PLAINTIFFS:

3AN-06-05630CI Volume: 002
State of Alaska vs. Eli Lilly & Co
Superior Court Civil

DEFENDANTS:

Vol. 2

Begin: 5/2/07
End: 7/9/07

CIVIL

ON APPEAL
Appeal to COA/Supreme

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CASE NO. 3AN-06-5630CI

Volume No. 2

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LANE POWELL
ATTORNEYS & COUNSELORS

Brewster H. Jamieson, Esq.
Direct Dial (907) 264-3325
JamiesonB@LanePowell.com

July 9, 2007

The Honorable Mark Rindner
Superior Court Judge
Alaska Court System
825 West Fourth Avenue, Room 638
Anchorage, Alaska 99501-2004

Re: **Citation of Supplemental Authority**
State of Alaska v. Eli Lilly and Company, Case No. 3AN-06-05630 CI

Dear Judge Rindner:

This firm represents defendant Eli Lilly and Company ("Lilly") in the above-referenced matter. This letter is a citation of supplemental authority made pursuant to Civil Rule 77(l). The supplemental authority referred to herein relates to Lilly's Response to Plaintiff's Motion Concerning Claims and Proofs, pages 17-20 and 34-41, filed May 7, 2007. Oral argument on the motion is scheduled for July 12, 2007.

Attached are the following:

1. Consent Judgment, *Charles Foti, Attorney General ex rel. State of Louisiana v. Janssen Pharmaceutica, Inc., et al.*, In the Twenty-Seventh Judicial District Court in and for the Parish of St. Landry, State of Louisiana, Civil Docket Nos. 04-3967-D and 04-3977-D, filed April 10, 2007.

2. Memorandum & Order; Motions for Summary Judgment, *In re Zyprexa Products Liability Litigation*, United States District Court, Eastern District of New York, Case Nos. 04-MD-11596, 05-CV-4115, 05-CV-2948, 06-CV-0021, 06-CV-6322, signed by Judge Jack B. Weinstein on June 28, 2007.

Thank you for considering the above and the attached.

Very truly yours,

LANE POWELL LLC

Brewster H. Jamieson

AEG:lg
Enclosures
cc: Eric T. Sanders, Esq. (w/enc.) (via fax and mail)
009867.0038/161146.1

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Consent Judgment | Memo & Order | E

4-10

IN THE TWENTY-SEVENTH JUDICIAL DISTRICT COURT
IN AND FOR THE PARISH OF ST. LANDRY
STATE OF LOUISIANA

CHARLES FOTI, ATTORNEY GENERAL
EX REL. STATE OF LOUISIANA,

VERSUS

JANSSEN PHARMACEUTICA, INC., ET AL

CIVIL DOCKET NO. 04-3967-D

CONSOLIDATED WITH

CHARLES FOTI, ATTORNEY GENERAL
EX REL. STATE OF LOUISIANA

VERSUS

JANSSEN PHARMACEUTICA, INC., ET AL

CIVIL DOCKET NO. 04-3977-D

2007 MAR 10 AM 11:43

CONSENT JUDGMENT

On February 26, 2007, Defendant's Motion to Compel came for hearing before the Court:

Present were: James B. Irwin, Monique M. Garsaud, Thomas F. Campion, Brian C. Anderson and James Guglielmo, Counsel for Defendant, Janssen Pharmaceutica, Inc.

Patrick C. Morrow, Jeffrey M. Bassett, Kenneth W. Dejean, Michael W. Perrin, Counsel for Plaintiff, State of Louisiana, *Ex. Rel.* Charles Foti, Attorney General

Kimberly Sullivan, representative of State of Louisiana, Charles Foti, Attorney General

After reviewing the briefs and hearing oral argument, but before issuing a ruling, the Court deferred to the parties for a resolution. The parties propose the following resolution, which the Court accepts and ORDERS accordingly:

Copies of Defendant's interrogatories and document requests and Plaintiff's initial responses and objections thereto were attached as Exhibit A through H to Defendant's motion. Those materials, as well as three documents representing Plaintiff's Amended Responses to Defendant's discovery requests (dated February 25, 2007) have been entered into the evidentiary record pertinent to Defendant's Motion to Compel.

Defendant's Motion to Compel will be taken off the calendar without prejudice to Defendant's right to reinstate it at a later time if necessary.

Plaintiff will withdraw its previous responses and objections to Defendant's discovery requests.

Within ninety (90) days from February 26, 2007, plaintiff will serve written responses to Defendant's discovery requests that are the subject of Defendant's Motion to Compel and produce all documents within plaintiff's possession, custody or control responsive to Defendant's discovery requests.

Plaintiff's written responses will contain complete answers to all interrogatories and indicate which documents are being produced in response to Defendant's document requests.

Insofar as discovery requests from Defendant which are presently pending, should Plaintiff object on the grounds of relevance or for other reasons (except attorney-client privilege), Plaintiff shall nevertheless produce documents responsive to the request, which documents are in the possession, custody or control of Plaintiff, subject to their objections. Plaintiff will submit allegedly privileged documents for *in camera* review.

Plaintiff will undertake a complete search for responsive documents consistent with its obligation as an institutional party to litigation and, if it lacks possession, custody or control of responsive documents, shall so state with a duty to supplement such response if responsive documents are located at a later time in accordance with Louisiana Code of Civil Procedure Article 1428. If such a supplementation occurs, Plaintiff will provide the Court and the Defendant with a good faith explanation as to why such documents were not discovered and produced after the initial complete search.

Plaintiff represents that certain documents and information requested are subject to the protection of patient medication information privacy laws. The Court finds that the claims and allegations contained in this action cannot fairly and properly be litigated unless Defendant has access to (a) records concerning the Medicaid-financed prescriptions of Risperdal and other anti-psychotic medications that plaintiff contends are superior to Risperdal, and (b) medical records of Medicaid patients who were prescribed Risperdal and other anti-psychotic medications that Plaintiff contends are superior to Risperdal. Accordingly, the Court directs Plaintiff to produce all such information pursuant to the

Protective Order currently in place. The Court understands that the parties will attempt to negotiate a further Order providing for the production of medical records and individual discovery of a representative sample of persons who received Medicaid-financed anti-psychotic medications (including Risperdal). If the parties are unable to agree on a stipulated Order, they shall submit competing proposed Orders and briefs explaining same. The Court will then issue an appropriate Order.

Respectfully submitted,

Patrick C. Morrow (Bar No. 9748)
James P. Ryan (Bar No. 11560)
Jeffrey M. Bassett (Bar No. 2840)
MORROW, MORROW, RYAN & BASSETT
324 West Landry Street
Post Office Drawer 1787
Opelousas, LA 70570-1787
(337) 948-4483

Kenneth W. Dejean (Bar No. 04817)
417 West University Avenue
Lafayette, LA 70502
(337) 235-5294

Kenneth T. Fibich (Bar No. 6952600)
W. Michael Leebron (Bar No. 12149000)
1401 McKinney, Ste. 18090
Houston, TX 77110
(713) 751-0025

Michael W. Perrin
440 Louisiana Avenue, Ste. 2100
Houston, TX 77002
(713) 425-7100

Counsel for State of Louisiana, ex rel. Charles C. Foti Jr., Attorney General

James B. Irwin, T.A. (Bar No. 7172)
Quentin F. Urquhart, Jr. (Bar No. 14475)
Monique M. Garsaud (Bar No. 25393)
Camala E. Capodice (Bar No. 29117)
IRWIN FRITCHIE URQUHART & MOORE LLC
400 Poydras Street, Suite 2700
New Orleans, LA 70130
(504) 310-2100

Attorneys for Janssen Pharmaceutica Inc.

Of Counsel:
Thomas F. Campion
DRINKER BIDDLE & REATH LLP
500 Campus Drive
Florham Park, NJ 07932-1047

Brian C. Anderson
O'MELVENY & MYERS LLP
1625 Eye Street, N.W.
Washington, D.C. 20006-4001

THUS DONE AND SIGNED this 10th day of April 2007.

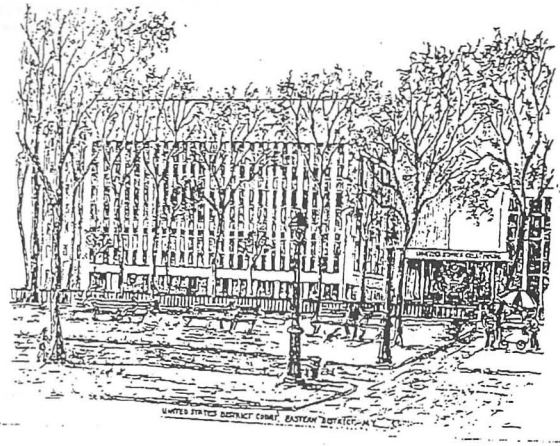
JUDGE DONALD HEBERT

000286

A B Memo & Order E

Jack B. Weinstein
Senior United States District Judge
Eastern District of New York
225 Cadman Plaza East
Brooklyn, N.Y. 11201

Tel: (718) 613-2520
Fax: (718) 613-2527



TO: Thomas Sobol, Hagens Berman Sobol Shapiro LLP ~ 617-482-3003
Nina M. Gussack, Pepper Hamilton LLP ~ 215-981-4307
James Shaughnessey, Milberg Weiss ~ 212-868-1229
Peter Woodin, JAMS ~ 212-972-0027

DATE: June 28, 2007 # OF PAGES WITH COVER: 15

RE: In re Zyprexa Products Liability Litigation, 04-MD-01596
UFCW Local 1776, Eric Taysg, and Mid-West National v. Eli Lilly & Co., 05-CV-4115 & 05-CV-2948
If you have any questions, please call Zainab Ahmad, Law Clerk, at 718-613-2523.

* Please distribute to parties not included on the distribution list.

A B C D E

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

----------X

In re: ZYPREXA PRODUCTS LIABILITY LITIGATION

----------X

UFCW LOCAL 1776 AND PARTICIPATING EMPLOYERS HEALTH AND WELFARE FUND, ERIC TAYAG, and MID-WEST NATIONAL LIFE INSURANCE COMPANY OF TENNESSEE, on behalf of themselves and others similarly situated,

Plaintiffs,

vs.

ELI LILLY AND COMPANY,

Defendant.

----------X

LOCAL 28 SHEET METAL WORKERS, on behalf of themselves and others similarly situated,

Plaintiffs,

vs.

ELI LILLY AND COMPANY,

Defendant.

----------X

SERGEANTS BENEVOLENT ASSOCIATION HEALTH AND WELFARE FUND, on behalf of themselves and others similarly situated,

Plaintiffs,

vs.

