include documentation of the bankruptcy filing and a description of any Federal health care program and/or FDA authorities implicated.

J. Notification of Communications with FDA. Within 30 days after the date of any written report, correspondence, or communication between Abbott and the FDA that materially discusses Abbott's or a Covered Person's actual or potential unlawful or improper promotion of PPG's products (including any improper dissemination of information about off-label indications), Abbott shall provide a copy of the report, correspondence, or communication to the OIG. Abbott shall also provide written notice to the OIG within 30 days after the resolution of any such disclosed off-label matter, and shall provide the OIG with a description of the findings and/or results of the matter, if any.

K. Field Force Monitoring and Review Efforts.

To the extent not already accomplished, within 120 days after the Effective Date, Abbott shall establish a comprehensive Field Force Monitoring Program (FFMP) to evaluate and monitor its PPG sales representatives' interactions with HCPs and HCIs. The FFMP shall be a formalized process designed to directly and indirectly observe the appropriateness of sales representatives' interactions with HCPs and HCIs and to identify

potential off-label promotional activities or other improper conduct. As described in more detail below, the FFMP shall include: 1) a Speaker Monitoring Program; 2) direct field observations (Observations) of sales representatives; and 3) the monitoring and review of other records relating to sales representatives' interactions with HCPs and HCIs (Records Reviews).

1. *Speaker Program Activities.* With regard to PPG's speaker programs, Abbott shall maintain processes to require all speakers to complete training and enter written agreements that describe the scope of work to be performed, the speaker fees to be paid, and compliance obligations for the speakers (including requirements that the speaker may only use Abbott approved materials and may not directly or indirectly promote the product for off-label uses.) Abbott shall maintain centralized electronic system(s) through which all such speaker programs are administered. These system(s) shall establish controls regarding eligibility and qualifications of speakers and venues for the programs and require that speakers are paid according to a centrally managed, pre-set rate structure determined based on a fair-market value analysis conducted by Abbott. Abbott shall maintain a comprehensive list of speaker program attendees through its centralized system(s). In addition, Abbott shall track and review the aggregate amount (including speaker fees, travel, and other expenses) paid to each speaker in connection with such speaker programs conducted during each Reporting Period. Abbott shall require certified evaluations by sales representatives or other Abbott personnel regarding whether a speaker program complied with Abbott requirements, and in the event of non-compliance, Abbott shall require the identification of the policy violation and ensure appropriate follow up activity to address the violation.

To the extent not already accomplished, Abbott shall institute a Speaker Monitoring Program under which Abbott compliance or other appropriately trained personnel who are independent from the functional area being monitored shall attend speaker programs during each Reporting Period and conduct live audits of 150 such programs (Speaker Program Audits). The programs subject to Speaker Program Audits shall be selected both on a risk-based targeting approach and on a sampling approach. For each program reviewed, personnel conducting the Speaker Program Audits shall review slide materials and other materials used as part of the speaker program, speaker statements made during the program, and Abbott representative activities during the program to assess whether the programs were conducted in a manner consistent with Abbott's Policies and Procedures. Abbott shall maintain the controls around speaker programs as described above, and shall conduct its Speaker Program Audits as described above throughout the term of the CIA.

2. *Observations.* As a component of the FFMP, Abbott U.S. compliance personnel (or other appropriately trained Abbott personnel who are independent from the functional area being monitored) shall conduct observations of U.S. sales representatives to assess whether the messages delivered and materials distributed to HCPs are consistent with applicable legal requirements and with Abbott's Policies and Procedures. These observations shall be full day ride-alongs with sales representatives (Observations), and each Observation shall consist of directly observing all meetings between a sales representative and HCPs during the workday. The Observations shall be scheduled throughout the year, selected by Abbott U.S. compliance personnel or other appropriately trained Abbott personnel who are independent from the monitored functional area both on a risk-based targeting approach and on a sampling approach, include each therapeutic area and actively promoted product, and be conducted across the United States. At the completion of each Observation, Abbott U.S. compliance personnel (or other appropriately trained Abbott personnel who are independent from the monitored functional area) shall prepare a report which includes:

1) the identity of the sales representative;
2) the identity of the monitoring personnel;
3) the date and duration of the Observation;
4) the product(s) promoted during the Observation;
5) an overall assessment of compliance with Abbott policy; and
6) the identification of any potential off-label promotional activity or other improper conduct by the sales representative.

Abbott U.S. compliance personnel (or other appropriately trained Abbott personnel who are independent from the monitored functional area) shall conduct at least 50 Observations during each Reporting Period.

3. *Records Reviews.* As a component of the FFMP, Abbott shall also review various types of records to assess PPG sales representatives' interactions with HCPs and HCIs in order to identify potential or actual compliance violations. For each Reporting Period, Abbott shall develop and implement a plan for conducting Records Reviews associated with at least three Government Reimbursed Products and a sampling of the representatives promoting those products in every separate region of the United States. The OIG shall have the discretion to identify up to three Government Reimbursed Products to be reviewed for each Reporting Period. The OIG will select the products based on information about Abbott's products provided by Abbott, upon request by the

OIG no later than 60 days prior to the beginning of the Reporting Period, and other information known to the OIG. If the OIG does not identify the Government Reimbursed Products to be reviewed within the first 30 days of the Reporting Period, Abbott shall select the three products to be reviewed.

These Records Reviews shall include the monitoring and review of: 1) records and systems relating to such sales representatives' interactions with HCPs and HCIs (including records from any available electronic detailing system(s) for the particular sales representative, sales communications from managers, sample distribution records, and expense reports); 2) requests for, or inquiries relating to, medical information about Government Reimbursed Products; 3) message recall studies or other similar records (such as Verbatims) purporting to reflect the details of sales representatives' interactions with HCPs and HCIs; 4) sales representatives' call notes; 5) sales representatives' e-mails and other electronic records; and 6) recorded results of the Observations of sales representatives and applicable notes or information from the sales representatives' managers.

4. *Reporting and Follow-up.* Personnel conducting the Speaker Program Audits, Observations, and Records Reviews shall have access to all relevant records and information necessary to assess potential or actual compliance violations. Results from the FFMP audits, including the identification of potential violations of policies and/or legal requirements, shall be compiled and reported to the U.S. Compliance Department for review and follow-up as appropriate. In the event that a potential violation of Abbott's Policies and Procedures or of legal or compliance requirements, including but not limited to potential off-label promotion, is identified during any aspect of the FFMP, Abbott shall investigate the incident consistent with established policies and procedures for the handling of investigations and shall take all necessary and appropriate responsive action (including disciplinary action) and corrective action, including the disclosure of Reportable Events pursuant to Section III.I above, if applicable. Any compliance issues identified during a Speaker Program Audit, Observation and/or Records Review and any corrective action shall be recorded in the files of the U.S. Compliance Department.

Abbott shall include a summary of the FFMP and the results of the FFMP as part of each Annual Report. As part of each Annual Report, Abbott also shall provide the OIG with copies of the Observation report for any instances in which it was determined that improper promotion occurred and a description of the action(s) that Abbott took as a result of such determinations. Abbott shall make the Observation reports for all other Observations available to the OIG upon request.

L. Monitoring of Non-Promotional Activities.

To the extent not already accomplished, within 120 days after the Effective Date Abbott shall develop and implement a monitoring program for the following types of activities: 1) consultant arrangement activities; 2) research-related activities; 3) publication activities; and 4) medical education grants. This program shall be referred to as the Non-Promotional Monitoring Program.

1. *Consultant Arrangement Activities.* To the extent that Abbott engages U.S.-based HCPs or HCIs for services that relate to Promotional Functions or to Product Related Functions other than for speaker programs, research-related activities, or publication activities (e.g., as a member of an advisory board or to attend consultant meetings), such HCPs or HCIs shall be referred to herein as Consultants. Abbott shall require all Consultants to enter written agreements describing the scope of work to be performed, the fees to be paid, and compliance obligations for the Consultants. Consultants shall be paid according to a centrally managed, pre-set rate structure that is determined based on a fair-market value analysis conducted by Abbott.

To the extent not already accomplished, within 120 days after the Effective Date, Abbott shall establish a process to develop annual budgeting plans that identify the business needs for, and the estimated numbers of, various Consultant engagements and activities to occur during the following year period. The Consultant budgeting plans shall also identify the budgeted amounts to be spent on Consultant-related activities. Abbott's U.S. compliance personnel shall be involved in the review and approval of such budgeting plans, including any subsequent modification of an approved plan. The purpose of this review shall be to ensure that Consultant arrangements and related events are used for legitimate purposes in accordance with applicable Abbott Policies and Procedures.

To the extent not already accomplished, within 120 days after the Effective Date, Abbott shall establish a process to ensure that a needs assessment has been completed to justify the retention of a Consultant prior to the retention of the Consultant. The needs assessment shall identify the business need for the retention of the Consultant and provide specific details about the consulting arrangement (e.g., information about the numbers and qualifications of the HCPs or HCIs to be engaged, the agenda for the proposed meeting, and a description of the proposed work to be done and type of work product to be generated.) Any deviations from the Consultant budgeting plans shall be documented

in the needs assessment form and shall be subject to review and approval by Abbott U.S. compliance personnel.

To the extent not already accomplished, within 120 days after the Effective Date, Abbott shall amend its policies and procedures in a manner designed to ensure that each Consultant performed the work for which the Consultant was engaged and that, as applicable, Abbott received the work product generated by the Consultant.

Within 120 days after the Effective Date, Abbott shall establish a Consultant Monitoring Program through which it shall conduct audits for each Reporting Period (Consultant Program Audits) of at least 50 Consultant arrangements with HCPs. The Consultant Monitoring Program shall review Consultant arrangements both on a risk-based targeting approach and on a sampling approach. Abbott U.S. compliance personnel (or other appropriately trained Abbott personnel who are independent from the monitored functional area) shall conduct Consultant Program Audits by reviewing needs assessment documents, consultant contracts, and materials relating to the program or work of the Consultant (including work product resulting from any program or event), in order to assess whether the programs and arrangements were conducted in a manner consistent with Abbott's Policies and Procedures. Results from the Consultant Program Audits, including the identification of potential violations of policies, shall be compiled and reported to the U.S. Compliance Department for review and follow-up as appropriate.

2. *Research-Related Activities.* To the extent that PPG engages U.S.-based HCPs or HCIs to conduct post-marketing clinical trials or post-marketing observational studies relating to Government Reimbursed Products, such HCPs and HCIs shall be referred to collectively as "Researchers". Abbott has represented that its policies and procedures require that PPG sales and marketing personnel may not direct Research, as defined in Section.III.B.3.q of this CIA, and may not control or unduly influence the decision to select a Researcher or site. Abbott has further represented that it requires Research funded or controlled by PPG to be approved by its medical and/or scientific organizations. Abbott has also represented that such Research and any resulting publications are intended to foster increased understanding of scientific, clinical or healthcare issues. Finally, Abbott has represented that it will not approve Research purely for the purpose of developing an article or reprint for PPG sales representative use. Abbott shall maintain these or equivalent standards, processes and practices, throughout the term of the CIA.

Abbott shall require all Researchers to enter written agreements describing the scope of the clinical research or other work to be performed, the fees to be paid, and compliance obligations for the Researchers. Researchers shall be paid according to a centrally managed, pre-set rate structure that is determined based on a fair-market value analysis conducted by Abbott.

To the extent not already accomplished, within 120 days after the Effective Date, Abbott shall establish an annual budgeting plan for Researchers that identifies the business or scientific need for, and the estimated numbers of, the various Researcher engagements and activities to occur during the year. The annual Researcher budgeting plan shall also identify the budgeted amounts to be spent on Researcher-related activities during the year. Abbott U.S. compliance personnel shall be involved in the review and approval of such budgeting plans, including any subsequent modification of an approved plan. The purpose of this review shall be to ensure that Research arrangements and related events are used for legitimate purposes in accordance with Abbott Policies and Procedures.

To the extent not already accomplished, within 120 days after the Effective Date, Abbott shall establish a process to ensure that a needs assessment has been completed to justify the retention of a Researcher prior to the retention of the Researcher. The needs assessment shall identify the business or scientific need for the information to be provided by the Researcher and provide specific details about the research arrangement (including, for example, information about the numbers and qualifications of the HCPs or HCIs to be engaged, a description of the proposed research to be done (including the research protocol) and type of work product to be generated). Any deviations from the Researcher budgeting plans shall be documented in the needs assessment form (or elsewhere, as appropriate) and shall be subject to review and approval by Abbott U.S. compliance personnel.