ELI LILLY AND COMPANY,

Defendant.

----------X

MEMORANDUM & ORDER
MOTIONS FOR SUMMARY JUDGMENT

04-MD-1596

05-CV-4115
05-CV-2948

06-CV-0021

06-CV-6322

JACK B. WEINSTEIN, Senior United States District Judge:

TABLE OF CONTENTS

I. Introduction

These are part of a series of cases based on injuries allegedly resulting from sale of the drug Zyprexa, manufactured by Eli Lilly & Company ("Lilly"). *See, e.g., In re Zyprexa Prods. Liab. Litig.*, No. 04-MD-1596, 2007 WL 1678078 (E.D.N.Y. June 11, 2007) (memorandum and order on motions for summary judgment in individual personal injury claims).

In June of 2005, Mid-West National Life Insurance Company of Tennessee filed a class action suit against Lilly seeking economic damages. Similar suits were initiated by UFCW Local 1776 and Participating Employers Health and Welfare Fund, and Eric Tayag, in August of 2005 (Michael Pronto and Michael Vanollo were later added as co-lead plaintiffs); Local 28 Sheet Metal Workers in January of 2006; and Sergeants Benevolent Association Health and Welfare Fund in November of 2006. Institutional plaintiffs in the instant cases are pension funds, labor unions, and insurance companies who cover members' health benefits and have paid for the drug Zyprexa when it was prescribed by physicians for their individual members or clients. An individual Zyprexa user who made co-payments is also named as a plaintiff.

Plaintiffs claim overpayment through direct purchase of Zyprexa. They allege that over an eleven-year period continuing to today Lilly withheld information, and disseminated misinformation, about the safety and efficacy of Zyprexa, and promoted and marketed it for uses

for which it was not indicated, and for patients who would have been better served by less expensive medications. The consequence, it is contended, was pricing of the drug at more than it would have sold for had the truth been known. The resulting excess payments are claimed as damages.

Five causes of action are asserted: violation of 18 U.S.C. 1962(c) (Racketeer Influenced and Corrupt Organization Act (RICO)); 18 U.S.C. 1962(d) (RICO); various state consumer protection statutes; common law fraud; and unjust enrichment.

Class certification is sought on the ground that anyone who paid for Zyprexa was charged more than they would have been in the absence of Lilly's fraud. The proposed class is defined as follows:

> All individuals and entities in the United States and its territories who, for purposes other than resale, purchased, reimbursed, and/or paid for Zyprexa during the period from September 1996 through the present. For purposes of the class definition, individuals and entities purchased Zyprexa if they paid all or some of the purchase price.

Subject matter jurisdiction is based upon 28 U.S.C. § 1331 (action arising under the laws of the United States) and 18 U.S.C. §§ 1962 and 1964(c) (RICO). Plaintiffs also invoke jurisdiction pursuant to 28 U.S.C. § 1332(d)(2) (Class Action Fairness Act). Venue is placed in the Eastern District of New York pursuant to 28 U.S.C. § 1391(b) and (c) (requiring that a substantial portion of the alleged improper conduct took place in the district where suit is commenced) and 18 U.S.C. § 1965 (RICO).

Under the present organization of the pharmaceutical industry, the official federal Food and Drug Administration (FDA), and the plaintiffs' bar, the courts are arguably in the strongest position to effectively enforce appropriate standards protecting the public from fraudulent

merchandising of drugs. *See, e.g.*, James Surowiecki, *A Drug on the Market*, The New Yorker, June 25, 2007, at 40 ("The U.S. has no rational system for 'post market surveillance' — the evaluation of drugs after they're approved. Instead, oversight is left to a motley collection of altruists, academics, lawyers, self-publicists, and drug companies . . . . Somehow, the truth is expected to rise to the surface from among all these competing interests and random decisions."). As Drs. Kesselheim and Avorn put it:

> [C]ase studies [of major pharmaceutical litigations, including Zyprexa] indicate that clinical trials and routine regulatory oversight as currently practiced often fail to uncover important adverse effects for widely marketed products. In each instance, the litigation process revealed new data on the incidence of adverse events, enabled reassessments of drug risks through better evaluation of data, and influenced corporate and regulatory behavior. In performing these tasks, lawyers and their clients often find themselves serving as drug safety researchers of last resort.

Aaron S. Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, Journal of the American Medical Association, January 17, 2007, at 308; *see also, e.g.*, Janet L. Dolgin & Joel Weintraub, *Biomedical Research and the Law: The Pharmaceutical Industry and its Relationship with Government, Academia, Physicians, and Consumers*, 35 Hofstra L. Rev. 681 (2006).

There is little doubt about the usefulness of Zyprexa for both on-label and some off-label purposes. It assists many people with serious debilitating diseases. It has substantially increased the quality of life of many thousands of people. Its salutary effect is evidenced by the fact that there have been no changes in plaintiffs' formularies which continue to include Zyprexa without restrictions. Many treating physicians continue to rely on it after what is by now extensive revelation of information about Zyprexa's risks and benefits. Nevertheless, the utility of Zyprexa does not trump plaintiffs' legal claims for fraud and overpricing.

II. Summary Judgment Law

Summary judgment is appropriate only if "there is no genuine issue as to any material fact . . . [in which case] the moving party is entitled to a judgment as a matter of law." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248, 106 S. Ct. 2505 (1986); *see also Mitchell v. Washingtonville Central School District*, 190 F.3d 1, 5 (2d Cir. 1999). "[O]nly disputes over facts that might affect the outcome of the suit under the governing law will properly preclude the entry of summary judgment. Factual disputes that are irrelevant or unnecessary will not be counted." *Anderson*, 477 U.S. at 248.

"In considering the motion, the court's responsibility is not to resolve disputed issues of fact but to assess whether there are factual issues to be tried." *Knight v. U.S. Fire Ins. Co.*, 804 F.2d 9, 11 (2d Cir. 1986). Critical is recognition of the jury's fact-finding primacy:

> It is well established that credibility assessments, choices between conflicting versions of the events, and the weighing of evidence are matters for the jury, not for the court on a motion for summary judgment. If, as to the issue on which summary judgment is sought, there is any evidence in the record from which a reasonable inference could be drawn in favor of the opposing party, summary judgment is improper.

Curry v. City of Syracuse, 316 F.3d 324, 333 (2d Cir. 2003) (quotation marks omitted).

III. Plaintiffs' Motion for Partial Summary Judgment

Plaintiffs' motion for partial summary judgment is based upon the following proposed findings: (1) third party payers ("TPPs") are purchasers of prescription drugs, and pharmaceutical benefit managers ("PBMs") act as agents for TPPs; (2) PBMs exercise no effective influence on the prescribing habits of physicians with regard to Zyprexa; (3) preemption is not applicable to or an issue in this litigation; (4) Zyprexa is not superior in efficacy to conventional antipsychotic medications or other atypical antipsychotic drugs; and (5) damages to the proposed class are at

least $3.7 billion.

The motion is without merit. (1) The relation of TPPs to PBMs in the case is unclear. (2) Determination of how Lilly's actions influenced what physicians prescribed will require a trial. (3) The court has already ruled that preemption does not apply, *In re Zyprexa, supra*, at Part III.A.6.a; a separate ruling is not required. (4) Zyprexa may be found by a jury to be considered preferable to other medications by knowledgeable prescribing physicians in specific cases, *see id.* at Part III.B. (5) It is not clear that plaintiffs can prove any damages, whether they attempt to prove overpayment on a case-by-case basis for each insured or through statistical analysis. *See id.; Blue Cross & Blue Shield of N.J., Inc. v. Philip Morris USA, Inc.*, 3 N.Y.3d 200 (N.Y. 2004) (finding statistical proof acceptable); *Empire Healthchoice, Inc. v. Philip Morris USA, Inc.*, 344 F.3d 211 (2d Cir. 2003)(same).

IV. Conclusion as to Plaintiffs' Motion for Partial Summary Judgment

Plaintiffs' motion for partial summary judgment is denied.

V. Defendant's Motion for Summary Judgment

Defendant moves for summary judgment on the ground that plaintiffs cannot satisfy the elements of any of their claims. Strength of proof is not the appropriate standard for a summary judgment decision. *See* Part II, *supra*. While the case is close, plaintiffs have sufficiently demonstrated for purposes of this motion that genuine issues of material fact exist with respect to their RICO and state substantive law claims.

A. Injury and Causation

As purchasers of Zyprexa, consumers and third party payers have standing to sue for economic damages; they have demonstrated a sufficient causal nexus between Lilly's alleged

fraud and their own claimed economic injuries. The Court of Appeals for the Second Circuit "and other courts have long recognized the right of [health care benefit providers] to recover from drug companies amounts that were overpaid due to illegal or deceptive marketing practices." *Desiano v. Warner-Lambert* Co., 326 F.3d 339, 350 (2d Cir. 2003).

Boiled down, this is an overpricing claim. The alleged injury is direct: plaintiffs overpaid from their own funds for Zyprexa because of Lilly's fraud. The case is distinguishable from a RICO suit by an insurance company dismissed by the Court of Appeals for the Second Circuit for failure to satisfying proximate cause requirements in *Laborers Loc. 17 Health & Benefits Fund v. Philip Morris*, 191 F. 3d 229 (2d Cir. 1999).

> In *Laborers Local 17*, the tobacco companies' alleged tort directly harmed only the smokers, who suffered both a health injury (smoking-related illness) and an economic injury (the purchase price of the fraudulently marketed cigarettes). The smokers' health injuries, in turn, caused economic losses to the insurance companies, who had to reimburse patients for the cost of their smoking-related illnesses. That case was therefore clearly one in which the plaintiffs' damages were entirely derivative of the injuries to their insured. For . . . without injury to the individual smokers, the plaintiffs would not have incurred any increased costs.

Desiano, 326 F.3d at 349 (quotation and citation omitted).

As purchasers of Zyprexa — i.e., those who paid for the product in whole or in part out of their personal funds — plaintiffs here allege a direct injury to themselves that is not dependent on any physician's decision or injury suffered by those who ultimately ingested Zyprexa. This case falls within the category of suits approved in *Desiano*:

> Plaintiffs' claim is that the Defendants' wrongful action was their misrepresentation of Rezulin's safety, and that this fraud directly caused economic loss to them as purchasers, since they would not have bought Defendants' product, rather than available cheaper alternatives, had they not been misled by Defendant's misrepresentations. Thus the damages — the excess money Plaintiffs paid Defendants for the Rezulin that they claim they would not have purchased 'but for' Defendants'

fraud — were in no way derivative of damages to a third party.

Desiano, 326 F.3d at 349 (quotation omitted).

In attempting to distinguish *Desiano*, Lilly emphasizes the fact that third party payer plaintiffs continue to include Zyprexa in their approved formularies. This fact has evidentiary relevance to the central claim of overpayment due to fraudulently-inflated prices, but it is not decisive. Probative force of this and other evidence of fraud and overpricing — or their contrary — present jury questions. Based on expert reports and available modes of economic analysis, a trier could determine that Zyprexa would have — or would not have — been sold for a reasonably precise computable lesser amount than it was sold for were it not for Lilly's alleged fraud. *See Schwab v. Philip Morris*, 449 F. Supp. 2d 992, 1065 (E.D.N.Y. 2006).

The allegation of economic harm in *Schwab* was structured in a manner similar to the instant plaintiffs' allegations:

> Plaintiffs here allege a simple and short chain of causation: defendants represented that 'light' cigarettes provided health benefits that they knew these cigarettes did not provide; plaintiffs believed the misrepresentation and so continued to buy 'light' cigarettes in larger numbers than they would have absent the fraud; this kept demand for 'light' cigarettes at a much higher level than it otherwise would have been; elevated demand allowed defendants to keep prices higher than they otherwise would have; and plaintiffs paid more for 'light' cigarettes than they otherwise would have.

Id. at 1049.

Present plaintiffs allege that Lilly represented that Zyprexa was safer and more efficacious than other available drugs; Lilly in fact knew this to be untrue; the misrepresentation led doctors to continue to prescribe, and plaintiffs to continue to pay for, greater amounts of Zyprexa than they would have absent the fraud; this kept demand for Zyprexa at a higher level than it otherwise would have been; elevated demand allowed Lilly to keep prices higher than they

otherwise would have been; and plaintiffs paid more for Zyprexa than they otherwise would have.

The economic analysis may be more difficult in this case than in *Schwab* because of the monopoly status provided by the patent laws to Lilly. In addition, the many competing modes of treatment available — other atypical antipsychotic drugs, first generation antipsychotic drugs, and non-pharmaceutical treatment — complicate the question of damages computation. While the required economic analysis may be somewhat more sophisticated than that required in *Schwab*, it appears to be within the competence of econometricians on both sides. *See Blue Cross & Blue Shield v. Philip Morris*, 344 F.3d 211, 222-28 (2d Cir. 2003) (finding statistical and aggregate proof appropriate and not in violation of right to jury and due process); *Blue Cross & Blue Shield of N.J. v. Philip Morris*, 3 N.Y.3d 200, 204 (N.Y. 2004) ("aggregate proof on issues of causation and damages was legally sufficient").

Once fraud has been proven, the burden of proving specifics of damages by the claimant is reduced. "Where injury is established, damages need not be demonstrated with precision." *Schwab*, 449 F. Supp. 2d at 1065 (E.D.N.Y. 2006); *see Blue Cross*, 344 F.3d at 224-25; *cf. Lee v. Joseph E. Seagram & Sons, Inc.*, 552 F.2d 447, 456 (2d Cir. 1977) ("When it is certain that damages have been caused by a breach of contract, and the only uncertainty is as to their amount, there can rarely be good reason for refusing, on account of such uncertainty, any damages whatever for the breach. A person violating his contract should not be permitted entirely to escape liability because the amount of damages which he has caused is uncertain.") (quotation and citation omitted).

Both the individual and institutional plaintiffs have laid out their own money for Zyprexa.

While it can be assumed for purposes of this motion that the drug was properly prescribed, payers may recover the difference between the price they paid for Zyprexa and the price they would have paid for Zyprexa but for Lilly's alleged fraud. *See, e.g.*, *Schwab*, 449 F. Supp. 2d at 1065 (approving use of price impact model to calculate damages). The questions of damages and their allocation is in some respects simpler here than in *Schwab* since the institutional and individual claimants can probably trace their own payments through contemporaneous writings.

B. Reliance

Where, as here, mail fraud and wire fraud are the alleged predicate acts forming the racketeering activity, justified reliance on the fraud is necessary to satisfy RICO's causation requirements. *See, e.g., Metromedia Co. v. Fugazy*, 983 F.2d 350, 368 (2d Cir. 1992). *But see Anza v Ideal Steel Supply Corp.*, 126 S.Ct. 1991, 2008 (2006) (Thomas, J., concurring in part and dissenting in part) (reaching a question not reached by the majority — whether reliance is required in a civil RICO suit predicated on mail and wire fraud — and concluding that "[b]ecause reliance cannot be read into [the mail or wire fraud statutes], nor into RICO itself, it is not an element of a civil RICO claim").

Defendant argues that plaintiffs' use of aggregate proof, rather than individualized proof, to establish reliance is impermissible. This assertion is without merit.

Statistical proof of reliance is appropriate in the RICO context where a "sophisticated, broad-based [scheme,] by [its] very nature . . . likely to be designed to distort the entire body of public knowledge rather than to individually mislead millions of people[,]" is alleged. *See Schwab*, 449 F. Supp. 2d at 1047; *id.* at 1115-17 (permitting generalized proof of reliance including "surveys, expert evidence on marketplace principles, and extrapolated and statistic

analysis of individuals and groups in the class"). Here, plaintiffs allege that Lilly intentionally engaged in a broad-based plan to misrepresent to the medical and scientific communities the nature of Zyprexa's benefits and risks, and that the scheme was successful in distorting the general body of knowledge about Zyprexa. These allegations, and the factual and expert proof that plaintiffs rely on to prove them, meet the standard for reliance established in *Falise v. American Tobacco Co.*, 94 F. Supp. 2d 316 (E.D.N.Y. 2000), and *Schwab*.

Defendant urges the court to distinguish this case from the cigarette industry cases decided in *Schwab* and *Falise* on the basis that there is no allegation that Lilly conspired with other companies within the pharmaceutical industry to distort the body of public knowledge concerning Zyprexa's risks. This distinction is of no moment: Lilly is the monopolistic purveyor of Zyprexa so there was no need for it to collaborate with any other manufacturer with respect to the dissemination of information about Zyprexa. While Lilly's competitors may have been expected to lay bare Zyprexa's flaws in the vigorous merchandising of their own products, such evidence would not be decisive on the question of reliance — rather, it would be for the trier to consider when examining the question of whether Lilly's alleged fraud was in fact successful in distorting scientific knowledge about Zyprexa. In addition, plaintiffs rely on evidence of cooperation of non-Lilly-employed experts and co-opted paid doctors to support their RICO theory.

C. Consumer Protection Statutes

Since a decision on class certification has not yet been made, it is not appropriate to now address the elements of specific state consumer protection statutes. There have been holdings in similar cases that suits by insurance companies to recover economic damages arising from the

fraudulently-inflated price of prescription drugs are not actionable under some states' consumer protection statutes. *See, e.g., In re Rezulin Prods. Liab. Litig.*, 392 F. Supp. 2d 597 (S.D.N.Y. 2005) (finding health care benefit providers could not recover from manufacturer for alleged overpayment for the prescription drug Rezulin under consumer protection statutes of New York, New Jersey, or Louisiana). If the class is certified, the substantive state law applicable under choice of law rules — as well as RICO — will be considered in defining the class.

VI. Conclusion as to Defendant's Motion for Summary Judgment

Though the question is a close one on the facts, defendant's motion for summary judgment is denied.

Allowing this and like suits to proceed may or may not increase the cost of pharmaceuticals and the efficacy of medical treatment in this country. It does, however, furnish backstop protection against under-regulated potentially dangerous activity by a market where *caveat emptor* largely rules. *Cf.*, Eric S. Lipton & David Barboza, *As More Toys are Recalled, Trail Ends in China*, N.Y. Times, June 20, 2007, at A1 ("Combined with the recent scares in the United States of Chinese-made pet food, and globally of Chinese-made pharmaceuticals and toothpaste, the string of toy recalls is inspiring new demands for stepped-up enforcement of safety by United States regulators and importers, as well as by the government and industry in China.").

Arguably, suits such as the present one do more good than harm. *See, e.g.*, authorities referred to in Part I, *supra*; *In re Zyprexa Prods. Liab. Litig.*, 2007 WL at *10 ("Whatever the advantages to available court procedures limiting the 'piling on' phenomena in mass tort cases, the process involves substantial transactional costs."). It is for the legislature, not this court, to

limit individual litigation-enforced remedies for fraud on consumers of pharmaceuticals.

VII. Daubert Motions

Plaintiffs move to exclude all or part of the proposed testimony of defendant Lilly's proffered experts, Charles M. Beasley, Jr., M.D., Ernst R. Berndt, Ph.D., Patrizia Cavazzoni, M.D., Iain Cockburn, Ph.D., David W. Feigal, Jr., M.D., William S. Gilmer, M.D., Silvio E. Inzucchi, M.D., David A. Kahn, M.D., Jeffrey S. McCombs, Ph.D., Michael A. Silver, M.D., and Gary Tollefson, M.D. The criteria for meeting *Daubert* requirements have been outlined in *In re Zyprexa Prods. Liab. Litig.*, *supra* at Part IV. Each of the challenged experts meet *Daubert* requirements. Each is a distinguished scientist whose expertise probably will be helpful in deciding relevant scientific and economic issues. Attacks on them by plaintiffs are primarily based on assessments of credibility best left for the trier. *In limine* motions respecting particular aspects of these and other experts' proposed testimony will be considered when it becomes clear what will be the detailed issues to be tried.

The court has evaluated plaintiffs' expert reports submitted on their motion by registered pharmacist Myron Winkelman; Doctor of Pharmacology Laura M. Plunkett; Master of Science in Pharmacology Terry D. Leach; Keith Bradbury; Marsha More, M.D.; Meredith Rosenthal, Ph.D.; Jeffrey E. Harris, M.D., Ph.D.; John Abramson, M.D.; Steven Klotz, M.D.; and John L. Gueriguian, M.D. All the plaintiffs' experts meet *Daubert* standards. *See id.*

VIII. Interlocutory Appeal

Section 1292(b) of title 18 of the United States Code provides that a district court judge may certify an order that is "not otherwise appealable" if the judge is "of the opinion that such order involves [1] a controlling question of law [2] as to which there is a substantial ground for

difference of opinion and [3] that an immediate appeal from the order may materially advance the ultimate termination of the litigation . . . ." 18 U.S.C. § 1292(b). Absent certification, an order denying summary judgment is not appealable. *See Sira v. Morton*, 380 F.3d 57, 66 (2d Cir. 2004) ("It is settled law that a denial of summary judgment is ordinarily not a final judgment from which an appeal will lie.").