To the extent that PPG provides financial or other support to U.S.-based HCPs or HCIs for IIS/ISS regarding Government Reimbursed Products, such HCPs and HCIs shall be referred to as "Investigators." Abbott has represented that its policies and procedures require that PPG sales and marketing personnel may not direct IIS/ISS and may not control or unduly influence the approval of IIS/ISS proposals. Abbott has further represented that PPG standards shall require all Investigators to enter into a written agreement describing the scope of the work to be performed, including any publications related to the research, any fees to be paid, and the compliance obligations of the

Investigators. Investigators shall be paid according to a centrally managed pre-set rate structure that is determined based on a fair market value analysis conducted by Abbott.

To the extent not already accomplished, within 120 days of the Effective Date, Abbott shall establish a process for the review and approval of such IIS/ISSs. The process shall require consideration of the business and scientific need for research by the potential Investigators, as well as review of specific details regarding the research arrangements (including, for example, information regarding the proposed research to be done and the type of work to be generated).

To the extent not already accomplished, within 120 days after the Effective Date, Abbott shall amend its policies and procedures in a manner designed to ensure that each Researcher and/or Investigator performed the work for which that individual was engaged.

Within 120 days after the Effective Date, Abbott shall establish a Researcher and Investigator Monitoring Program through which it shall conduct audits for each Reporting Period (Researcher and Investigator Program Audits) of at least 30 Researcher arrangements and 15 Investigator arrangements with HCPs or HCIs. The Researcher and Investigator Monitoring Program shall review Researcher and Investigator arrangements both on a risk-based targeting approach and on a sampling approach. Abbott U.S. compliance personnel (or other appropriately trained Abbott personnel who are independent from the functional area being monitored) shall conduct the Researcher and Investigator Program Audits by reviewing needs assessment documents, proposal and/or protocol documents, approval documents, contracts, and payments in order to assess whether the programs and arrangements were supported by Abbott and performed by the Researchers and Investigators in a manner consistent with Abbott's Policies and Procedures. Results from the Researcher and Investigator Program Audits, including identification of potential violations of policies, shall be compiled and reported to the U.S. Compliance Department for review and follow-up as appropriate.

3. *Publication Activities.* To the extent that Abbott engages U.S.-based HCPs or HCIs to produce articles or other publications relating to Government Reimbursed Products (collectively "Publication Activities") such HCPs or HCIs shall be referred to as Authors. Abbott has represented that its standards and processes for the development and submission of scientific publications involving Government Reimbursed Products (including results from post-marketing clinical trials or post-marketing observational studies conducted with Researchers) require review and approval by PPG's medical,

scientific and/or regulatory affairs organizations prior to Abbott submission and incorporate ICMJE criteria for identifying Authors, including the requirements that the Author provide substantial contributions to the publication and provide final review of the content to be published. Abbott further requires that Authors disclose financial or other support provided by Abbott. Abbott shall maintain these or equivalent standards, processes and practices throughout the term of the CIA, and further shall require that scientific publications be published in a timely manner and present scientific information in a balanced way that does not exclude or inappropriately downplay negative safety or health information.

Abbott shall require all Authors to enter written agreements describing the scope of work to be performed, the fees to be paid in connection with the Publication Activities, and compliance obligations of the Authors. Authors shall be paid according to a centrally managed, pre-set rate structure that is determined based on a fair-market value analysis conducted by Abbott.

To the extent not already accomplished, within 120 days after the Effective Date, Abbott shall establish a process to develop annual plans that identify the business needs for and the estimated numbers of various Publication Activities (Publications Plans). Each Publications Plan shall also identify the budgeted amounts to be spent on Publication Activities. Abbott's U.S. compliance personnel shall be involved in the review and approval of such annual Publications Plans, including any modification of an approved plan. The purpose of this review shall be to ensure that Publication Activities and related events are used for legitimate purposes in accordance with Abbott Policies and Procedures.

To the extent not already accomplished, within 120 days after the Effective Date, Abbott shall establish a needs assessment process for Publication Activities. This process shall ensure that a needs assessment has been completed prior to the retention of an Author for a Publication Activity. The needs assessment shall provide specific details about Publication Activities to be performed (including a description of the proposed work to be done, type of work product to be generated, and the purpose for the work.) Any deviations from the Publications Plan shall be documented in the needs assessment form (or elsewhere, as appropriate) and shall be subject to review and approval by Abbott U.S. compliance personnel.

Within 120 days after the Effective Date, Abbott shall establish a Publication Monitoring Program through which it shall conduct audits for each Reporting Period of at

least 30 Publication Activities. The Publication Monitoring Program shall select publications for review both on a risk-based targeting approach and on a sampling approach. Abbott U.S. compliance personnel conducting the Publication Monitoring Program (or other appropriately trained Abbott personnel who are independent from the functional area being monitored) shall review needs assessment documents, proposal documents, approval documents, contracts, payments and materials relating to the Publication Activities (including work product resulting from the Activities), in order to assess whether the activities were conducted in a manner consistent with Abbott's Policies and Procedures. Results from the Publication Monitoring Programs, including the identification of potential violations of policies, shall be compiled and reported to the U.S. Compliance Department for review and follow-up as appropriate.

4. *Medical Education Grant Activities.* Abbott represents that it has established a Grants Management System within the finance organization of its U.S. Proprietary Pharmaceuticals Division (PPD), which is the exclusive mechanism through which requestors may seek or be awarded grants for independent medical education activities supported by PPD. PPG represents that its sales and marketing departments have no involvement in, or influence over, the review and approval of medical education grants in the United States. Grant requests shall be submitted to a grant management department(s) in the PPG finance organization(s) (or another organization that is separate from sales and marketing) and all such requests shall be processed in accordance with standardized criteria developed by the grant management department(s). Abbott shall continue the medical education grant process described above (or an equivalent process) throughout the term of the CIA, and shall notify the OIG in writing at least 60 days prior to the implementation of any new process or system subsequent to the Effective Date.

To the extent not already accomplished, within 120 days after the Effective Date, Abbott shall establish a Grants Monitoring Program through which it shall conduct audits for each Reporting Period of at least 30 medical education grants in the United States. The Grants Monitoring Program shall select grants for review both on a risk-based targeting approach and on a sampling approach. Abbott U.S. compliance personnel (or other appropriately trained Abbott personnel who are independent from the monitored functional area) shall conduct Grants Monitoring by reviewing proposal documents (including grant requests), approval documents, contracts, payments and materials relating to the grant office's review of the requests, and documents and materials relating to the grants and any events or activities funded through the grants in order to assess whether the activities were conducted in a manner consistent with Abbott's Policies and Procedures. Results from the Grant Monitoring Program, including the identification of

potential violations of policies, shall be compiled and reported to the U.S. Compliance Department for review and follow-up as appropriate.

5. *Follow Up Reviews and Reporting.* In the event that a potential violation of Abbott's Policies and Procedures or of legal or compliance requirements, including but not limited to potential improper promotion, is identified during any aspect of the Non-Promotional Monitoring Program, Abbott shall investigate the incident consistent with established Policies and Procedures for the handling of investigations and shall take all necessary and appropriate responsive action (including disciplinary action) and corrective action, including the disclosure of Reportable Events pursuant to Section III.I above, if applicable. Any compliance issues identified during any Non-Promotional Monitoring Program referenced above, and any corrective action, shall be recorded in the files of the U.S. Compliance Department.

Abbott shall include a summary of the Non-Promotional Monitoring Program and the results of the Non-Promotional Monitoring Program as part of each Annual Report. As part of each Annual Report, Abbott also shall provide the OIG with descriptions of any instances identified through the Non-Promotional Monitoring Program in which it was determined that improper promotion of Government Reimbursed Products occurred or the activities violated Abbott's requirements or Policies and Procedures, and a description of the action(s) that Abbott took as a result of such determinations. Abbott shall make the documents relating to the Non-Promotional Monitoring Program available to the OIG upon request.

M. Notice to Health Care Providers and Entities. Within 90 days after the Effective Date, Abbott shall send, by first class mail, postage prepaid with delivery confirmation, a notice containing the language set forth below to all HCPs and HCIs that PPG currently details. This notice shall be dated and shall be signed by Abbott's Vice President, Proprietary Pharmaceuticals, United States. The body of the letter shall state the following:

> As you may be aware, Abbott recently entered into a global civil, criminal, and administrative settlement with the United States and individual states in connection with the promotion and use of one of its products. This letter provides you with additional information about the settlement, explains Abbott's commitments going forward, and provides you with access to information about those commitments.

In general terms, the Government alleged that Abbott unlawfully promoted Depakote for uses not approved by the Food & Drug Administration (FDA) and that Abbott engaged in other improper conduct relating to Depakote. To resolve these matters, Abbott pled guilty to a misdemeanor criminal violation of the Federal Food, Drug & Cosmetic Act (FDCA) and agreed to pay a criminal fine and forfeiture amounts of $700 million. In addition, the Government alleged that Abbott violated the False Claims Act and Abbott entered into a civil settlement to resolve these allegations pursuant to which Abbott agreed to pay $800 million to the Federal Government and State Medicaid programs. More information about this settlement may be found at the following: **[Abbott shall include a link to the USAO, OCL, and Abbott websites in the letter.]**

As part of the federal settlement, Abbott also entered into a five-year corporate integrity agreement with the Office of Inspector General of the U.S. Department of Health and Human Services. The corporate integrity agreement is available at http://oig.hhs.gov/fraud/cia/index.html. Under this agreement, Abbott agreed to undertake certain obligations designed to promote compliance with Federal health care program and FDA requirements. We also agreed to notify healthcare providers about the settlement and inform them that they can report any questionable practices by Abbott's representatives to Abbott's Compliance Department or the Food & Drug Administration (FDA).

Please call Abbott at **XXXX** or **visit us at [insert name of web link]** if you have questions about the settlement referenced above or to report any instances in which you believe that an Abbott representative inappropriately promoted a product or engaged in other questionable conduct. Alternatively, you may report any improper conduct associated with prescription drug marketing committed by an Abbott Representative to the FDA's Office of Prescription Drug Promotion at 301-796-1200. You should direct medical questions or concerns about the products to **XXXXX.**

The CECO (or a designee) shall maintain a log of all calls and messages received in response to the notice. The log shall include a record and summary of each call and message received (whether anonymous or not), the status of the call or message, and any corrective action taken in response to the call or message. The log of all calls and messages received in response to the notice shall be made available to OIG upon request.

As part of the Implementation Report and each Annual Report, Abbott shall provide to the OIG a summary of the calls and messages received.

N. Reporting of Physician Payments.

1. *Reporting of Payment Information.* Quarterly Reporting: On or before January 1, 2013, Abbott shall post in a prominent position on its website an easily accessible and readily searchable listing of all U.S.-based physicians and Related Entities who or which received Payments (as defined in Section III.N.2) directly or indirectly from PPG during the third quarter of 2012 and the aggregate value of such Payments. Thereafter, 60 days after the end of each calendar quarter, Abbott shall post on its website a report of the cumulative value of the Payments provided to each physician and Related Entity during the preceding calendar quarter.

Annual Reporting: On or before March 31, 2013, and 90 days after the end of each subsequent calendar year, Abbott shall post on its website a report of the cumulative value of the Payments provided to all U.S.-based physicians and Related Entities directly or indirectly from PPG and reported in accordance with the preceding paragraph during the prior applicable calendar year. Each quarterly and annual report shall be easily accessible and readily searchable.

Each listing made pursuant to this Section III.N shall include a complete list of all individual physicians or Related Entities to whom or which PPG made Payments in the preceding quarter or year (as applicable). Each listing shall be arranged alphabetically according to the physicians' last name or name of Related Entity. The Payment amounts in the lists shall be reported in the actual amount paid for all physicians or Related Entity on the listing. For each physician, the applicable listing shall include the following information: i) physician's full name; ii) name of any Related Entities (if applicable); iii) city and state of the physician's practice or the Related Entity; and (iv) the aggregate value of the payment(s) in the preceding quarter or year (as applicable). If payments for multiple physicians have been made to one Related Entity, the aggregate value of all payments to the Related Entity will be the reported amount.

2. *Definitions and Miscellaneous Provisions.*

(i) Abbott shall continue to make each annual listing and the most recent quarterly listing of Payments as described above in Section III.N available on its website during the term of the CIA. Abbott shall retain and make available to OIG, upon request, all supporting documentation, correspondence, and records related to all

applicable Payments and to the annual and/or quarterly listings of Payments. Nothing in this Section III.N affects the responsibility of Abbott to comply with (or liability for noncompliance with) all applicable Federal health care program requirements and state laws as they relate to all applicable Payments made to physicians or Related Entity.