Section 1292(b)'s requirements are not met in this case, even though both the substantive and procedural law relied upon by the parties are in a state of flux and not free from doubt. An immediate appeal might save considerable costs in discovery, preparation for trial, and trial. But an interlocutory appeal should await a decision on the critical question of class certification — an issue not yet considered by the court. When that question is decided by this court, the Court of Appeals can in its discretion decide the class certification issue under Rule 23(f) of the Federal Rules of Civil Procedure. For this reason, upon deciding on class certification this court plans to certify an interlocutory appeal under § 1292(b) so the class-procedural and substantive merits can be considered together by the appellate court. *See* Karen Schwartz et al., *Some Problems Dealing With Class Action Disputes*, 163 F.R.D. 369, 385 (1995) (recommending that merits and class certification be considered together).

SO ORDERED.

Jack B. Weinstein

Date: June 28, 2007
Brooklyn, N.Y.

RINDNER

Not used 6/22/07

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

ORDER

The Court, upon consideration of Defendant Eli Lilly & Company's Motion for Protective Order to Bar the Deposition of Sidney Taurel, and the State's response thereto, and being otherwise fully apprised in the matter;

The Court finds good cause for issuance of a protective order barring the deposition of Sidney Taurel, and

IT IS ORDERED that the Plaintiff's notice of deposition of Sidney Taurel is hereby quashed.

ORDERED this _____ day of _____, 2007.

The Honorable Mark Rindner
Judge of the Superior Court

I certify that on May 25, 2007, a copy of the foregoing was served by hand-delivery on:

Eric T. Sanders, Esq., Feldman Orlansky & Sanders
500 L Street, Suite 400, Anchorage, Alaska 99501-5911

[signature]

002867.0038/160760.1

MAY 25 2007

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

A B C D E

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

ORDER

THIS COURT having reviewed the defendant's Motion for Nonresident Attorney for Permission to Appear and Participate, as well as all responses thereto;

HEREBY ORDERS that Eric J. Rothschild of Pepper Hamilton LLP, 3000 Two Logan Square, Philadelphia, Pennsylvania 19103-2799, phone number 215-981-4881, may appear and participate as attorney for defendant in the above-captioned action in association with Brewster H. Jamieson.

DATED this 19th day of June, 2007.

The Honorable Mark Rindner

I certify that on June 15, 2007, a copy of the foregoing was served by mail on:

Eric T. Sanders, Esq.
Feldman Orlansky & Sanders
500 L. Street, Suite 400
Anchorage, Alaska 99501-5917

Nanci L. Biggerstaff, CPS, PLS
009867.0038/160937.1

I certify that on June 19, 2007 a copy of the above was mailed to each of the following at their addresses of record:
Sanders Jamieson

Administrative Assistant

000303

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

ORDER

THIS COURT, having upon considered defendant's Unopposed Motion for Extension of Time to file its Reply Re Defendant Eli Lilly and Company's Motion for Protective Order to Bar the Deposition of Sidney Taurel, all responses thereto, as well as applicable law;

IT IS HEREBY ORDERED that defendant's motion is GRANTED.

DATED this 19 day of June, 2007.

The Honorable Mark Rindner
Judge of the Superior Court

I certify that on June 15, 2007, a copy of the foregoing was served by hand on:

Eric T. Sanders, Esq.
Feldman Orlansky & Sanders
500 L. Street, Suite 400
Anchorage, Alaska 99501-5911

Nanci L. Bigelstaff, CPS, PLS
009867.0038/160970.1

I certify that on June 19, 2007 a copy of the above was mailed to each of the following at their addresses of record:

Sanders Jamieson

Administrative Assistant

000304

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

RINDNER

FILED
STATE OF ALASKA
THIRD DISTRICT
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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

DEFENDANT ELI LILLY AND COMPANY'S REPLY MEMORANDUM IN SUPPORT OF MOTION FOR PROTECTIVE ORDER TO BAR THE DEPOSITION OF SIDNEY TAUREL

INTRODUCTION

The State makes no pretense that the deposition of Sidney Taurel is necessary to develop Alaska-specific facts, nor does it identify any new information that Mr. Taurel, and Mr. Taurel alone, can provide. Rather, it is apparent that the State's only goal in seeking to depose Mr. Taurel is to rehash with him the same general liability issues and allegations that have been thoroughly covered in earlier MDL depositions, in the hope of obtaining an interesting sound bite. The State has failed to demonstrate any legitimate need for Mr. Taurel's deposition, much less the unique personal knowledge that the case law requires.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

ARGUMENT

I. MR. TAUREL'S DEPOSITION IS IMPROPER UNLESS HE HAS UNIQUE KNOWLEDGE OF RELEVANT FACTS UNAVAILABLE THROUGH LESS INTRUSIVE DISCOVERY.

The State offers no authority to contest the governing legal standard: Mr. Taurel's deposition is improper unless he has (1) unique knowledge of relevant facts that is (2) unavailable from less intrusive discovery. *See, e.g., Celerity, Inc. v. Ultra Clean Holding, Inc.*, 2007 WL 205067, *4 (N.D. Cal. 2007); *WebSideStory, Inc. v. NetRatings, Inc.*, 2007 WL 1120567, *2 (S.D. Cal. 2007); *Six West Retail Acquisition, Inc. v. Sony Theatre Mgmt. Corp.*, 203 F.R.D. 98, 102 (S.D.N.Y. 2001). The State's arguments regarding Lilly's alleged failure to show good cause are not only inconsistent with this legal standard, but also overlook the fact that this Court's discretion to limit burdensome discovery under Rule 26(b)(2) is not limited by the good cause standard of Rule 26(c). In limiting burdensome discovery, "[t]he court may act upon its own initiative … or pursuant to a motion under paragraph (c)." Alaska R. Civ. P. 26(b)(2) (emphasis added); *see also Gibson v. GEICO General Ins. Co.*, 153 P.3d 312, 317 (Alaska 2007) ("a conclusion that the burden of the discovery outweighed its likely benefit would have been within the court's discretion."); *Mullin v. State*, 2003 WL 22208506, *4 (Alaska App. 2003) (holding that trial court did not abuse its discretion under Rule 26(b)(2)(i) and (iii) by restricting discovery where "there were other ways for [proponent] to prove the same thing").

II. THE STATE HAS NOT SHOWN THAT MR. TAUREL HAS UNIQUE KNOWLEDGE OF RELEVANT FACTS UNAVAILABLE THROUGH LESS INTRUSIVE DISCOVERY.

The State ignores the Court's admonition that its ten depositions in this case focus on Alaska-specific issues, and makes no attempt to explain why Mr. Taurel's deposition is relevant to discovery of Alaska-specific facts. Indeed, in both of the two depositions the State has taken so far, the State has asked only about general liability issues with no particular connection to Alaska.

This failure to identify a single Alaska-specific reason for Mr. Taurel's deposition is fatal to the State's argument. To the extent the State wants to explore general liability issues with Mr. Taurel that have no particular connection to Alaska, that ground has already been covered in the Zyprexa MDL. The State's primary basis for seeking Mr. Taurel's deposition is his involvement with Lilly's Policy and Strategy Committee. According to the State, however, prior discovery of the activities of Lilly's Policy and Strategy Committee has already revealed "damning evidence" of Lilly's liability. State's Memorandum at 10. Thus, by the State's own description of the evidence already discovered – which Lilly obviously disputes – further discovery on these general liability issues would be cumulative.

The State also seeks to justify Mr. Taurel's deposition by his membership on Lilly's Board of Directors and on Board committees, in particular the Board's Public Policy and Compliance Committee. *See* State's Memorandum at 9-10. Although the State refers

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

to the Policy and Strategy Committee and the Board's Public Policy and Compliance Committee interchangeably, they are not the same committee. The Policy and Strategy Committee is an internal corporate committee comprised of Lilly management, *see* Exhibit A to State's Memorandum at 415-16, while the Public Policy and Compliance Committee is a Board committee comprised of independent directors. *See* Exhibit C to State's Memorandum. Moreover, the State has not explained how Board activities are relevant to its case. The Plaintiff's Steering Committee in the Zyprexa MDL – of which the State's counsel, Blair Hahn, is a member – found no need to depose Mr. Taurel or others about Board activities. The State has no greater need for Mr. Taurel's deposition in this case, in which discovery is focused on Alaska, than did the Plaintiff's Steering Committee in the Zyprexa MDL, which was national in scope.

The gist of the State's argument is not that Mr. Taurel has unique personal knowledge about any of the issues relevant to liability in this case, but simply that his deposition should be permitted to "clarify[] the extent of Taurel's involvement or knowledge of these issues…." State's Memorandum at 3. In other words, the State wants to rehash with Mr. Taurel the *same* facts and issues that have already been explored in depositions of witnesses who were directly involved with, and knowledgeable about, those issues. This is precisely the type of cumulative, unreasonably burdensome discovery that courts do not permit. *See, e.g., Harris v. Computer Assocs. Int'l, Inc.*, 204 F.R.D. 44, 46-47

(E.D.N.Y. 2001) ("When a vice president can contribute nothing more than a lower level employee, good cause is not shown to take the deposition."). Unique personal knowledge unavailable from less intrusive discovery is an "essential component of the standard for an apex deposition." *Celerity*, 2007 WL 205067, *4.

Thus, the fact that Mr. Taurel may have been present at discussions concerning Zyprexa does not justify his deposition, particularly here, where the State has not even attempted to determine by less burdensome discovery whether Mr. Taurel was present at the particular meetings it wishes to question him about. *See* Lilly's Memorandum at 10; *see also Folwell v. Hernandez*, 210 F.R.D. 169, 175 (M.D.N.C. 2002) (denying deposition of CEO to inquire about corporate policies and stating that "[f]or these topics, plaintiffs must use the Rule 30(b)(6) deposition method."). The defendant in this case is Eli Lilly and Company, not Mr. Taurel. Contrary to what the State implies in its memorandum, liability does not turn on whether "Taurel knew or should have known" any particular facts, State's Memorandum at 16, but on the collective knowledge and actions of Lilly as a corporation – facts that have already been thoroughly explored in the Zyprexa MDL. Accordingly, notwithstanding the State's hope to obtain a sound bite from Mr. Taurel, there is nothing of substance that his deposition will add to the extensive discovery on liability issues that has already been conducted.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

The State's own cases do not support its legal arguments, and are readily distinguishable. For example, in *WebSideStory, Inc. v. NetRatings, Inc.*, 2007 WL 1120567 (S.D. Cal. 2007), the court affirmed the general legal standard that "[w]hen a high-level corporate executive lacks unique or superior knowledge of the facts in dispute, courts have found that good cause exists to prohibit the deposition." 2007 WL 1120567 at *2. Under circumstances very different than those here, the court allowed the deposition of the plaintiff's CEO, where the plaintiff's own Rule 26 disclosure had listed the CEO as a potential trial witness, the CEO was one of only a few remaining employees who had been with the company throughout the relevant period, and was one of only two individuals who had performed a market share analysis relevant to the plaintiff's alleged damages. Even given those facts, the court did not simply permit the deposition to proceed without restriction, but ordered the defendant to first complete a Rule 30(b)(6) deposition "that could satisfy some of [defendant]'s needs," and limited the CEO's deposition to areas where he had "unique, first-hand knowledge." *Id.*, *5 (emphasis added).

Likewise, in *Six West Retail Acquisition, Inc. v. Sony Theatre Mgmt. Corp.*, 203 F.R.D. 98 (S.D.N.Y. 2001), the court recognized that "[u]nless it can be demonstrated that a corporate official has some unique knowledge of the issues in the case, it may be appropriate to preclude a redundant deposition of [a] highly-placed executive." *Id.*, at 102 (punctuations omitted). Unlike this case, however, in *Six West* there was "ample evidence

of [the CEO]'s hands-on involvement in" the transaction at issue and "unique knowledge on a number of relevant issues," justifying his deposition. *Id.*, at 104-06.

In re Bridgestone/Firestone, Inc. Tires Prod. Liab. Litig., 205 F.R.D. 535 (S.D. Ind. 2002) is similarly distinguishable. There, the plaintiffs were permitted to depose Ford's Chairman and CEO, William Ford, Jr., only after producing considerable evidence of Mr. Ford's "personal knowledge of and involvement in certain relevant matters" regarding Ford's recall of Firestone tires. *Id.*, at 536. In fact, Mr. Ford himself was on record publicly acknowledging his significant involvement: "I've been behind the scenes on this. I've been involved in every step of the way. I ended up not taking any vacation this summer because of this."[1]

Finally, the State relies on several cases from the District of Kansas, none of which supports its position. *See Horsewood v. Kids "R" Us*, 1998 WL 526589 (D. Kan. 1998), *Pepsi Cola Bottling Co. of Pittsburgh, Inc. v. Pepsico, Inc.*, 2002 WL 922082 (D. Kan. 2002); *Van Den Eng v. Coleman*, 2005 WL 3776352 (D. Kan. 2005). The legal analysis in these cases falls well outside the mainstream,[2] and, in any event, they are factually

[1] *See In re Bridgestone/Firestone*, Plaintiffs' Response to Ford Motor Company's Objections to Magistrate Judge's Order Compelling Deposition of William Clay Ford, Jr., 2001 WL 34136077 (detailing CEO's public statements of involvement).

[2] *Compare, e.g., Van Den Eng*, 2005 WL 3776352, *2-*3 (stating that "the Court is unaware of any federal case" applying a "special test" for depositions of apex executives and that "cases from this district have applied the usual protective order standards when considering Apex Official depositions") (*citing Horsewood* and *Pepsi Cola*) *with Cardenas v. Prudential* (continued . . .)

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

distinguishable. In *Horsewood*, an employment case, the court permitted the deposition of the defendant's vice president for human resources who participated in the implementation and enforcement of employment policies at issue in the case. 1998 WL 526589 at *1, *7. In *Pepsi Cola*, the court permitted the deposition of Pepsico's president and chief financial officer and the vice-chairman of its board of directors, based on their involvement in Pepsico's plan to consolidate and change the terms of its contractual relationship with the plaintiff and other Pepsi bottling companies. 2002 WL 922082 at *2-*3. Finally, *Van Den Eng* did not involve an apex executive at all, but rather, the defendant's former CEO, who

(. . . continued)
Ins. Co., 2003 WL 21293757, *1 (D. Minn. 2003) ("courts frequently restrict efforts to depose senior executives"); *Oklahoma v. Tyson Foods, Inc.*, 2007 WL 649335, *3 (N.D. Okla. 2007) ("The law governing depositions of 'apex' employees is well articulated…."); *Baine v. General Motors Corp.*, 141 F.R.D. 332, 334 (M.D. Ala. 1991) ("The legal authority is fairly unequivocal in circumstances such as these … the deposition would not be allowed where the information could be had through interrogatories, deposition of a designated spokesperson, or deposition testimony of other persons."); *Celerity, Inc. v. Ultra Clean Holding, Inc.*, 2007 WL 205067 (N.D. Cal. 2007) ("Where a high-level decision maker removed from the daily subjects of the litigation has no unique personal knowledge of the facts at issue, a deposition of the official is improper. This is especially so where the information sought in the deposition can be obtained through less intrusive discovery methods (such as interrogatories) or from depositions of lower-level employees with more direct knowledge of the facts at issue."); *Porter v. Eli Lilly and Co.*, 2007 WL 1630697, *3 (N.D. Ga. 2007) ("a plaintiff must show that the executive would have personal knowledge of the events in question and a plaintiff has no other means of obtaining the information."); *WebSideStory, Inc. v. Netratings, Inc.*, 2007 WL 1120567, *2 (S.D. Cal. 2007) ("[W]hen a party seeks to take the deposition of an official at the highest level or "apex" of a corporation, the court may exercise its authority under the federal rules to limit discovery."); *Harris v. Computer Assocs. Int'l, Inc.*, 204 F.R.D. 44, 46-47 (E.D.N.Y. 2001) ("When a vice president can contribute nothing more than a lower level employee, good cause is not shown to take the deposition."); *Folwell v. Hernandez*, 210 F.R.D. 169, 174 (M.D.N.C. 2002) ("Even when an executive does have personal knowledge about a case, the court still may fashion a remedy which reduces the burden on the executive.").

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

was no longer employed by the defendant and whose current occupation, if any, was unknown. 2005 WL 3776352 at *2 & n.3.

None of these cases involved the deposition of a current CEO, as here. To the extent they permitted depositions of lower-level executives with more direct personal knowledge than the CEO, they are consistent with Lilly's position: numerous Lilly executives with greater personal involvement in the events at issue have been deposed, including its President and Chief Operating Officer, its Vice President and Chief Medical Officer, and other lower-level executives. The State has identified no new information to be gained from deposing Lilly's highest-ranking executive, and nothing in the cases the State relies on supports its attempt to take the deposition of Mr. Taurel.

CONCLUSION

For the reasons stated above and in Lilly's initial Memorandum, Lilly respectfully requests that the Court issue a protective order barring the deposition of Sidney Taurel.

DATED this 19th day of June, 2007.

Attorneys for Defendant

PEPPER HAMILTON LLP
Andrew R. Rogoff, admitted *pro hac vice*
3000 Two Logan Square, 18th & Arch Streets
Philadelphia, PA 19103
(215) 981-4000

LANE POWELL LLC

By _____
Brewster H. Jamieson, ASBA No. 8411122
Andrea E. Girolamo-Welp, ASBA No. 0211044

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

I certify that on June 19, 2007, I caused a copy of the foregoing to be personally served by Elite Courier Service on:

Eric T. Sanders, Esq.
Feldman Orlansky & Sanders
500 L. Street, Suite 400
Anchorage, Alaska 99501-5911

009867.0038/161005.1

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

UNOPPOSED MOTION FOR EXTENSION OF TIME

Defendant Eli Lilly and Company, by and through counsel, hereby moves the court for an extension of time until Tuesday, June 17, 2007, to file its Reply Re Defendant Eli Lilly and Company's Motion for Protective Order to Bar the Deposition of Sidney Taurel.

Defendant's counsel spoke with plaintiff's counsel, who indicated that plaintiff does not oppose this extension of time.

DATED this 15th day of June, 2007.

LANE POWELL LLC
Attorneys for Defendant

By _____
Brewster H. Jamieson, ASBA No. 8411122

I certify that on June 15, 2007, a copy of the foregoing was served by hand on:

Eric T. Sanders, Esq.
Feldman Orlansky & Sanders
500 L. Street, Suite 400
Anchorage, Alaska 99501-5911

_____
Nanci L. Biggerstaff, CPS, PLS
009867.0038/156254.1

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

*Tuesday, July 17, 2007

000315

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

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THIRD DISTRICT
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BY: DEPUTY CLERK

MOTION OF NONRESIDENT ATTORNEY FOR PERMISSION TO APPEAR AND PARTICIPATE

Pursuant to Alaska R. Civ. P. 81(a)(2), defendant moves to permit Eric J. Rothschild of Pepper Hamilton LLP, 3000 Two Logan Square, Philadelphia, Pennsylvania 19103-2799, phone number 215-981-4881, to appear and participate as attorney for defendant in the above-captioned action. Mr. Rothschild, as shown by the attached certificate, is a member in good standing of the Bar of the Commonwealth of Pennsylvania and is not otherwise disqualified from practicing law in the State of Alaska.

Applicant will be associated with Brewster H. Jamieson, ASBA No. 8411122, of Lane Powell LLC, whose address is 301 West Northern Lights Boulevard, Suite 301, Anchorage, Alaska 99503-2648, phone number 907-277-9511, and who is authorized to practice in this court and the courts of this state. Brewster H. Jamieson consents to this association.

Pursuant to Civil Rule 81(a)(2)(D), proof of payment of the fee required to be paid to the Alaska Bar Association is also attached.

DATED this 15th day of June, 2007.

LANE POWELL LLC
Attorneys for Defendant

By _____
Brewster H. Jamieson, ASBA No. 8411122

I certify that on June 15, 2007, a copy of the foregoing was served by mail on:

Eric T. Sanders, Esq.
Feldman Orlansky & Sanders
500 L. Street, Suite 400
Anchorage, Alaska 99501-5911

_____
Nanci L. Biggerstaff, CLS, PLS
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LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

A B C D E

Supreme Court of Pennsylvania

CERTIFICATE OF GOOD STANDING

Eric Jonathan Rothschild, Esq.

DATE OF ADMISSION

April 26, 1994

The above named attorney was duly admitted to the bar of the Commonwealth of Pennsylvania, and is now a qualified member in good standing.