(ii) For purposes of Section III.N.1, "Payments" is defined to include all "payments or transfers of value" as that term is defined in §1128G(e)(10) under Section 6002 of the Patient Protection and Affordable Care Act (Public Law 111-148) (Affordable Care Act) and any regulations promulgated thereunder. The term Payments includes, by way of example, the types of payments or transfers of value enumerated in §1128G(a)(1)(A)(vi) of the Affordable Care Act. The term includes all payments or transfers of value made to Related Entities on behalf of, at the request of, for the benefit or use of, or under the name of a physician for whom Abbott would otherwise report a Payment if made directly to the physician. The term Payments also includes any payments or transfers of value made, directly by Abbott or by a vendor retained by Abbott to a physician or Related Entity in connection with, or under the auspices of, a co-promotion arrangement.

(iii) For purposes of its annual and quarterly website postings as described above, and only with regard to payments made pursuant to product research or development agreements and clinical investigations as set forth in § 1128G(c)(E) of the Affordable Care Act, Abbott may delay the inclusion of such payments on its website listings consistent with § 1128G(c)(E) of the Act and any subsequent regulations promulgated thereunder.

(iv) The term "Payments" does not include transfers of value or other items that are not included in or are excluded from the definition of "payment" as set forth in § 1128G(e)(10) under Section 6002 of the Affordable Care Act and any regulations promulgated thereunder.

(v) For purposes of this Section III.N, the term "Related Entity" is defined to be any entity by or in which any physician receiving Payments is employed, has tenure, or has an ownership interest.

O. Other Transparency/Disclosure Initiatives.

Abbott represents that it posts, at least annually, information on its company website regarding educational grants and charitable donations to U.S medical and other health care professional organizations, patient organizations, academic institutions,

hospitals, medical education companies and other scientific associations in amounts of more than $200. The information posted on the company website includes: (1) definitions for the types of grants and donations posted; (2) list of recipients in alphabetical order; and (3) payment amount and purpose. Abbott shall continue to post (and provide updates to) the above-described information about PPG-supported educational grants and charitable donations throughout the term of this CIA. Abbott shall notify the OIG in writing at least 60 days prior to any change in the substance of its policies regarding the funding of such educational grants and charitable donations or posting of the above-referenced information relating to such funding.

Abbott represents that it requires all Consultants to fully comply with all applicable disclosure obligations relating to their relationship with Abbott that may be externally imposed on the Consultants based on their affiliation with formulary or P&T committees or committees associated with the development of treatment protocols or standards. Abbott shall continue this requirement throughout the term of this CIA. Abbott represents that within 120 days after the Effective Date, Abbott shall, if necessary, amend its policies relating to Consultants to explicitly state that Abbott requires all Consultants to fully comply with all applicable disclosure obligations relating to their relationship with Abbott that may be externally imposed on the Consultants based on their affiliation with formulary, P&T committees, or committees associated with the development of treatment protocols or standards or that are required by any HCI, medical committee, or other medical or scientific organization with which the Consultants are affiliated. In addition, for any amendment to its contracts with Consultants and in any new contracts with Consultants entered into after 150 days following the Effective Date, Abbott shall include an explicit requirement that the Consultants fully comply with all applicable disclosure requirements, as referenced above in this paragraph. Abbott shall continue these disclosure requirements throughout the term of this CIA.

Abbott represents that it expects all Authors of scientific publications to fully comply with the International Committee of Medical Journal Editors (ICMJE) criteria regarding authorship and disclosure of their relationship with Abbott and to disclose any potential conflicts of interest, including any financial or personal relationships that might be perceived to bias their work. Abbott further represents that it expects all Authors to fully comply with all other applicable disclosure obligations that may be externally imposed on them based on their affiliation with any publication, HCI, medical committee, or other medical or scientific organization, including scientific journals. Within 120 days after the Effective Date, Abbott, if necessary, shall amend its policies relating to Authors to explicitly state Abbott's requirement about full disclosure by Authors consistent with

the requirements of any publication, HCI, medical committee or other medical or scientific organization with which the Authors are affiliated. In addition, for any amendments to its contracts with Authors and in any new contracts with Authors entered into after 150 days following the Effective Date, Abbott shall include an explicit requirement that Authors disclose in their manuscripts, journal submissions, and elsewhere as appropriate or required, any potential conflicts of interest, including their financial or personal relationship with Abbott, the names of any individuals who have provided editorial support for any manuscript or other publication, and all funding sources for the study or publication.

To the extent not already accomplished, within 120 days after the Effective Date, Abbott shall register all clinical studies and report results of such clinical studies on the National Institutes of Health (NIH) sponsored website (www.clinicaltrials.gov) in compliance with all current federal requirements. Abbott shall continue to comply with Federal health care program requirements, or other applicable requirements relating to the registration and results reporting of clinical studies throughout the term of this CIA. In addition, if there is a change in Federal health care program requirements, FDA requirements, NIH requirements, or other applicable requirements relating to registration and results reporting of clinical study information, Abbott shall fully comply with such requirements. Abbott also represents that its standards, processes and practices require that Abbott notify appropriate regulatory authorities, ethics committees and investigators of the discontinuation of clinical studies, and that Abbott shall maintain these or equivalent standards, processes and practices regarding discontinuation of clinical studies throughout the term of the CIA.

To the extent not already accomplished, within 120 days after the Effective Date, Abbott shall post or make available information on its company website about postmarketing commitments (PMCs) as defined by the FDA for Government Reimbursed Products. The Abbott website or links included therein shall provide access to general information about the PMC process, descriptions of ongoing Abbott studies, and information about the nature and status of FDA post-marketing commitments. Abbott shall continue to post or make available the above-described information about PMCs on its website or links included therein throughout the term of this CIA.

IV. CHANGES TO BUSINESS UNITS OR LOCATIONS

A. Change or Closure of Unit or Location. In the event that, after the Effective Date, Abbott changes locations or closes a business unit or location related to or engaged

in any of the Covered Functions, Abbott shall notify OIG of this fact as soon as possible, but no later than within 30 days after the date of change or closure of the location.

B. Purchase or Establishment of New Unit or Location. In the event that, after the Effective Date, Abbott purchases or establishes a new business unit or location related to or engaged in any of the Covered Functions, Abbott shall notify OIG no later than five days after the date that the purchase or establishment of the new business unit or location is publicly disclosed by Abbott. This notification shall include the address of the new business unit or location, phone number, fax number, the location's Federal health care program provider number and/or supplier number(s) (if applicable); and the name and address of each Federal health care program contractor to which Abbott currently submits claims (if applicable). Each new business unit or location and all Covered Persons at each new business unit or location shall be subject to the applicable requirements of this CIA.

C. Sale of Unit or Location. In the event that, after the Effective Date, Abbott proposes to sell any or all of its business units or locations that are subject to this CIA, Abbott shall notify OIG of the proposed sale at no later than five days after the sale is publicly disclosed by Abbott. This notification shall include a description of the business unit or location to be sold, a brief description of the terms of the sale, and the name and contact information of the prospective purchaser. This CIA shall be binding on the purchaser of such business unit or location, unless otherwise determined and agreed to in writing by the OIG.

V. IMPLEMENTATION AND ANNUAL REPORTS

A. Implementation Report. Within 150 days after the Effective Date, Abbott shall submit a written report to OIG summarizing the status of its implementation of the requirements of this CIA (Implementation Report). The Implementation Report shall, at a minimum, include:

1. the name, address, phone number, and position description of the CECO required by Section III.A, and a summary of other noncompliance job responsibilities the CECO may have;

2. the names and positions of the members of the U.S. Pharmaceutical Compliance Committee required by Section III.A;

3. the names of the members of the Board of Directors or Board Committee referenced in Section III.A.3;

4. the names and positions of the Certifying Employees required by Section III.A.4;

5. a copy of Abbott's Code of Business Conduct required by Section III.B.1;

6. the number of individuals required to complete the Code of Business Conduct certification required by Section III.B.1, the percentage of individuals who have completed such certification, and an explanation of any exceptions (the documentation supporting this information shall be available to OIG, upon request);

7. a summary of all Policies and Procedures required by Section III.B.3 (a copy of such Policies and Procedures shall be made available to OIG upon request);

8. (a) a copy of the letter (including all attachments) required by Sections II.C.8 and III.B.2 sent to each party employing Third Party Personnel; (b) a list of all such existing co-promotions and other applicable agreements with the party employing the Third Party Personnel; and (b) a description of the entities' response to Abbott's letter;

9. the following information regarding each type of training required by Section III.C:

a. a description of such training, including a summary of the topics covered, the length of sessions, and a schedule of training sessions; and

b. the number of individuals required to be trained, percentage of individuals actually trained, and an explanation of any exceptions.

A copy of all training materials and the documentation supporting this information shall be available to OIG, upon request.

10. the following information regarding the IRO(s): (a) identity, address, and phone number; (b) a copy of the engagement letter; and (c) information to demonstrate that the IRO has the qualifications outlined in Appendix A; (d) a summary and description of any and all current and prior engagements and agreements between

Abbott and the IRO; and (e) a certification from the IRO regarding its professional independence and objectivity with respect to Abbott;

11. a description of the Disclosure Program required by Section III.F;

12. a description of the process by which Abbott fulfills the requirements of Section III.G regarding Ineligible Persons;

13. a certification by the CECO that the notice required by Section III.M was mailed to each HCP and HCI, the number of HCPs and HCIs to whom the notice was mailed, a sample copy of the notice required by Section III.M, and a summary of the calls or messages received in response to the notice;

14. a certification from the CECO that, if required under Section III.N and to the best of his/her knowledge, information regarding Payments has been posted on Abbott's website as required by Section III.N;

15. a list of all of Abbott's locations (including locations and mailing addresses) engaged in Covered Functions; the corresponding name under which each location is doing business; the corresponding phone numbers and fax numbers; each location's Federal health care program provider number and/or supplier number(s) (if applicable); and the name and address of any each Federal health care program contractor to which Abbott currently submits claims (if applicable);

16. a description of Abbott's corporate structure, including identification of any parent and sister companies, subsidiaries, and their respective lines of business; and

17. the certifications required by Section V.C.

B. Annual Reports. Abbott shall submit to OIG annually a report with respect to the status of, and findings regarding, Abbott's compliance activities for each of the five Reporting Periods (Annual Report).

Each Annual Report shall include, at a minimum:

1. any change in the identity, position description, or other noncompliance job responsibilities of the CECO and any change in the membership of the U.S. Pharmaceutical Compliance Committee, the Board of Directors or Board Committee, or the group of Certifying Employees described in Sections III.A.2-4;

2. a copy of the resolution by the Board or Board Committee required by Section III.A.3;

3. the number of individuals required to review Abbott's Code of Business Conduct and complete the certifications required by Section III.B.1, the percentage of individuals who have completed such certifications, and an explanation of any exceptions (the documentation supporting this information shall be available to OIG, upon request);

4. a summary of any significant changes or amendments to the Policies and Procedures required by Section III.B and the reasons for such changes (e.g., change in applicable requirements);

5. (a) a copy of the letter (including all attachments) required by Sections II.C.8 and III.B.2 sent to each party employing Third Party Personnel; (b) a list of all such existing co-promotions and other applicable agreements with the party employing the Third Party Personnel; and (c) a description of the entities' response to Abbott's letter;

6. the following information regarding each type of training required by Section III.C:

   a. a description of the initial and annual training, including a summary of the topics covered, the length of sessions, and a schedule of training sessions; and

   b. the number of Covered Persons required to complete the General and Specific Training, percentage of individuals who completed the training, and an explanation of any exceptions.

A copy of all training materials and the documentation supporting this information shall be available to OIG, upon request.