Witness my hand and official seal
Dated: June 14, 2007

John W. Person, Jr., Esq.
Deputy Prothonotary

000317

A B C D E

RINDNER

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ALASKA BAR ASSOCIATION
P.O. Box 100279, Anchorage, Alaska 99510-0279
(907) 272-7469

Customer's Order No.	Phone No.	Date
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500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

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A B C D E

RINDNER

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Case No. 3AN-06-05630 CI
	)	
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	
	)	

PLAINTIFF'S RESPONSE TO DEFENDANT'S OUTLINE OF UNRESOLVED ISSUES REGARDING THE SUPPLEMENTAL SCHEDULING ORDER AND PROTECTIVE ORDER

Plaintiff State of Alaska ("the State") provides the following response to Defendant Eli Lilly and Company's ("Lilly") Notice of Filing Defendant's Supplemental Scheduling Order, Protective Order, and Outline of Unresolved Issues Regarding the Orders, filed June 8, 2007. On June 7, 2007, the State filed versions of these two orders that it believes are simpler, more concise, and more consistent with the practices and procedures of this Court. While Lilly has accurately listed the areas of disagreement between the parties regarding each order, it has not fairly characterized the substance of those disagreements.

FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

D

A B C D E

I. Scheduling Order

The State has no problem with certain aspects of Lilly's requests for federal-state coordination. However, as to other critical aspects, Lilly's idea of coordination is *frustration* of the State's discovery. Lilly repeatedly states that it has produced 15 million documents in the MDL proceedings to which the State has access, and that some of the State's counsel actually participated in that litigation. This may be accurate; but the Court has previously recognized that this is a separate case with its own unique discovery needs, legal theories of liability, and elements of damages. That said, because there is overlap of issues between the two litigations, there will obviously be some overlap in discovery. The State recognizes this and believes it is making a good faith effort to accommodate Lilly in this regard. Nevertheless, the State has some well-founded concerns it has attempted to address in its versions of the orders.

A. Nature of the Case

The State does not believe there is any disagreement of substance here.

B. Discovery

As noted above, the State is attempting to accommodate Lilly's desire to avoid duplicative discovery of documents previously produced in the MDL. However, Lilly's provision regarding duplicative discovery is on its face much broader in scope, allowing Lilly to object to discovery requests even where it has not previously produced all documents responsive to the requests.

FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

The discovery process in the MDL was unusual in that while the Plaintiff's Steering Committee ("PSC") issued requests for production to Lilly calling for the production of documents regarding particular subject matters, the MDL Special Discovery Master issued a case management order ("CMO 9") (attached as Exhibit A) which only required Lilly to produce responsive documents from about 60 specified officers' and employees' custodial files. In addition, Lilly produced certain electronic databases. While this method of production may have satisfied the needs of the PSC in the MDL discovery proceedings regarding individual personal injury cases based primarily on common law claims of negligent failure to warn, it is not the method of discovery agreed to by the parties in this case. Further discovery of other categories of documents, or documents from the files of other witnesses, will no doubt be necessary here because discovery in the MDL did not focus on the use of Zyprexa in Medicaid programs in general or Alaska's program in particular. Nor did the MDL discovery focus on Lilly's marketing of Zyprexa in Alaska. However, Lilly's proposed language would allow it to object to the State's discovery requests if it deems those requests duplicative of those made during the MDL proceedings even though Lilly may not have produced all responsive documents to a similar request made in the MDL.

The State's version of the scheduling order protects Lilly from truly duplicative discovery, but does not prohibit the State from probing areas of relevant inquiry in this case which may not have been uncovered during the MDL proceedings.

FELDMAN ORLANSKY
& SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

1. Who may be present at depositions (Lilly's Paragraph II(C)(1) / the State's Paragraph F(1)).

The State has simply proposed the more practical version of essentially the same provision. The persons referred to in both versions are the only ones allowed to attend depositions absent court order or agreement of the parties. Most if not all of these people will have already signed the protective order prior to the deposition. The protective order governs the circumstances under which and to whom disclosure of confidential documents may be made. If it appears unauthorized disclosure of confidential information is going to occur during the course of a deposition, then that situation may be addressed as necessary if and when it arises. A sweeping exclusionary provision is unnecessary.

2. Coordination of depositions and duplicative depositions (Lilly's Paragraphs II(C)(3) and (4) / the State's Paragraphs E and F(4)).

The State's version of the scheduling order contains provisions dealing with both coordination and duplicative depositions. The State believes the provisions on these subjects in its version of the order comport more closely with the Court's previous recognition of the State's discovery needs in this case. The State has agreed to use its best efforts at coordination where required by the Court. Further, the State's version of the order preserves Lilly's right to object to any deposition it believes is improper under the Alaska Rules of Civil Procedure. The State has issued three deposition notices to

FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

date, and Lilly has already objected to one without the aid of the superfluous language it proposes in its version of the order.

II. Protective Order

A. Use of Discovery Materials (Paragraph 2 in each version)

The State has no intention of breaching the terms of any protective order in place in this litigation. Nor does the State have any intention of aiding and abetting the breach of any such orders. Nevertheless, the State's version of the protective order reflects the reality that documents covered by this confidentiality order or one in another lawsuit may become public and that, without regard to how they became public, they can then no longer be considered confidential after such public disclosure. While Lilly suggests a party could make the documents public and profit from doing so by having the confidentiality designation rendered null, the Court has the power to hold accountable any party who violates the protective order. That power would certainly serve to either (a) discourage any such violations, or (b) punish any such violations so that there is no advantage for the violating party resulting from its actions. Lilly's proposed language would defy reason by maintaining a façade of confidentiality and burdening non-offending parties with restrictions no longer justified by the circumstances.

FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

B. Use of Alaska-specific discovery materials outside of Alaska (Paragraph 2 in each version)

Lilly's version of the protective order reflects Lilly's anti-coordination position when coordination potentially benefits someone else. Lilly is happy for the State to have the benefit of the MDL discovery and wants it to coordinate its depositions with other litigants because it saves Lilly the trouble of duplicative effort. However, Lilly is unwilling to allow the State's discovery in this litigation to be used in other Zyprexa litigation because that may save some other party from duplicative effort. Notwithstanding Lilly's double standard, both versions of the protective order actually provide for the sharing of confidential information outside of this case in Paragraph 6(f), which allows disclosure to other attorneys in Zyprexa lawsuits, subject to the terms of the protective order. Thus, the State's proposed language is consistent with other provisions of the protective order.

C. Privilege logs (Paragraph 3 in each version)

Contrary to Lilly's statement that the PSC had no trouble challenging redactions and documents withheld on claims of privilege in the MDL proceedings, those challenges were made exceedingly difficult by the nature of the privilege log produced by Lilly. It was not done by bates range or document number, but rather by witness. While the PSC "muddled through," it was only through the Herculean efforts of attorneys devoted to that particular task. The same should not be required here when it is unnecessary and the

FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

Alaska Rules of Civil Procedure provide a simple solution. All the State has asked in its version of the protective order is that Lilly produce a log which complies with the provisions of Rule 26(b)(5) of the Alaska Rules. The State's version of the protective order tracks the language of Rule 26(b)(5) almost verbatim, and Lilly has articulated no reason why the parties should not be expected to comply with that rule in this case.

D. Coverage of non-party witnesses (Paragraph 10(a) in each version)

Paragraph 6(g) of both versions of the protective order allows the disclosure of confidential information to persons noticed for depositions. Paragraph 10(a) of both versions of the protective order provides further that a deponent may be shown confidential information as long as the deponent already knows of the information or "if the provisions of paragraph 6 are complied with." The additional language proposed by Lilly in its version of Paragraph 10(a) is unnecessary and burdensome to parties noticing depositions of witnesses outside of their control. The protective order must already be signed by a party or witness prior to disclosure of the confidential information. Lilly's proposed language adds nothing to this requirement except for an unnecessary and undue burden upon a party noticing a deposition. If during the course of a deposition it appears confidential information may be disclosed to a deponent who has not signed the protective order, that issue can be addressed as necessary.

FELDMAN ORLANSKY
& SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

III. Conclusion

For the foregoing reasons, the State respectfully requests that the Court enter the versions of the Scheduling Order and Protective Order submitted by it on June 7, 2007.

RESPECTFULLY SUBMITTED this 15 day of June, 2007.

FELDMAN, ORLANSKY & SANDERS
Counsel for Plaintiff

BY _____
Eric T. Sanders
Alaska Bar No. 7510085

GARRETSON & STEELE
Matthew L. Garretson
Joseph W. Steele
5664 South Green Street
Salt Lake City, UT 84123
(801) 266-0999
Counsel for Plaintiff

RICHARDSON, PATRICK,
WESTBROOK & BRICKMAN, LLC
H. Blair Hahn
Christiaan A. Marcum
P.O. Box 1007
Mt. Pleasant, SC 29465
(843) 727-6500
Counsel for Plaintiff

FELDMAN ORLANSKY
& SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

Certificate of Service
I hereby certify that a true and correct copy of **Plaintiff's Response to Defendant's Outline of Unresolved Issues Regarding the Supplemental Scheduling Order and Protective Order** was served by mail on:

Brewster H. Jamieson
Lane Powell LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648

By Peggy S. Crowl
Date 6/15/07

FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK

In re: ZYPREXA PRODUCTS LIABILITY LITIGATION

MDL No. 1596 (JBW) (ASC)

THIS DOCUMENT APPLIES TO:
ALL CASES

CASE MANAGEMENT ORDER NO. 9

(Document Production – Schedule and Scope; Depositions)

In order to facilitate the orderly conduct of discovery in the above-referenced MDL proceeding in light of the Court-ordered trial date of December 5, 2005, and following consultations between the Plaintiffs' Steering Committee ("PSC") and Eli Lilly and Company ("Lilly"), and having considered the written submissions of the parties, and following conferences with the parties and Special Discovery Master Peter H. Woodin on these and related issues, most recently on March 7, 2005, IT IS HEREBY ORDERED:

Document Production Schedule

1. As of the date of this Order, Lilly has produced approximately 2.4 million pages of documents in this MDL proceeding. Additionally, Lilly has produced two relational electronic databases (Regulatory Activities Planning and Tracking (RAPT), and IMPACT) which total approximately 40 MBs of data.

2. Among the documents produced to date, Lilly has produced hardcopy documents and emails (totaling approximately 775,000 document pages) associated with the following medical, regulatory or marketing individuals:

Robert W. Baker
Charles M. Beasley
David Biloon
Greg Bopp[illegible]

Melanie Bruno
Patrizia Cavazzoni
Michael Clayman
Jared G. Kerr
Michael W. Magdycz
Glyn Parkin
Timothy F. Parshall
Michelle Sharp
Mauricio F. Tohen
Vincent E. Trttax
Robert Van Lier

Production of the electronic documents associated with these individuals will be completed by March 15, 2005.