7. a complete copy of all reports prepared pursuant to Sections III.E, along with a copy of the IRO's engagement letters;

8. Abbott's response to the reports prepared pursuant to the reviews outlined in Sections III.E, along with corrective action plan(s) related to any issues raised by the reports;

9. a summary and description of any and all current and prior engagements and agreements between Abbott and the IRO (if different from what was submitted as part of the Implementation Report);

10. a certification from the IRO regarding its professional independence and objectivity with respect to Abbott;

11. a summary of the disclosures in the disclosure log required by Section III.F that relate to Federal health care programs, FDA requirements, or Government Reimbursed Products;

12. any changes to the process by which Abbott fulfills the requirements of Section III.G regarding Ineligible Persons;

13. a summary describing any ongoing investigation or legal proceeding required to have been reported pursuant to Section III.H. The summary shall include a description of the allegation, the identity of the investigating or prosecuting agency, and the status of such investigation or legal proceeding;

14. a summary of Reportable Events (as defined in Section III.I) identified during the Reporting Period and the status of any corrective and preventative action relating to all such Reportable Events;

15. a summary describing any written communication with the FDA required to have been reported pursuant to Section III.J. This summary shall include a description of the matter and the status of the matter;

16. a summary of the FFMP and the results of the FFMP required by Section III.K, including copies of the Observation report for any instances in which it was determined that improper promotion occurred and a description of the action(s) that Abbott took as a result of such determinations;

17. a summary of the Non-Promotional Monitoring Program and the results of the program described in Section III.L, including detailed description of any identified instances in which it was determined that the activities violated Abbott's policies or that improper promotion of Government Reimbursed Products occurred and a description of the action(s) Abbott took as a result of such determinations;

18. a summary of the calls and messages received in response to the notice required by Section III.M and the disposition of those calls and messages;

19. a description of all changes to the most recently provided list of Abbott's locations (including addresses) as required by Section V.A.15; the corresponding name under which each location is doing business; and the corresponding phone numbers and fax numbers;

20. a description of any additional, updated, supplemental or changed information submitted to any Compendia in accordance with Section III.B.3.p; and a description of all arrangements, processing fees, and other payments or financial support (if any) with or made to any Compendia evaluated during the annual review described in Section III.B.3.p; and

21. the certifications required by Section V.C.

The first Annual Report shall be received by OIG no later than 90 days after the end of the first Reporting Period. Subsequent Annual Reports shall be received by OIG no later than the anniversary date of the due date of the first Annual Report.

C. Certifications.

1. Certifying Employees: In each Annual Report, Abbott shall include the certifications of Certifying Employees as required by Section III.A.4;

2. Chief Ethics and Compliance Officer: In each Implementation Report and Annual Report, Abbott shall include the following individual certification by the CECO:

1. to the best of his or her knowledge, except as otherwise described in the report, Abbott is in compliance with the requirements of this CIA;

2. he or she has reviewed the report and has made reasonable inquiry regarding its content and believes that the information in the report is accurate and truthful;

3. Abbott's: 1) Policies and Procedures as referenced in Section III.B.3 above; 2) templates for standardized contracts and other similar documents; and 3) the training materials used for purposes of Section III.C all have been reviewed by competent legal counsel and have been found to be in compliance with all applicable Federal health care program and FDA requirements. In addition, to the best of his or her knowledge, Abbott's promotional materials containing claims or information about Government Reimbursed Products and other materials and information intended to be disseminated outside Abbott have been reviewed by competent regulatory, medical, or, as appropriate, legal counsel in accordance with applicable Policies and Procedures to ensure that legal, medical, and regulatory concerns have been addressed by Abbott and brought to the attention of the appropriate individuals when required, and that the materials and information when finally approved are in compliance with all applicable Federal health care program and FDA requirements. If the applicable legal requirements have not changed, after the initial review of the documents listed above, only material changes to the documents must be reviewed by competent regulatory, medical and/or legal counsel. The certification shall include a description of the document(s) reviewed and approximately when the review was completed. The documentation supporting this certification shall be available to OIG, upon request; and

4. Abbott's call plans for Government Reimbursed Products were reviewed at least once during the Reporting Period (consistent with Section III.B.3.g) and, for each product the call plans were found to be consistent with Abbott's policy objectives as referenced above in Section III.B.3.g.

D. Designation of Information. Abbott shall clearly identify any portions of its submissions that it believes are trade secrets, or information that is commercial or financial and privileged or confidential, and therefore potentially exempt from disclosure under the Freedom of Information Act (FOIA), 5 U.S.C. § 552. Abbott shall refrain from identifying any information as exempt from disclosure if that information does not meet the criteria for exemption from disclosure under FOIA.

VI. NOTIFICATIONS AND SUBMISSION OF REPORTS

Unless otherwise stated in writing after the Effective Date, all notifications and reports required under this CIA shall be submitted to the following entities:

OIG: Administrative and Civil Remedies Branch
Office of Counsel to the Inspector General
Office of Inspector General
U.S. Department of Health and Human Services
Cohen Building, Room 5527
330 Independence Avenue, S.W.
Washington, DC 20201
Telephone: 202.619.2078
Facsimile: 202.205.0604

Abbott: Robert Funck
Chief Ethics and Compliance Officer
Abbott Laboratories
Dept. 036X, Bldg. AP6C-1
100 Abbott Park Road
Abbott Part, IL 60064
Telephone: 847.937.1231
Facsimile: 847.938.1957

Unless otherwise specified, all notifications and reports required by this CIA may be made by certified mail, overnight mail, hand delivery, or other means, provided that there is proof that such notification was received. For purposes of this requirement, internal facsimile confirmation sheets do not constitute proof of receipt. Upon request by OIG, Abbott may be required to provide OIG with an electronic copy of each notification or report required by this CIA in searchable portable document format (pdf), either instead of or in addition to, a paper copy.

VII. OIG INSPECTION, AUDIT, AND REVIEW RIGHTS

In addition to any other rights OIG may have by statute, regulation, or contract, OIG or its duly authorized representative(s) may examine or request copies of Abbott's books, records, and other documents and supporting materials and/or conduct on-site reviews of any of Abbott's locations for the purpose of verifying and evaluating: (a) Abbott's compliance with the terms of this CIA; and (b) Abbott's compliance with the

requirements of the Federal health care programs in which it participates and with all applicable FDA requirements. The documentation described above shall be made available by Abbott to OIG or its duly authorized representative(s) at all reasonable times for inspection, audit, or reproduction. Furthermore, for purposes of this provision, OIG or its duly authorized representative(s) may interview any of Abbott's employees, contractors, or agents who consent to be interviewed at the individual's place of business during normal business hours or at such other place and time as may be mutually agreed upon between the individual and OIG. Abbott shall assist OIG or its duly authorized representative(s) in contacting and arranging interviews with such individuals upon OIG's request. Abbott's employees may elect to be interviewed with or without a representative of Abbott present.

VIII. DOCUMENT AND RECORD RETENTION

Abbott shall maintain for inspection all documents and records relating to reimbursement from the Federal health care programs and to compliance with this CIA for six years (or longer if otherwise required by law) from the Effective Date.

IX. DISCLOSURES

Consistent with HHS's FOIA procedures, set forth in 45 C.F.R. Part 5, OIG shall make a reasonable effort to notify Abbott prior to any release by OIG of information submitted by Abbott pursuant to its obligations under this CIA and identified upon submission by Abbott as trade secrets, or information that is commercial or financial and privileged or confidential, under the FOIA rules. With respect to such releases, Abbott shall have the rights set forth at 45 C.F.R. § 5.65(d).

X. BREACH AND DEFAULT PROVISIONS

Abbott is expected to fully and timely comply with all of its CIA obligations.

A. Stipulated Penalties for Failure to Comply with Certain Obligations. As a contractual remedy, Abbott and OIG hereby agree that failure to comply with certain obligations as set forth in this CIA may lead to the imposition of the following monetary penalties (hereinafter referred to as "Stipulated Penalties") in accordance with the following provisions.

1. A Stipulated Penalty of $2,500 (which shall begin to accrue on the day

after the date the obligation became due) for each day Abbott fails to establish and implement any of the following obligations as described in Section III:

a. a Chief Ethics and Compliance Officer;

b. a U.S. Pharmaceutical Compliance Committee;

c. the Board of Directors or Board Committee compliance obligations, including the resolution from the Board or Board Committee;

d. a written Code of Business Conduct;

e. written Policies and Procedures;

f. the training of Covered Persons, Relevant Covered Persons, and Board Members;

g. a Disclosure Program;

h. Ineligible Persons screening and removal requirements;

i. notification of Government investigations or legal proceedings;

j. reporting of Reportable Events;

k. notification of written communications with FDA as required by Section III.J;

l. a program for FFMP as required by Section III.K;

m. a program for Non-Promotional Monitoring Program as required by Section III.L;

n. notification to HCPs and HCIs as required by Section III.M; and

o. posting of any Payments as required by Section III.N.

2. A Stipulated Penalty of $2,500 (which shall begin to accrue on the day after the date the obligation became due) for each day Abbott fails to engage and use an IRO as required in Section III.E and Appendices A-B.

3. A Stipulated Penalty of $2,500 (which shall begin to accrue on the day after the date the obligation became due) for each day Abbott fails to submit the Implementation Report or any Annual Reports to OIG in accordance with the requirements of Section V by the deadlines for submission.

4. A Stipulated Penalty of $2,500 (which shall begin to accrue on the day after the date the obligation became due) for each day Abbott fails to submit any IRO Review report in accordance with the requirements of Section III.E and Appendix B.

5. A Stipulated Penalty of $1,500 for each day Abbott fails to grant access as required in Section VII. (This Stipulated Penalty shall begin to accrue on the date Abbott fails to grant access.)

6. A Stipulated Penalty of $5,000 for each false certification submitted by or on behalf of Abbott as part of its Implementation Report, Annual Report, additional documentation to a report (as requested by the OIG), or otherwise required by this CIA.

7. A Stipulated Penalty of $1,000 for each day Abbott fails to comply fully and adequately with any obligation of this CIA. OIG shall provide notice to Abbott stating the specific grounds for its determination that Abbott has failed to comply fully and adequately with the CIA obligation(s) at issue and steps Abbott shall take to comply with the CIA. (This Stipulated Penalty shall begin to accrue 10 days after Abbott receives this notice from OIG of the failure to comply.) A Stipulated Penalty as described in this Subsection shall not be demanded for any violation for which OIG has sought a Stipulated Penalty under Subsections 1- 6 of this Section.

B. Timely Written Requests for Extensions. Abbott may, in advance of the due date, submit a timely written request for an extension of time to perform any act or file any notification or report required by this CIA. Notwithstanding any other provision in this Section, if OIG grants the timely written request with respect to an act, notification, or report, Stipulated Penalties for failure to perform the act or file the notification or report shall not begin to accrue until one day after Abbott fails to meet the revised deadline set by OIG. Notwithstanding any other provision in this Section, if OIG denies such a timely written request, Stipulated Penalties for failure to perform the act or file the

notification or report shall not begin to accrue until three business days after Abbott receives OIG's written denial of such request or the original due date, whichever is later. A "timely written request" is defined as a request in writing received by OIG at least five business days prior to the date by which any act is due to be performed or any notification or report is due to be filed.

C. Payment of Stipulated Penalties.

1. *Demand Letter.* Upon a finding that Abbott has failed to comply with any of the obligations described in Section X.A and after determining that Stipulated Penalties are appropriate, OIG shall notify Abbott of: (a) Abbott's failure to comply; and (b) OIG's exercise of its contractual right to demand payment of the Stipulated Penalties (this notification is referred to as the "Demand Letter").

2. *Response to Demand Letter.* Within 10 days after the receipt of the Demand Letter, Abbott shall either: (a) cure the breach to OIG's satisfaction and pay the applicable Stipulated Penalties or (b) request a hearing before an HHS administrative law judge (ALJ) to dispute OIG's determination of noncompliance, pursuant to the agreed upon provisions set forth below in Section X.E. In the event Abbott elects to request an ALJ hearing, the Stipulated Penalties shall continue to accrue until Abbott cures, to OIG's satisfaction, the alleged breach in dispute. Failure to respond to the Demand Letter in one of these two manners within the allowed time period shall be considered a material breach of this CIA and shall be grounds for exclusion under Section X.D.

3. *Form of Payment.* Payment of the Stipulated Penalties shall be made by electronic funds transfer to an account specified by OIG in the Demand Letter.

4. *Independence from Material Breach Determination.* Except as set forth in Section X.D.1.d, these provisions for payment of Stipulated Penalties shall not affect or otherwise set a standard for OIG's decision that Abbott has materially breached this CIA, which decision shall be made at OIG's discretion and shall be governed by the provisions in Section X.D, below.

D. Exclusion for Material Breach of this CIA.

1. *Definition of Material Breach.* A material breach of this CIA means:

a. a repeated or flagrant violation of the obligations under this CIA,

including, but not limited to, the obligations addressed in Section X.A;

b. a failure by Abbott to report a Reportable Event and take corrective action as required in Section III.I;

c. a failure to engage and use an IRO in accordance with Section III.E and Appendices A-B;

d. a failure to respond to a Demand Letter concerning the payment of Stipulated Penalties in accordance with Section X.C; or

e. a failure of the Board or Board Committee to issue a resolution in accordance with Section III.A.3.

2. *Notice of Material Breach and Intent to Exclude*. The parties agree that a material breach of this CIA by Abbott constitutes an independent basis for Abbott's exclusion from participation in the Federal health care programs. Upon a determination by OIG that Abbott has materially breached this CIA and that exclusion is the appropriate remedy, OIG shall notify Abbott of: (a) Abbott's material breach; and (b) OIG's intent to exercise its contractual right to impose exclusion (this notification is hereinafter referred to as the "Notice of Material Breach and Intent to Exclude").

3. *Opportunity to Cure*. Abbott shall have 30 days from the date of receipt of the Notice of Material Breach and Intent to Exclude to demonstrate to OIG's satisfaction that:

a. Abbott is in compliance with the obligations of the CIA cited by OIG as being the basis for the material breach;

b. the alleged material breach has been cured; or

c. the alleged material breach cannot be cured within the 30 day period, but that: (i) Abbott has begun to take action to cure the material breach; (ii) Abbott is pursuing such action with due diligence; and (iii) Abbott has provided to OIG a reasonable timetable for curing the material breach.

4. *Exclusion Letter*. If, at the conclusion of the 30 day period, Abbott fails to satisfy the requirements of Section X.D.3, OIG may exclude Abbott from participation in the Federal health care programs. OIG shall notify Abbott in writing of its determination to exclude Abbott (this letter shall be referred to hereinafter as the "Exclusion Letter"). Subject to the Dispute Resolution provisions in Section X.E, below, the exclusion shall go into effect 30 days after the date of Abbott's receipt of the Exclusion Letter. The exclusion shall have national effect and shall also apply to all other Federal procurement and nonprocurement programs. Reinstatement to program participation is not automatic. After the end of the period of exclusion, Abbott may apply for reinstatement by submitting a written request for reinstatement in accordance with the provisions at 42 C.F.R. §§ 1001.3001-.3004.

E. Dispute Resolution

1. *Review Rights*. Upon OIG's delivery to Abbott of its Demand Letter or of its Exclusion Letter, and as an agreed-upon contractual remedy for the resolution of disputes arising under this CIA, Abbott shall be afforded certain review rights comparable to the ones that are provided in 42 U.S.C. § 1320a-7(f) and 42 C.F.R. Part 1005 as if they applied to the Stipulated Penalties or exclusion sought pursuant to this CIA. Specifically, OIG's determination to demand payment of Stipulated Penalties or to seek exclusion shall be subject to review by an HHS ALJ and, in the event of an appeal, the HHS Departmental Appeals Board (DAB), in a manner consistent with the provisions in 42 C.F.R. § 1005.2-1005.21. Notwithstanding the language in 42 C.F.R. § 1005.2(c), the request for a hearing involving Stipulated Penalties shall be made within 10 days after receipt of the Demand Letter and the request for a hearing involving exclusion shall be made within 25 days after receipt of the Exclusion Letter.

2. *Stipulated Penalties Review*. Notwithstanding any provision of Title 42 of the United States Code or Title 42 of the Code of Federal Regulations, the only issues in a proceeding for Stipulated Penalties under this CIA shall be: (a) whether Abbott was in full and timely compliance with the obligations of this CIA for which OIG demands payment; and (b) the period of noncompliance. Abbott shall have the burden of proving its full and timely compliance and the steps taken to cure the noncompliance, if any. OIG shall not have the right to appeal to the DAB an adverse ALJ decision related to Stipulated Penalties. If the ALJ agrees with OIG with regard to a finding of a breach of this CIA and orders Abbott to pay Stipulated Penalties, such Stipulated Penalties shall become due and payable 20 days after the ALJ issues such a decision unless Abbott requests review of the ALJ decision by the DAB. If the ALJ decision is properly

appealed to the DAB and the DAB upholds the determination of OIG, the Stipulated Penalties shall become due and payable 20 days after the DAB issues its decision.

3. *Exclusion Review.* Notwithstanding any provision of Title 42 of the United States Code or Title 42 of the Code of Federal Regulations, the only issues in a proceeding for exclusion based on a material breach of this CIA shall be:

a. whether Abbott was in material breach of this CIA;

b. whether such breach was continuing on the date of the Exclusion Letter; and

c. whether the alleged material breach could not have been cured within the 30-day period, but that: (i) Abbott had begun to take action to cure the material breach within that period; (ii) Abbott has pursued and is pursuing such action with due diligence; and (iii) Abbott provided to OIG within that period a reasonable timetable for curing the material breach and Abbott has followed the timetable.

For purposes of the exclusion herein, exclusion shall take effect only after an ALJ decision favorable to OIG, or, if the ALJ rules for Abbott, only after a DAB decision in favor of OIG. Abbott's election of its contractual right to appeal to the DAB shall not abrogate OIG's authority to exclude Abbott upon the issuance of an ALJ's decision in favor of OIG. If the ALJ sustains the determination of OIG and determines that exclusion is authorized, such exclusion shall take effect 20 days after the ALJ issues such a decision, notwithstanding that Abbott may request review of the ALJ decision by the DAB. If the DAB finds in favor of OIG after an ALJ decision adverse to OIG, the exclusion shall take effect 20 days after the DAB decision. Abbott shall waive its right to any notice of such an exclusion if a decision upholding the exclusion is rendered by the ALJ or DAB. If the DAB finds in favor of Abbott, Abbott shall be reinstated effective on the date of the original exclusion.

4. *Finality of Decision.* The review by an ALJ or DAB provided for above shall not be considered to be an appeal right arising under any statutes or regulations. Consequently, the parties to this CIA agree that the DAB's decision (or the ALJ's decision if not appealed) shall be considered final for all purposes under this CIA.

XI. EFFECTIVE AND BINDING AGREEMENT

Abbott and OIG agree as follows:

A. Except as provided in clause F below, this CIA shall be binding on the successors, assigns, and transferees of Abbott;

B. This CIA shall become final and binding on the date the final signature is obtained on the CIA;

C. This CIA constitutes the complete agreement between the parties and may not be amended except by written consent of the parties to this CIA;

D. The undersigned Abbott signatories represent and warrant that they are authorized to execute this CIA. The undersigned OIG signatory represents that he is signing this CIA in his official capacity and that he is authorized to execute this CIA.

E. This CIA may be executed in counterparts, each of which constitutes an original and all of which constitute one and the same CIA. Facsimiles of signatures shall constitute acceptable, binding signatures for purposes of this CIA.

F. If, in connection with the Transaction, Abbott causes the Pharmaceutical Company to expressly agree to be bound by all of the terms and conditions of, and to assume all the obligations of Abbott under, this CIA, then the Transaction shall automatically, and without any further action by Abbott, the Diversified Company, the Pharmaceutical Company, the OIG, the United States or any instrumentality thereof, effect a novation of this CIA as of the Effective Time of the Transaction, with the Pharmaceutical Company becoming the party to and replacing Abbott in all respects under this CIA, whereupon the Pharmaceutical Company shall be fully responsible for complying with the CIA, and neither Abbott nor the Diversified Company shall have any obligation or liability under this CIA whatsoever.

ON BEHALF OF ABBOTT LABORATORIES

Robert E Funck

5/4/12

ROBERT E. FUNCK
Vice President, Chief Ethics and
Compliance Officer
Abbott Laboratories

DATE

5/4/12

ETHAN M. POSNER, ESQ.
Covington & Burling
Counsel for Abbott Laboratories

DATE

ON BEHALF OF THE OFFICE OF INSPECTOR GENERAL OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES

5/6/12

GREGORY E. DEMSKE
Chief Counsel to the Inspector General
Office of Inspector General
U. S. Department of Health and Human Services

DATE

Mary E. Riordan

5/7/12

MARY E. RIORDAN
Senior Counsel
Office of Inspector General
U. S. Department of Health and Human Services

DATE

5/7/12

GREGORY LINDQUIST
Associate Counsel
Office of Inspector General
U. S. Department of Health and Human Services

DATE

Appendix A to Corporate Integrity Agreement

Independent Review Organization

This Appendix contains the requirements relating to the Independent Review Organization (IRO) required by Section III.E of the CIA.

A. IRO Engagement.

Abbott shall engage an IRO (or IRO(s)) that possesses the qualifications set forth in Paragraph B, below, to perform the responsibilities in Paragraph C, below. The IRO shall conduct the review in a professionally independent and objective fashion, as set forth in Paragraph D. Within 30 days after OIG receives the information identified in Section V.A.10 of the CIA or any additional information submitted by Abbott in response to a request by OIG, whichever is later, OIG will notify Abbott if the IRO is unacceptable. Absent notification from OIG that the IRO is unacceptable, Abbott may continue to engage the IRO.

If Abbott engages a new IRO during the term of the CIA, this IRO shall also meet the requirements of this Appendix. If a new IRO is engaged, Abbott shall submit the information identified in Section V.A.10 of the CIA to OIG within 30 days of engagement of the IRO. Within 30 days after OIG receives this information or any additional information submitted by Abbott at the request of OIG, whichever is later, OIG will notify Abbott if the IRO is unacceptable. Absent notification from OIG that the IRO is unacceptable, Abbott may continue to engage the IRO.

B. IRO Qualifications.

The IRO shall:

1. assign individuals to conduct the IRO Reviews who have expertise in the pharmaceutical industry and have expertise in applicable Federal health care program and FDA requirements that relate to the Covered IRO Functions, including expertise relating to research regarding pharmaceutical products , publication activities associated with such research, and marketing and promotional activities associated with pharmaceutical products. The assigned individuals shall be experienced in risk identification and mitigation in relation to pharmaceutical product marketing and promotion. The assigned individuals also shall be knowledgeable about the general requirements of the Federal health care programs under which Abbott products are reimbursed;

2. assign individuals to design and select the samples for the IRO Transactions Reviews who are knowledgeable about appropriate statistical sampling techniques; and

3. have sufficient staff and resources to conduct the reviews required by the CIA on a timely basis.

C. IRO Responsibilities.

The IRO shall:

1. perform each component of each IRO Review in accordance with the specific requirements of the CIA;

2. follow all applicable Federal health care program and FDA requirements in making assessments in each IRO Review;

3. if in doubt of the application of a particular Federal health care program or FDA requirement, request clarification from the appropriate authority (e.g., CMS or FDA);

4. respond to all OIG inquiries in a prompt, objective, and factual manner; and

5. prepare timely, clear, well-written reports that include all the information required by Appendix B to the CIA.

D. Independence and Objectivity.

The IRO must perform the IRO Reviews in a professionally independent and objective fashion, as defined in the most recent Government Auditing Standards issued by the United States Government Accountability Office.

E. IRO Removal/Termination.

1. *Abbott Termination of IRO.* If Abbott terminates its IRO or if the IRO withdraws from the engagement during the term of the CIA, Abbott must submit a notice explaining its reasons for termination or the reason for withdrawal to OIG no later than 30 days after termination or withdrawal. Abbott must engage a new IRO in accordance with Paragraph A of this Appendix and within 60 days of the termination or withdrawal of the IRO.

2. *OIG Removal of IRO.* In the event OIG has reason to believe that the IRO does not possess the qualifications described in Paragraph B, is not independent and/or objective as set forth in Paragraph D, or has failed to carry out its responsibilities as described in Paragraph C, OIG may, at its sole discretion, require Abbott to engage a new

IRO in accordance with Paragraph A of this Appendix. Abbott must engage a new IRO within 60 days of termination of the IRO.

Prior to requiring Abbott to engage a new IRO, OIG shall notify Abbott of its intent to do so and provide a written explanation of why OIG believes such a step is necessary. To resolve any concerns raised by OIG, Abbott may present additional information regarding the IRO's qualifications, independence or performance of its responsibilities. OIG will attempt in good faith to resolve any differences regarding the IRO with Abbott prior to requiring Abbott to terminate the IRO. However, the final determination as to whether or not to require Abbott to engage a new IRO shall be made at the sole discretion of OIG.