3. By April 15, 2005, Lilly will complete production of hardcopy documents, emails and electronic documents associated with the following forty-eight (48) individuals designated by the PSC:

Mike Ackerman
Alanis Affonso
Kristen Anderson
Mike Bardick
Bruce Basson
Alan Breier
Michael Clayman
Susanne Clifford
Brian Dean
Paul Eisenberg
Tim Franson
Man C. Fung
James Gregory
Jim Gregory
Melissa Halkyard
Philip Hallstedt
Mark Heiman
Ken Hornbuckle
Ken Inglis
Jack Jordan
Bruce Kinon
John Krueger
Kenneth C. Kwong
John Lechleiter
Gerhard Mayr

Exhibit A, Page 2 of 6
SOA Response to Lilly's Outline of Unresolved Issues Re Supplemental Scheduling Order and Protective Order
Case No. 3AN-06-05630 CI

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A B C D E

Cassandra Mahlman
David Noesges
Stephen Paul
Matthew Pike
Zohar Porat
Jeff Powell
Eric Prouty
Jeffrey T. Ramsey
John Richards
Ralph Robinson
William Robinson
Gino Sarfini
Jim Senecal
Pari Shambayati
Margaret Sowell
Lorenzo Tallarigo
Sidney Thurel
Jo Taylor
Gary Tollefson
Denise Torres
Albertus Van den Bergh
Doug Williamson
Chito Zuluet

4. If Lilly determines that it will be unable to meet this April 15th deadline, Lilly's counsel, on or before March 16, 2005, shall seek an extension by way of motion, for good cause shown, to Special Discovery Master Woodin. The PSC may respond to the motion on or before March 21, 2005, and the Special Master will rule promptly thereafter whether the deadline may be extended.

5. Lilly will produce the following electronic databases by the dates indicated:

Clinical Trial Systems (CTS): On or before April 1, 2005
Adverse Event Reporting System (Clintrace): On or before April 25, 2005

The production of additional electronic databases and other electronic data sources has been the subject of continuing discussion by counsel for the parties, and nothing in this Order shall impair the PSC's right to move to compel the production of additional electronic data sources, or Lilly's right to oppose any such motion.

6. Lilly will continue to produce other documents responsive to the PSC's discovery requests on a bi-weekly rolling basis. By no later than March 18, 2005, Lilly will identify those documents and other electronic data sources that that have not previously been identified and/or produced and which are responsive to the PSC's First Request for Production of Documents. Except for documents concerning the labeling of Zyprexa in Great Britain and Japan (see below), Lilly will complete its document production on or before June 15, 2005

Redaction and Privilege Logs

7. Redaction logs for Document Production Waves 1 through 17 and for the IND/NDA production have been produced to the PSC. Hereafter, redaction logs will be produced to the PSC within two weeks of each Document Production Wave.

8. Privilege logs for Document Production Waves 1 through 13 have been produced to the PSC. Hereafter, privilege logs will be produced to the PSC on a monthly basis covering subsequent Production Waves.

Production of Foreign Labeling

9. Lilly will produce, on or before August 1, 2005, all documents concerning the labeling of Zyprexa in Great Britain and Japan.

Depositions

10. Depositions will be conducted in accordance with the Federal Rules of Civil Procedure and the Local Rules of the United States District Court for the Eastern District of New York. All counsel are expected to accommodate reasonable requests to modify usual deposition procedures because of the special needs of an individual deponent. Any dispute concerning the extent of accommodation that may be necessary may be brought to Special Discovery Master Woodin for an immediate ruling.

11. Lilly may begin to take the depositions of plaintiffs immediately. Beginning April 1, 2005, Lilly may begin to take the depositions of physicians who may have prescribed Zyprexa to or otherwise treated individual plaintiffs whose cases were originally filed in the Eastern District of New York. Lilly may begin to take the depositions of prescribing and treating physicians for other plaintiffs beginning May 1, 2005.

Dated: New York, New York
March 10, 2005

3/10/05

Peter H. Woodin
Special Discovery Master

Exhibit A, Page 5 of 6
SOA Response to Lilly's Outline of Unresolved Issues Re Supplemental Scheduling Order and Protective Order
Case No. 3AN-06-05630 CI

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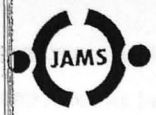

THE RESOLUTION EXPERTS

Offices Nationwide

www.jamsadr.com

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3/11/05

Fax Cover

To: The Honorable Jack B. Weinstein Phone: 718-260-2520 Fax: 718-260-2527

From: Peter H. Woodin Phone: 212-594-4454

Date: March 10, 2005 Pages (Including Cover): 6

Re: In re Zyprexa Product Liability Litigation (MDL-1596) (EDNY)

Comments:

Dear Judge Weinstein:

I am faxing to you, for filing in the Zyprexa MDL, a copy of Case Management Order No. 9, which I issued today to the parties.

Very truly yours,
Peter Woodin

1350 Broadway • 22nd Floor • New York, NY 10018 • Tel 212.594.4454 • Fax 212.594.4474

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RINDNER

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Case No. 3AN-06-05630 CI
	)	
ELI LILLY AND COMPANY,	)	
	)	
Defendant.	)	
	)	

NOTICE OF PLEADING TO BE FILED UNDER SEAL

The Plaintiff's Memorandum in Opposition to Defendant Eli Lilly and Company's Motion for Protective Order to Bar the Deposition of Sidney Taurel and the exhibits attached thereto, filed on June 8, 2007, contain CONFIDENTIAL information. Thus, the parties request that the pleading be filed under seal in the attached envelope.

RESPECTFULLY SUBMITTED this 12 day of June, 2007.

FELDMAN, ORLANSKY & SANDERS
Counsel for Plaintiff

BY _____

Eric T. Sanders
Alaska Bar No. 7510085
500 L Street
Suite 400
Anchorage, AK 99501
(907) 272-3538

FELDMAN ORLANSKY
& SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

000334

A B C D E

GARRETSON & STEELE
Matthew L. Garretson
Joseph W. Steele
5664 South Green Street
Salt Lake City, UT 84123
(801) 266-0999
Counsel for Plaintiff

RICHARDSON, PATRICK,
WESTBROOK & BRICKMAN, LLC
H. Blair Hahn
Christiaan A. Marcum
P.O. Box 1007
Mt. Pleasant, SC 29465
(843) 727-6500
Counsel for Plaintiff

Certificate of Service
I hereby certify that a true and correct copy of the **Notice of Pleading to be Filed Under Seal** was served by messenger on:

Brewster H. Jamieson
Lane Powell LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648

By _____
Date 6/12/07

FELDMAN ORLANSKY
& SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, vs. ELI LILLY AND COMPANY, Defendant.	Case No. 3AN-06-5630 CIV

ORDER GRANTING EXTENSION TO FILE OPPOSITION TO MOTION FOR PROTECTIVE ORDER TO BAR DEPOSITION OF SIDNEY TAUREL

IT IS ORDERED that the Motion for Extension of Time to File Opposition to Motion for Protective Order to Bar Deposition of Sidney Taurel is GRANTED. Plaintiff shall have until Friday, June 8, 2007, to file its opposition to the Motion for Protective Order.

DATED this 0 day of June, 2007.

BY THE COURT

Mark Rindner
Superior Court Judge

JUN 05 2007

LAW OFFICES
FELDMAN ORLANSKY
& SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

I certify that on June 8, 2007 a copy of the above was mailed to each of the following at their addresses of record:
Sanders Jamieson

Administrative Assistant

000336

A B C D E

RINDNER

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

Filed in the Trial Courts
State of Alaska, Third District
JUN 08 2007
Clerk of the Trial Courts
By _____ Deputy

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

ELI LILLY COMPANY'S PRELIMINARY WITNESS LIST

Pursuant to the Court's Standard Pre-trial Scheduling Order entered in this action, Defendant Eli Lilly and Company ("Lilly") hereby submits its Preliminary Witness List. Lilly's ability to identify witnesses to testify at trial is limited by uncertainty about the scope and nature of evidence that will be heard in this case, and the State's refusal to identify witnesses with knowledge about facts relevant to its lawsuit.

In its pending Motion Concerning Claims and Proofs, the State argues that it can prove that misrepresentations and off-label promotion by Lilly caused doctors to write prescriptions that they otherwise would not have, without ever identifying the physicians who experienced the alleged misconduct, or the Lilly employees who allegedly perpetrated it. The State also argues that it can prove that the use of Zyprexa caused diabetes and other injuries without identifying any patients who are suffering from these conditions, or producing their medical records so that their treatment history, time of diagnosis, confounding risk factors, and other relevant information can be ascertained. The State does not intend to present such individualized evidence itself, and has taken the position that Lilly is not entitled to discovery of this information to develop its defense. Accordingly, at this

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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time, Lilly is not able to identify the patients, physicians, or persons who communicated with physicians who might be called to testify in this matter.

In addition, the State's failure to provide information about any communications between Lilly and the State of Alaska giving rise to the State's causes of action hampers Lilly's ability to identify witnesses who may testify at trial.

Subject to these limitations, Lilly advises it may call the following witnesses to testify at the trial in this matter. All current and former Lilly employees should be contacted through counsel. Lilly reserves the right to supplement and amend this list in accordance with the applicable Alaska Rules of Civil Procedure, as discovery has just begun in this matter. Retained expert witnesses will be identified at a later date.