APPENDIX B TO CIA FOR ABBOTT LABORATORIES

INDEPENDENT REVIEW ORGANIZATION REVIEWS

I. Covered Functions Review, General Description

As specified more fully below, Abbott shall retain an Independent Review Organization (IRO) to perform reviews (IRO Reviews) to assist Abbott in assessing and evaluating its systems, processes, policies, procedures, and practices related to certain of Abbott's Promotional Functions and Product Related Functions, including Managed Healthcare Related Functions, as well as Abbott's Risk Assessment and Mitigation Processes (collectively "Covered IRO Functions"). The IRO Review shall consist of two components - a systems review (Systems Review) and a transactions review (Transactions Review) as described more fully below. Abbott may engage, at its discretion, a single IRO to perform both components of the IRO Review provided that the entity has the necessary expertise and capabilities to perform both.

If there are no material changes in Abbott's systems, processes, policies, and procedures relating to the Covered IRO Functions, the IRO shall perform the Systems Review for the first and fourth Reporting Periods. If Abbott materially changes its systems, processes, policies, and procedures relating to the Covered IRO Functions, the IRO shall perform a Systems Review for the Reporting Period(s) in which such changes were made in addition to conducting the Review for the first and fourth Reporting Periods. The additional Systems Review(s) shall consist of: 1) an identification of the material changes; 2) an assessment of whether other systems, processes, policies, and procedures previously reported did not materially change; and 3) a review of the systems, processes, policies, and procedures that materially changed. The IRO shall conduct the Transactions Review for each Reporting Period of the CIA.

II. IRO Systems Review

A. Description of Reviewed Policies and Procedures

The Covered IRO Functions Systems Review shall be a review of Abbott's systems, processes, policies, and procedures (including the controls on those systems, processes, policies, and procedures) relating to certain of the Covered IRO Functions. Where practical, Abbott personnel may compile documentation, schedule and organize interviews, and undertake other efforts to assist the IRO in performing the Systems

Review. The IRO is not required to undertake a de novo review of the information gathered or activities undertaken by Abbott in accordance with the preceding sentence.

Specifically, the IRO shall review Abbott's systems, processes, policies, and procedures associated with the following (hereafter "Reviewed Policies and Procedures"):

1) Abbott's systems, processes, policies, and procedures applicable to the manner in which Abbott representatives (including sales representatives, marketing personnel, personnel from the Integrated Managed Healthcare group, and/or GMA departments) handle requests or inquiries relating to information about the uses of Government Reimbursed Products (including non-FDA-approved (*i.e.,* off-label) uses of Government Reimbursed Products) and the dissemination of materials relating to the uses of these products. This review shall include:

a) the manner in which Abbott sales representatives handle requests for information about off-label uses of Government Reimbursed Products (*e.g.*, by referring all such requests to GMI personnel at Abbott);

b) the manner in which GMA personnel, including those at Abbott's headquarters, handle and respond to requests for information about off-label uses of Government Reimbursed Products (including tracking the requests and using pre-approved materials for purposes of responding to the request);

c) the form and content of information and materials related to Government Reimbursed Products disseminated to physicians, pharmacists, or other health care professionals (collectively "HCPs"), and health care institutions (HCIs), payors, and formulary decision-makers by Abbott;

d) Abbott's systems, processes, policies, and procedures (including the Inquiries Database) to track requests for information about off-label uses of products and responses to those requests;

e) the manner in which Abbott collects and supports information reported in any systems used to track and respond to requests for product information, including its Inquiries Database;

f) the processes and procedures by which GMI, the Office of Ethics and Compliance, or other appropriate individuals within Abbott identify situations in which it appears that off-label or other improper promotion may have occurred; and

g) Abbott's processes and procedures for investigating, documenting, resolving, and taking appropriate disciplinary action for potential situations involving improper promotion.

2) Abbott's systems, processes, policies, and procedures applicable to the manner and circumstances under which its GMA personnel (including any medical science liaisons, clinical executives, or analogous personnel) participate in meetings or events with HCPs or HCIs (either alone or with sales representatives) regarding Government Reimbursed Products and the role of the medical personnel at such meetings or events;

3) Abbott's systems, processes, policies, and procedures relating to Abbott's internal review of promotional materials related to Government Reimbursed Products disseminated to HCPs, HCIs and government payors and individuals or entities acting on behalf of HCPs or HCIs;

4) Abbott's systems, policies, processes and procedures relating to incentive compensation for Relevant Covered Persons who are sales representatives, with regard to whether the systems, policies, processes, and procedures are designed to ensure that financial incentives do not inappropriately motivate such individuals to engage in the improper promotion, sales, and marketing of Government Reimbursed Products. This shall include a review of the bases upon which compensation is determined and the extent to which compensation is based on product performance. To the extent that Abbott establishes different methods of compensation for different Government Reimbursed Products, the IRO shall review each type of compensation arrangement separately;

5) Abbott's systems, processes, policies, and procedures relating to the development and review of call plans (as defined in Section III.B.3.g of the

CIA) for Government Reimbursed Products. This shall include a review of the bases upon which HCPs and HCIs belonging to specified medical specialties are included in, or excluded from, the call plans based on expected utilization of Government Reimbursed Products for FDA-approved uses or non-FDA-approved uses;

6) Abbott's systems, processes, policies, and procedures relating to Sample Distribution Plans (as defined in Section III.B.3.h of the CIA). This shall include a review of the bases upon, and circumstances under, which HCPs and HCIs belonging to specified medical specialties or types of clinical practice may receive samples from Abbott (including, separately, from Abbott sales representatives and other Abbott personnel or components). It shall also include a review of whether samples of Products are distributed by Abbott through sales representatives or are distributed from a central location and the rationale for the manner of distribution;

7) Abbott's systems (including any centralized electronic systems), processes, policies, and procedures relating to PPG speaker programs, speaker training programs, and all events and expenses relating to such engagements or arrangements;

8) Abbott's systems, processes, policies, and procedures relating to non-speaker related consultant or other fee-for-service arrangements PPG entered into with HCPs or HCIs as defined in Section III.L.1 of the CIA) and all events and expenses relating to such engagements and arrangements;

9) Abbott's systems, processes, policies, and procedures relating to Abbott's funding, directly or indirectly, of Third Party Educational Activities (as defined in Section II.C.9 of the CIA) and all events and expenses relating to such activities;

10) Abbott's systems, processes, policies, and procedures relating to the submission of information about any Government Reimbursed Product to any compendia such as Drugdex or other published source of information used in connection with the determination of coverage by a Federal health care program for the product ("Compendia"). This includes any initial submission of information to any Compendia and the submission of any

additional, updated, supplemental, or changed information, (e.g., any changes based on Abbott's discovery of erroneous or scientifically unsound information or data associated with the information in the Compendia). The review shall also assess Abbott's processes relating to its annual review of all arrangements, processing fees, or other payments or financial support (if any) provided to any Compendia;

11) Abbott's systems, processes, policies, and procedures relating to sponsorship of Research, as defined in Section III.B.3.q and Section III.L.2 of the CIA, and to Publication Activities as defined in Section III.L.3 of the CIA including the decision to provide financial or other support for such research; the manner in which support is provided for such research; and publication activities associated with research, including the publication of information about the trial outcomes;

12) Abbott's systems, processes, policies and procedures relating to authorship of any articles or other publications about Government Reimbursed Products or therapeutic areas or disease states that may be treated with Government Reimbursed Products, as defined in Section III.B.3.r and Section III.L.3 of the CIA, including, but not limited to, the disclosure of any and all relationships between the author and Abbott, the identification of all authors or contributors (including professional writers, if any) associated with a given publication, and the scope and breadth of research results made available to each author or contributor;

13) Abbott's systems, policies, processes, and procedures applicable to the manner and circumstances under which PPG personnel (including sales representatives, medical science liaisons, or analogous personnel) participate in meetings with government payors, pharmacy benefit managers (PBMs), or other individuals or entities under contract with or acting on behalf of government payors (collectively, "Government payors") regarding Government Reimbursed Products and the role of the Abbott personnel at such meetings;

14) the form and content of information and materials disseminated by Abbott to Government payors and Abbott's systems, policies, processes, and procedures relating to Abbott's internal review and approval of

information and materials related to Government Reimbursed Products disseminated to Government payors by Abbott; and

15) Abbott's systems, processes, policies and procedures relating to Risk Assessment and Mitigation Processes, as defined in Section III.D of the CIA. This shall include a review of the processes for developing, maintaining and using the regulatory history documents for Government Reimbursed Products, and the processes and standards relating to the conduct of the PPD Material Review Board, PPD Management Review, PPG Safety Review Board and PPG Safety Council meetings. This review shall include:

a) a review of the systems, standards, and processes for developing, maintaining and using the regulatory history documents and a review of the type of information included in regulatory history documents to assess whether those systems, standards, and processes are resulting in documents that contain the appropriate information to assist in the identification of potential promotional risks associated with the product;

b) a review of the functional areas of the Abbott organization that participate in the PPD Review Board, PPD Management Review, PPG Safety Review Board, and PPG Safety Council meetings and the information considered during each respective type of meeting to assess whether each type of cross-functional board or group is provided the appropriate responsibilities and sources of information to identify potential risks associated with Government Reimbursed Products and Abbott activities relating to such products;

c) a review of the systems, standards, and processes used by the PPD Review Board, PPD Management Review, PPG Safety Review Board, and PPG Safety Council to generate follow-up action items for identified risks associated with Government Reimbursed Products and Abbott activities relating to such products to assess how follow-up or action items are generated for identified risks and whether additional follow-up or action items would be appropriate; and

d) a review of the systems, standards, and processes used by the PPD Review Board, PPD Management Review, PPG Safety Review Board, and PPG Safety Council to track and manage follow-up or action items to assess whether all such items are appropriately tracked and implemented or resolved, including identifying individuals responsible for the follow-up or action item.

B. IRO Systems Review Report

The IRO shall prepare a report based upon each Systems Review. For each of the Reviewed Policies and Procedures identified in Section II.A above, the report shall include the following items:

1) a description of the documentation (including policies) reviewed and any personnel interviewed;

2) a detailed description of Abbott's systems, policies, processes, and procedures relating to the items identified in Sections II.A.1-15 above, including a general description of Abbott's control and accountability systems (e.g., documentation and approval requirements, and tracking mechanisms) and written policies regarding the Reviewed Policies and Procedures;

3) a description of the manner in which the control and accountability systems and the written policies relating to the items identified in Sections II.A.1-15 above are made known or disseminated within Abbott;

4) a detailed description of any system(s) used to track and respond to requests for information about Government Reimbursed Products (including the Inquiries Database);

5) findings and supporting rationale regarding any weaknesses in Abbott's systems, processes, policies, and procedures relating to the Reviewed Policies and Procedures, if any; and

6) recommendations to improve any of the systems, policies, processes, or procedures relating to the Reviewed Policies and Procedures, if any.

III. IRO Transaction Review

As described more fully below in Sections III.A-F, the Transactions Review shall include: (1) a review of Abbott's call plans and Abbott's call plan review process; (2) a review of Sampling Events as defined below in Section III.B; (3) a review of records relating to a sample of the Payments that are reported by Abbott pursuant to Section III.N of the CIA; (4) a review of records relating to Abbott's Risk Assessment and Mitigation Processes; (5) a review of Research and Publications Activities as set forth below in Section III.D; and (6) a review of up to three additional items identified by the OIG in accordance with Section III.E.1.b of the CIA (hereafter "Additional Items"). The IRO shall report on all aspects of its reviews.

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A. IRO Review of Abbott's Call Plans and Call Plan Review Process

The IRO shall conduct a review and assessment of Abbott's review of its call plans for Government Reimbursed Products as set forth in Section III.B.3.g of the CIA. Abbott shall provide the IRO with: i) a list of Government Reimbursed Products promoted by Abbott during the Reporting Period; ii) information about the FDA-approved uses for each such product; and iii) the call plans for each such product. Abbott shall also provide the IRO with information about the reviews of call plans that Abbott conducted during the Reporting Period and any modifications to the call plans made as a result of Abbott's reviews.

For each call plan, the IRO shall select a sample of 50 of the HCPs and HCIs included on the call plan. For each call plan, the IRO shall compare the sampled HCPs and HCIs against the criteria (e.g., medical specialty or practice area) used by Abbott in conducting its review and/or modifying the call plan. The IRO shall seek to determine whether Abbott followed its criteria and Policies and Procedures in reviewing and modifying the call plan.

The IRO shall note any instances in which it appears that the sampled HCPs or HCIs on a particular call plan are inconsistent with Abbott's criteria relating to the call plan and/or Abbott's Policies and Procedures. The IRO shall also note any instances in which it appears that Abbott failed to follow its criteria or Policies and Procedures.

B. IRO Review of the Distribution of Samples of Abbott Government Reimbursed Products

The IRO shall conduct a review and assessment of the distribution of samples of Government Reimbursed Products to HCPs and HCIs. Abbott shall provide the IRO with: i) a list of Government Reimbursed Products for which Abbott distributed samples during the Reporting Period; ii) information about the FDA-approved uses for each such product; and iii) information about Abbott's policies and procedures relating to the distribution of samples of each type of product, including Abbott's Sample Distribution Plan showing which types of samples may be distributed by sales representatives to HCPs and HCIs of particular medical specialties or types of clinical practices. Abbott shall also provide the IRO with information about the reviews of Sample Distribution Plans that Abbott conducted during the Reporting Period as set forth in Section III.B.3.h of the CIA and any modifications to the distribution plans made as a result of Abbott's reviews.

For each Government Reimbursed Product for which Abbott distributed samples during the Reporting Period, the IRO shall randomly select a sample of 50 separate instances in which Abbott provided samples of the product to HCPs or HCIs. Each such instance shall be known as a "Sampling Event."

For each Sampling Event, the IRO shall review all documents and information relating to the distribution of the sample to the HCP or HCI. The reviewed materials shall include materials about the following: 1) the quantity, dosage, and form of the Abbott product provided to the HCP or HCI; 2) the identity and type of medical specialty or clinical practice of the HCP or HCI; 3) which individual Abbott sales representative or department provided the sample to the HCP or HCI; and 4) the manner and mechanism through which the sample was requested (e.g., sample request form, letter or call to Sample Operations).

For each Sampling Event, the IRO shall evaluate whether the sample was provided to an HCP or HCI whose medical specialty or clinical practice is consistent with the uses of the Government Reimbursed Product approved by the FDA and whether the sample was distributed by an Abbott representative in a manner consistent with Abbott's sample distribution policy for the product(s) provided during the Sampling Event. To the extent that a sample was provided to an HCP or HCI by an Abbott representative other than a sales representative, the IRO shall contact the HCP or HCI by letter. The letter shall request that the HCP or HCI: 1) verify that he/she/it received the quantity and type of samples identified by the IRO as the Sampling Event; 2) verify that he/she/it requested the samples provided during the Sampling Event; 3) explain or confirm its type of medical specialty or clinical practice; and 4) identify the basis for requesting the sample (e.g., conversations with a Abbott sales representative, conversation with a representative

of Abbott's GMI department, independent research or knowledge of the HCP or HCI, etc.).

For each Sampling Event, the IRO shall compare the medical specialty and type of clinical practice of the HCPs and HCIs that received the sample with uses of the Government Reimbursed Product approved by the FDA. The IRO shall note any instances in which it appears that the medical specialty or clinical practice of the HCPs or HCIs that received a sample during a Sampling Event were not consistent with the uses of the Government Reimbursed Product approved by the FDA. For each such situation, the IRO shall note the process followed by Abbott in determining that it was appropriate to provide a sample to such HCP or HCI and the basis for such determination. The IRO shall also note any instances in which it appears that Abbott failed to follow its Sample Distribution Plan for the Government Reimbursed Products (s) provided during the Sampling Event.

C. IRO Review of Physician Payment Listings

1. Information Contained in Physician Payment Listings

For purposes of the IRO review as set forth in this Section III.C, each annual listing of physicians and Related Entities who received Payments (as defined in Section III.N of the CIA) from PPG shall be referred to as the "Physician Payment Listing" or "Listing." For each physician and Related Entity, each Physician Payment Listing shall include the following information: i) physician's full name; ii) name of Related Entity (if applicable); iii) city and state of the physician's practice or the Related Entity; and (iv) the aggregate value of the Payment(s) in the preceding year(s).

For purposes of this IRO review, the term "Control Documents" shall include all documents or electronic records associated with each Payment reflected in the Physician Payments Listing for a sampled physician and/or Related Entity. For example, the term "Control Documents" includes, but is not limited to, documents relating to the nature, purpose, and amount of all Payments reflected in the Listing; contracts relating to the Payment(s) reflected in the Listing; documents relating to the occurrence of Payment(s) reflected in the Listing; documents reflecting any work product generated in connection with the Payment(s); documents submitted by sales representatives or headquarters personnel to request approval for the Payment(s); and business rationale or justification forms relating to the Payment(s).

2. Selection of Sample for Review

For each Reporting Period, the OIG shall have the discretion to identify up to 50 physicians or Related Entities from the applicable Physician Payment Listing that will be subject to the IRO review described below. If the OIG elects to exercise this discretion, it shall notify the IRO at least 90 days prior to the end of the Reporting Period, of the physicians and/or Related Entities subject to the IRO review. If the OIG elects not to exercise its discretion as described above, the IRO shall randomly select 50 physicians and/or Related Entities to be included in the review. For each selected physician and/or Related Entity, the IRO shall review the entry in the Physician Payment Listing and the Control Documents relating to Payments reflected in the Listing identified by the IRO as necessary and sufficient to validate the Payment information in the Listing.

3. IRO Review of Control Documents for Selected Physicians and/or Related Entities

For each physician and/or Related Entity selected as part of the sample, the IRO shall review the Control Documents identified by the IRO as necessary and sufficient to validate each Payment reflected in the Listing to evaluate the following:

a) Whether Control Documents are available relating to each Payment reflected in the Listing for the sampled physician and/or Related Entity;

b) Whether the Control Documents were completed and archived in accordance with the requirements set forth in Abbott's policies;

c) Whether the aggregate value of the Payment(s) as reflected in the Listing for the sampled Physician is consistent with the value of the Payments(s) reflected in the Control Documents; and

d) Whether the Control Documents reflect that Abbott's policies were followed in connection with Payment(s) reflected in the Listing (e.g., all required written approvals for the activity were obtained in accordance with Abbott's policies).

4. Identification of Material Errors and Additional Review

A Material Error is defined as any of the following:

a) A situation in which all required Control Documents relating to Payments reflected in the Listing for the sampled physician and/or Related Entity do not exist and:

i. no corrective action was initiated prior to the selection of the sampled physicians and/or Related Entities; or

ii. the IRO cannot confirm that Abbott otherwise followed its policies and procedures relating to the entry in the Listing for the sampled physician or Related Entity, including its policies and procedures relating to any Payment(s) reflected in the Listing; or

b) Information or data is omitted from key fields in the Control Documents that prevents the IRO from assessing compliance with Abbott's policies and procedures, and the IRO cannot obtain this information or data from reviewing other Control Documents.

If a Control Document does not exist, but Abbott has initiated corrective action prior to the selection of the sampled physicians and/or Related Entities, or if a Control Document does not exist but the IRO can determine that Abbott otherwise followed its policies and procedures with regard to each entry in the Listing for a sampled physician or Related Entity, the IRO shall consider such a situation to be an exception (rather than a Material Error) and the IRO shall report the situation as such. Similarly, the IRO shall note as exceptions any Control Documents for which non-material information or data is omitted.

If the IRO identifies any Material Errors, the IRO shall conduct such Additional Review of the underlying Payment associated with the erroneous Control Documents as may be necessary to determine the root cause of the Material Errors. For example, the IRO may need to review additional documentation and/or conduct interviews with appropriate personnel to identify the root cause of the Material Error(s) discovered.

D. IRO Review of Risk Assessment and Mitigation Processes

As described briefly in Section III.D of the CIA, Abbott implemented certain standardized risk assessment and mitigation standards, processes, and practices that are collectively known as the "Risk Assessment and Mitigation Processes". Abbott's Risk Assessment and Mitigation Processes include:

1) regulatory history documents developed by Regulatory Affairs and used by Regulatory Affairs, Medical, Marketing and/or Legal functions to identify and mitigate potential promotional risks associated with actively promoted Government Reimbursed Products. These documents contain the relevant regulatory history relating to advertising and promotion of the Government Reimbursed Product, including agency feedback, product labeling history, and FDA enforcement activity (if any) with respect to the product and/or the product class;

2) activities of the PPD Material Review Board, which conducts cross-functional reviews (by Medical, Regulatory Affairs, Marketing Operations, Commercial and Quality Assurance) of certain promotional and non-promotional materials;

3) activities of the PPD Management Review Board, which is a management level forum that reviews the outcomes of PPD Material Review Board meetings and identifies additional action items as appropriate and includes members from Quality and Regulatory. Responsibilities include review of contact from relevant government agencies;

4) activities of the PPG Safety Review Board, which oversees cross-functional activities related to PPG products and monitors operational performance relevant to drug safety. Members include senior representatives from Pharmacovigilance, Clinical Development and Regulatory Affairs; and

5) activities of the PPG Safety Council, which provides PPG management oversight, governance, and review of significant safety issues involving PPG products. Members include senior management of Research & Development, Regulatory Affairs and Legal Regulatory & Compliance.

Regulatory Affairs and/or Quality are represented in all of the above-referenced review teams. Based on the outcomes of these Risk Assessment and Mitigation

Processes, PPG develops and implements actions designed to mitigate any identified risks. Abbott shall maintain these or equivalent standards, processes, and practices throughout the term of the CIA.

The IRO shall conduct annual reviews and assessments of Abbott's Risk Assessment and Mitigation Processes. In connection with the IRO review, Abbott shall provide the IRO with a list of Government Reimbursed Products promoted by Abbott during the Reporting Period and a list of PPD Material Review Board, PPD Management Review, PPG Safety Review Board and PPG Safety Council meetings that occurred during the Reporting Period. At least 120 days prior to the end of the Reporting Period, Abbott shall provide to OIG a list of Government Reimbursed Products promoted by Abbott. OIG shall have the option to select and notify Abbott (no later than 90 days prior to the end of the Reporting Period) of three Government Reimbursed Products to be reviewed by the IRO in connection with the review of the Risk Assessment and Mitigation Process. If OIG does not identify products for review, the IRO shall select the products to be reviewed.

For each Reporting Period, the IRO will review the following records with respect to each of the following elements of the Risk Assessment and Mitigation Processes:

1) Regulatory history documents: with respect to three (3) currently promoted Government Reimbursed Products and a sample of ten (10) promotional materials related to each product that were approved during the Reporting Period and which are currently in use, the IRO will review whether: (a) there is an approved regulatory history document; (b) the regulatory history document has been reviewed by Regulatory Affairs at least annually to ensure it is complete and current; (c) required training on the regulatory history documents has been provided to Covered Persons responsible for creating, reviewing and/or approving proposed promotional materials related to Government Reimbursed Products; and (d) for the selected promotional materials, there is documentation showing that the regulatory history documents were used as required by existing policies and procedures.

2) PPD Material Review Board: the IRO will review whether: (a) meetings of the PPD Material Review Board took place as per policies and procedures; (b) agendas and meeting minutes were prepared and retained; (c) materials or other documentation were presented at or reviewed in the

meeting(s); and (d) follow up or action items were identified and, if so, were acted upon and/or resolved.

3) PPD Management Review: the IRO will review whether: (a) meetings of the PPD Management Review Committee took place as per policies and procedures; (b) agendas and meeting minutes were prepared and retained; (c) materials or other documentation were presented at or reviewed in the meeting(s); and (d) follow up or action items were identified and, if so, acted upon and/or resolved.

4) PPG Safety Review Board: the IRO will review whether: (a) meetings occurred as specified in the applicable policies and procedures; (b) required core members attended the meetings; (c) agendas, materials or other documentation were presented at or reviewed in the meeting(s) as per policies and procedures; (d) meeting minutes were timely published to members as per policies and procedures; (e) decisions were documented and communicated to Safety Review Board Members as per policies and procedures; (f) Issue Management Teams were formed as per procedures and, if so, whether the Team's progress was monitored; and (g) follow up or action items were identified and, if so, were acted upon and/or resolved.

5) PPG Safety Council: the IRO will review any topics referred to the Safety Council during the review period and determine whether: (a) a meeting was scheduled as per policies and procedures; (b) appropriate representatives from the key functional areas per the applicable policy (which does not include sales or marketing) attended the meeting; (c) agendas, materials or other documentation were presented at or reviewed in the meeting; (d) meeting minutes were timely published to members as required; (e) follow up or action items were identified and, if so, were documented, acted upon and/or resolved.

E. IRO Review of Research and Publications Activities

The IRO shall conduct a review and assessment of Abbott's Research and Publications Activities as described in Section III.L of the CIA.

Review of Research Activities: Abbott shall provide the IRO with a list of Research activities (as defined in Section III.B.3.q of the CIA) that occurred during the Reporting Period, and the IRO shall select a sample of 15 such activities, which sample includes a

review of each type of Research (*i.e.*, post-marketing clinical trials, investigator-initiated studies (IIS), and post-marketing observational studies.) The IRO shall review samples of each type of Research in proportion to the relative numbers of each type of Research that occurred during the reporting period. Abbott shall provide the IRO with documents relating to the Research Activities sufficient for the IRO to conduct the reviews outlined below.

For each sampled Research activity, the IRO will review whether: (i) the activity was approved consistent with Abbott's standards, policies, procedures and processes, including obtaining required medical, scientific and/or regulatory approvals to confirm the activity was reviewed to determine there is a legitimate, scientific need or merit for the activity; (ii) there is an executed written agreement with the Researcher that meets the requirements of Abbott's standards, policies and procedures; and (iii) the Research was initiated, directed and/or funded by Abbott's Global Pharmaceutical Research and Development organization pursuant to Abbott's policies.

In addition, if PPG discontinues any PPG clinical study for a Government Reimbursed Product during a Reporting Period for safety-related reasons pursuant to Abbott's policies, Abbott shall provide the IRO with copies of notifications that Abbott provided to regulatory authorities, ethics committees, and investigators about the discontinuation of the studies. The IRO shall review the notifications to determine whether Abbott notified regulatory authorities, ethics committees, and investigators in accordance with applicable Abbott standards, policies, procedures, and processes.

Review of Publication Activities: Abbott shall provide the IRO with a list of Publication Activities (as defined in Section III.L.3 of the CIA) that occurred during the Reporting Period, and the IRO shall select a sample of 20 Publication Activities for review. More specifically, the IRO shall review Publication Activities associated with 10 abstracts and 10 manuscripts. Abbott shall provide the IRO with copies of the Publications and documents relating to the Publication Activities sufficient for the IRO to conduct the review outlined below.

The IRO will review the selected Publication Activities to test whether the Publication Activity was consistent with Abbott's standards, policies, procedures and processes, including those that require: i) review and approval by PPG's medical, scientific and/or regulatory affairs organizations prior to Abbott submission to verify the content presents scientific information in a balanced way that does not exclude or inappropriately downplay negative safety or health information; ii) incorporation of ICMJE criteria for identifying Authors; iii) disclosure of financial or other support provided by Abbott; iv)

acknowledgement of other contributors; v) disclosure of potential conflicts of interest; vi) access to data; and vii) avoidance of redundant publications (unless permitted by a journal/congress or otherwise of scientific value).

F. IRO Review of Additional Items

As set forth in Section III.E.1.b of the CIA, for each Reporting Period, the OIG at its discretion may identify up to three additional items for the IRO to review (hereafter "Additional Items"). No later than 150 days prior to the end of the applicable Reporting Period, the OIG shall notify Abbott of the nature and scope of the IRO review to be conducted for each of the Additional Items. Prior to undertaking the review of the Additional Items, the IRO and/or Abbott shall submit an audit work plan to the OIG for approval and the IRO shall conduct the review of the Additional Items based on a work plan approved by the OIG. The IRO shall include information about its review of each Additional Item in the Transactions Review Report (including a description of the review conducted for each Additional Item; the IRO's findings based on its review for each Additional Item; and the IRO's recommendations for any changes in Abbott's systems, processes, policies, and procedures based on its review of each Additional Item).

Abbott may propose to the OIG that its internal audit(s) and/or reviews conducted as part of the Field Force Monitoring Program described in Section III.K of the CIA or the Monitoring of Non-Promotional Activities Program described in Section III.L of the CIA be substituted, subject to the Verification Review requirements set forth below, for one or more of the Additional Items that would otherwise be reviewed by the IRO for the applicable Reporting Period. The OIG retains sole discretion over whether, and in what manner, to allow Abbott's internal audit work and monitoring activities to be substituted for a portion of the Additional Items review conducted by the IRO.

In making its decision, the OIG agrees to consider, among other factors, the nature and scope of Abbott's planned internal audit work and monitoring activities, the results of the Transactions Review(s) during prior Reporting Period(s), and Abbott's demonstrated audit capabilities to perform the proposed audit work internally. If the OIG denies Abbott's request to permit its internal audit work or monitoring activities to be substituted for a portion of the IRO's review of Additional Items in a given Reporting Period, Abbott shall engage the IRO to perform the Review as outlined in this Section III.

If the OIG agrees to permit certain of Abbott's internal audit work for a given Reporting Period to be substituted for a portion of Additional Items review, such internal work would be subject to verification by the IRO (Verification Review). In such an

instance, the OIG would provide additional details about the scope of the Verification Review to be conducted by the IRO. However, for purposes of any Verification Review, the IRO shall review at least 20% of the sampling units reviewed by Abbott in its internal audits.

G. Transactions Review Report

For each Reporting Period, the IRO shall prepare a report based on its Transactions Review. The report shall include the following:

1) General Elements to Be Included in Report

a) Review Objectives: A clear statement of the objectives intended to be achieved by each part of the review;

b) Review Protocol: A detailed narrative description of the procedures performed and a description of the sampling unit and universe utilized in performing the procedures for each sample reviewed; and

c) Sources of Data: A full description of documentation and other information, if applicable, relied upon by the IRO in performing the Transactions Review.

2) Results to be Included in Report

The following results shall be included in each Transaction Review Report:

(Relating to the Call Plan Reviews)

a) a list of the Government Reimbursed Products promoted by Abbott during the Reporting Period and a summary of the FDA-approved uses for such products;

b) for each Government Reimbursed Product which was promoted during the Reporting Period: i) a description of the criteria used by Abbott in developing or reviewing the call plans and for including or excluding specified types of HCPs or HCIs from the call plans; ii) a description of the review

conducted by Abbott of the call plans and an indication of whether Abbott reviewed the call plans as required by Section III.B.3.g of the CIA; iii) a description of all instances for each call plan in which it appears that the HCPs and HCIs included on the call plan are inconsistent with Abbott's criteria relating to the call plan and/or Abbott's Policies and Procedures; and iv) a description of all instances in which it appears that Abbott failed to follow its criteria or Policies and Procedures relating to call plans or the review of the call plans;

c) the findings and supporting rationale regarding any weaknesses in Abbott's systems, processes, policies, procedures, and practices relating to Abbott's call plans or the review of the call plans, if any;

d) recommendations, if any, for changes in Abbott's systems, processes, policies, procedures, and practices that would correct or address any weaknesses or deficiencies uncovered during the Transactions Review with respect to call plans or the review of the call plans;

(Relating to the Sampling Event Reviews)

e) for each Government Reimbursed Product distributed during the Reporting Period: i) a description of Sample Distribution Plan (including whether sales representatives may provide samples for the product and, if so, to HCPs or HCIs of which medical specialty or type of clinical practice a sales representative may provide samples); ii) a detailed description of any instances in which it appears that the medical specialty or clinical practice of the HCPs or HCIs that received a sample during a Sampling Event was not consistent with the uses of the product approved by the FDA. This description shall include a description of the process followed by Abbott in determining that it was appropriate to provide a sample to such HCP or HCI and the basis for such determination; and iii) a detailed description of any instances in which it appears that Abbott failed to follow its Sample Distribution Plan for

the Government Reimbursed Product(s) provided during the Sampling Event;

f) the findings and supporting rationale regarding any weaknesses in Abbott's systems, processes, policies, procedures, and practices relating to Abbott's distribution of samples of Government Reimbursed Products, if any;

g) recommendations, if any, for changes in Abbott's systems, processes, policies, procedures, and practices that would correct or address any weaknesses or deficiencies uncovered during the Transactions Review with respect to the distribution of samples;

(Relating to the Physician Payment Listing Reviews)

h) a description of the entries in the Physician Payment Listing for each physician or Related Entity sampled and a description of Control Documents reviewed in connection with each selected physician or Related Entity;

i) for each sampled physician or Related Entity, findings and supporting rationale as to whether: (i) all required Control Documents exist; (ii) each Control Document was completed in accordance with all of the requirements set forth in the applicable Abbott policy; (iii) the aggregate value of the Payment(s) as reflected in the Listing for the sampled physician or entity is consistent with the value of the Payment(s) reflected in the Control Documents; (iv) each Control Document reflects that Abbott's policies were followed in connection with the underlying activity reflected in the document (e.g., all required approvals were obtained); and (v) disciplinary action was undertaken in those instances in which Abbott policies were not followed;

j) for each sampled physician or Related Entity unit reviewed, an identification and description of all exceptions discovered. The report shall also describe those instances in which corrective action was initiated prior to the selection of the

sampled physicians or Related Entities, including a description of the circumstances requiring corrective action and the nature of the corrective action;

k) if any Material Errors are discovered in any sample unit reviewed, a description of the error, the Additional Review procedures performed and a statement of findings as to the root cause(s) of the Material Error;

(Relating to the Review of Risk Assessment Mitigation Processes)

l) a list of Government Reimbursed Products promoted by Abbott during the Reporting Period; an identification of the three Government Reimbursed Products for which regulatory history documents and associated promotional materials were reviewed by the IRO for the reporting period; and a description of the promotional materials that were reviewed for each of the three Government Reimbursed Products;

m) a list of the PPD Material Review Board, PPD Management Review, PPG Safety Review Board and PPG Safety Council meetings that occurred during the Reporting Period; a description of the types of materials that were reviewed in connection with the meetings for each board or group; a description of the types of risks that may have been identified during the meetings; and a description of the types of follow-up or action items that may have been reviewed and/or identified during the meetings;

n) for each set of PPD Material Review Board, PPD Management Review, PPG Safety Review Board and PPG Safety Council meetings for which follow-up or action items were identified as a way to address identified risks, whether the follow-up or action items were completed and/or addressed;

o) for each set of regulatory history documents reviewed (including associated promotional materials) and each set of PPD Material Review Board, PPD Management Review, PPG Safety Review Board and PPG Safety Council meetings

reviewed, an identification and description of all instances in which required activity was not completed in accordance with applicable Abbott standards, policies, procedures and processes (including an explanation of the way in which the activity failed to meet Abbott standards, policies, procedures, and processes);

p) for each set of regulatory history documents reviewed (including associated promotional materials) and each set of PPD Material Review Board, PPD Management Review, PPG Safety Review Board and PPG Safety Council meetings reviewed, the IRO's findings and supporting rationale regarding any weaknesses or deficiencies in Abbott's systems, processes, policies, procedures, and practices relating to the Risk Assessment and Mitigation Processes, if any;

q) recommendations, if any, for changes in Abbott's systems, processes, policies, procedures, and practices that would correct or address any weaknesses or deficiencies uncovered during the Transactions Review with respect to the Risk Assessment and Mitigation Processes;

(Relating to the Review of Research and Publication Activities)

r) a description of each Research Activity reviewed, including an identification of the types of documents and information reviewed in connection with each sampled Research Activity and an assessment of whether the reviewed Research Activity and/or related documentation was completed in accordance with applicable Abbott standards, policies, procedures and processes;

s) for each discontinued clinical study reviewed by the IRO (if any), a description of the discontinued study; and an assessment of whether Abbott notified all regulatory authorities, ethics committees, and investigators about the discontinuation in accordance with Abbott's standards, processes and practices;

t) a description of each Publication Activity reviewed, including an identification of the types of documents and information reviewed in connection with each sampled Publication

Activity and an assessment of whether the reviewed Publication Activity and/or related documentation was completed in accordance with applicable Abbott standards, policies, procedures and processes;

u) for each Research and Publication Activity reviewed, an identification and description of all instances in which required activity and/or documentation was not completed in accordance with applicable Abbott standards, policies, procedures and processes (including an explanation of the way in which the reviewed Research or Publication Activity failed to meet Abbott standards, policies, procedures, and processes);

v) the IRO's findings and supporting rationale regarding any weaknesses or deficiencies in Abbott's systems, processes, policies, procedures, and practices relating to Abbott's Research and Publications Activities, if any;

x) recommendations, if any, for changes in Abbott's systems, processes, policies, and procedures that would correct or address any weaknesses or deficiencies uncovered during the Transactions Review with respect to Research and Publications Activities.

(Relating to the Review of Additional Items)

y) for each Additional Item reviewed, a description of the review conducted;

z) for each Additional Item reviewed, the IRO's findings based on its review;

aa) for each Additional Item reviewed, the findings and supporting rationale regarding any weaknesses in Abbott's systems, processes, policies, procedures, and practices relating to the Additional Item, if any;

bb) for each Additional Item reviewed, recommendations, if any, for changes in Abbott's systems, processes, policies, and

procedures that would correct or address any weaknesses or deficiencies uncovered during the review.