The following witnesses may be asked to testify about the State of Alaska's reimbursement policies relating to Zyprexa:

1. David Campana, Medicaid Pharmacy Program Manager
   c/o State of Alaska's Dept. of Health and Social Services
   Division of Health Care Services
   4501 Business Park Blvd., Suite 24
   Anchorage, AK 99503

2. Jack Gilbertson, Former Commissioner
   Dept. of Health and Social Services
   [address unknown]

3. Bill Hogan, Deputy Commissioner
   c/o State of Alaska's Dept. of Health and Social Services
   Division of Health Care Services
   4501 Business Park Blvd., Suite 24
   Anchorage, AK 99503

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

4. Karleen Jackson, Commissioner
c/o State of Alaska's Dept. of Health and Social Services
Division of Health Care Services
4501 Business Park Blvd., Suite 24
Anchorage, AK 99503

5. Bob Labbe, Former Deputy Commissioner
Dept. of Health and Social Services
[address unknown]

6. Nathaniel Miles **Attorney-Client Privilege**
c/o Pepper Hamilton LLP
3000 Two Logan Square
18th & Arch Streets
Philadelphia, PA 19103
(215) 981-4000

7. Karen Perdue, Former Commissioner
Dept. of Health and Social Services
[address unknown]

8. Kevin Walters **Attorney-Client Privilege**
c/o Pepper Hamilton LLP
3000 Two Logan Square
18th & Arch Streets
Philadelphia, PA 19103
(215) 981-4000

The following witnesses may be asked to testify in response to allegations in Plaintiffs' Complaint:

1. Robert Baker, M.D. **Attorney-Client Privilege**
c/o Pepper Hamilton LLP
3000 Two Logan Square
18th & Arch Streets
Philadelphia, PA 19103
(215) 981-4000

2. Patricia Cavazzoni, M.D. — **Attorney-Client Privilege**
c/o Pepper Hamilton LLP
3000 Two Logan Square
18th & Arch Streets
Philadelphia, PA 19103
(215) 981-4000

3. Steve Guyman — **Attorney-Client Privilege**
c/o Pepper Hamilton LLP
3000 Two Logan Square
18th & Arch Streets
Philadelphia, PA 19103
(215) 981-4000

4. David Noesges — **Attorney-Client Privilege**
c/o Pepper Hamilton LLP
3000 Two Logan Square
18th & Arch Streets
Philadelphia, PA 19103
(215) 981-4000

5. Eric Schultz — **Attorney-Client Privilege**
c/o Pepper Hamilton LLP
3000 Two Logan Square
18th & Arch Streets
Philadelphia, PA 19103
(215) 981-4000

6. Michelle Sharp — **Attorney-Client Privilege**
c/o Pepper Hamilton LLP
3000 Two Logan Square
18th & Arch Streets
Philadelphia, PA 19103
(215) 981-4000

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

7. Gary Tollefson, M.D.
c/o Pepper Hamilton, LLP
3000 Two Logan Square
18th and Arch Streets
Philadelphia, PA 19103
(215) 981-4000

Attorney-Client Privilege

DATED this 8th day of June, 2007.

Attorneys for Defendant

PEPPER HAMILTON LLP
Andrew R. Rogoff, admitted *pro hac vice*
3000 Two Logan Square
18th & Arch Streets
Philadelphia, PA 19103
(215) 981-4000

LANE POWELL LLC

By _____
Brewster H. Jamieson, ASBA No. 8411122
Andrea E. Girolamo-Welp, ASBA No. 0211044

I certify that on June 8, 2007, a copy of the foregoing was served by hand on:

Eric T. Sanders, Esq.
Feldman Orlansky & Sanders
500 L. Street, Suite 400
Anchorage, Alaska 99501-5911

_____

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LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

NOTICE OF FILING DEFENDANT'S SUPPLEMENTAL SCHEDULING ORDER, PROTECTIVE ORDER, AND OUTLINE OF UNRESOLVED ISSUES REGARDING THE ORDERS

COMES NOW Defendant Eli Lilly and Company ("Lilly") and provides notice to the Court that after a series of discussions, the parties were unable to reach agreement on a handful of provisions contained in the Supplemental Scheduling Order and the Protective Order. Lilly believes that its version of the orders (attached to this Notice) most accurately reflect this Court's directives on the items still at issue between the parties, as opposed to the State's version of the orders submitted to the Court on June 7, 2007.

Lilly outlines below the areas that the parties were unable to resolve between themselves with respect to the two orders and why it believes that Lilly's version should be adopted by this Court. Finally, in light of the contents of this Notice and its attachments, Lilly respectfully requests that the Court enter its versions of the Supplemental Scheduling Order and Protective Order.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

I. SCHEDULING ORDER

As a global and preliminary request, Lilly again urges the Court to place a high value on federal-state coordination, which it believes is critical to conserving the resources of all courts and all parties.

A. Nature of the Case

Because of the magnitude and complexity of the case, Lilly suggests that the case be characterized as "non-routine." The parties agree, however, to exempt the case from the initial disclosure requirements of Rule 26(a)(1) and the thirty-interrogatory limit of Rule 33(a). Lilly and plaintiff have simply placed the latter provision in different sections of the Order. It does not matter to Lilly where it is placed.

B. Discovery

Recognizing that plaintiff may require Alaska-specific discovery that was not requested in the MDL, Lilly includes a provision allowing for non-duplicative discovery requests in paragraph II(A). Lilly also includes language that would authorize it to object to duplicative discovery, which is appropriate in view of the fact that counsel for the State of Alaska (i) participated in MDL discovery on behalf of certain personal injury plaintiffs, and (ii) enjoys access to the MDL document depository. Lilly requests that the Court endorse these provisions with respect to discovery as they comport with the Alaska-specific parameters of this action.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

1. Plaintiff Objects to Paragraph II(C)(1) of the Order.

Paragraph II(C)(1) excludes persons who had not signed the Protective Order from attending those parts of a deposition in which documents covered by that Order are being used. This provision comports with common sense and carries out the spirit of the Protective Order; to do otherwise would eviscerate the Protective Order. Lilly requests that the Court endorse this provision.

2. Plaintiff Objects to the (i) Coordination-of-Depositions Provision in Paragraph II(C)(3) and the (ii) Prohibition Without Good Cause of Duplicative Depositions in Paragraph II(C)(4).

The provisions contained in paragraphs II(C)(3) and II(C)(4) attempt to conserve the parties' resources, but not unduly restrict plaintiff from taking depositions that are non-duplicative or Alaska-specific. Lilly requests that the Court endorse these provisions in the interests of economy as tempered by balance and fairness.

II. PROTECTIVE ORDER

A. Use of Discovery Materials

Lilly drafted paragraph 2 of this Order to exempt from coverage any documents that had become public "without a breach of the terms of this Order," a phrase that plaintiff demands be deleted. In the MDL, Lilly has already suffered a breach of the protective order through the actions of a plaintiff's expert and an Anchorage lawyer. *See In re Zyprexa Products Liability Litigation*, 474 F.Supp.2d 385 (E.D.N.Y. 2007). Lilly cannot fathom why the State of Alaska believes it—or, as in the MDL, a party's expert who had endorsed the

MDL protective order—should be able to make documents public in breach of the order, and then be able to take the position that the documents are not covered by the order. Therefore, Lilly requests that this language be included in the Protective Order.

B. Use of Alaska-Specific Documents Outside of Alaska.

Although, at the last hearing, this Court endorsed the utility of an Alaska-specific Protective Order, plaintiff again attempts to undermine that concept by seeking to eliminate the restriction of the use of confidential documents produced in the Alaska litigation to the Alaska litigation. Paragraph 2 of the proposed order limits the use of documents produced in this case to "this case"; plaintiff prefers to strike that phrase and insert "Zyprexa litigation," so that Alaska discovery can be used for any other litigation—precisely the "second bite at the apple" that this Court forbade. Therefore, Lilly requests that the Court endorse its version of the Order and include the limitation to "this case."

C. Privilege Logs.

Plaintiff next objects to the use of a procedure described in paragraph 3 that has worked well for years in the MDL, imposing additional requirements on privilege logs that are not required by the MDL court. Suffice it to say that, on the basis of logs provided by Lilly in the MDL, plaintiffs have had no difficulty challenging certain redactions by Lilly and, indeed, prevailing on certain such claims. Therefore, Lilly requests that the Court endorse the use of a separate log in the circumstances described in that paragraph.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

D. Coverage of Non-Party Witnesses.

Finally, plaintiff seeks to excise virtually all of paragraph 10(a), which (i) establishes a procedure by which non-party witnesses can be bound by the terms of the Protective Order, and (ii) was the subject of a ruling by the MDL court after the parties failed to agree on that provision. The provision in Lilly's version of the Protective Order tracks the language approved by the MDL court.

DATED this 8th day of June, 2007.

Attorneys for Defendant

PEPPER HAMILTON LLP
Andrew R. Rogoff, admitted *pro hac vice*
3000 Two Logan Square
18th & Arch Streets
Philadelphia, PA 19103
(215) 981-4000

LANE POWELL LLC

By _____
Brewster H. Jamieson, ASBA No. 8411122
Andrea E. Girolamo-Welp, ASBA No. 0211044

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

I certify that on June 8, 2007, a copy of the foregoing was served by hand on:

Eric T. Sanders, Esq.
Feldman Orlansky & Sanders
500 L. Street, Suite 400
Anchorage, Alaska 99501-5911

_____

009867.0038/160898.1

RINDNER

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, vs. ELI LILLY AND COMPANY, Defendant.	Case No. 3AN-06-5630 CIV

NOTICE OF FILING PLAINTIFF'S PROPOSED SUPPLEMENTAL SCHEDULING ORDER

As discussed at the April 6, 2007 status hearing, the parties have been attempting to agree on the terms of a supplemental scheduling order that the Court can issue. Because it is apparent that the parties cannot reach an agreement on this subject, the plaintiff is now submitting its proposed supplemental scheduling order for the Court's consideration.

DATED this 7 day of June, 2007.

FELDMAN ORLANSKY & SANDERS
Counsel for Plaintiff

BY _____
Eric T. Sanders
AK Bar No. 7510085

LAW OFFICES
FELDMAN ORLANSKY
& SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

000347

D

A B C D E

GARRETSON & STEELE
Matthew L. Garretson
Joseph W. Steele
Counsel for Plaintiff

RICHARDSON, PATRICK, WESTBROOK
& BRICKMAN, LLC
H. Blair Hahn
Counsel for Plaintiff

Certificate of Service
I hereby certify that a true and correct copy of **Notice of Filing Plaintiff's Proposed Supplemental Scheduling Order, and Supplemental Scheduling Order** was served by messenger on:

Brewster H. Jamieson
Lane Powell LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648

By Peggy S Crowe
Date 6/7/07

LAW OFFICES
FELDMAN ORLANSKY
& SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
vs.	)	
	)	
ELI LILLY AND COMPANY,	)	
	)	Case No. 3AN-06-5630 CIV
Defendant.	)	
	)	

NOTICE OF FILING PLAINTIFF'S PROPOSED PROTECTIVE ORDER

The parties acknowledge that the Court should issue an order to protect confidential material that may be produced in this case, but are unable to agree on the terms of that order. Accordingly, the plaintiff is now submitting its proposed Protective Order for the Court's consideration.

DATED this 7 day of June, 2007.

FELDMAN ORLANSKY & SANDERS
Counsel for Plaintiff

BY _____
Eric T. Sanders
AK Bar No. 7510085

LAW OFFICES
FELDMAN ORLANSKY
& SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

GARRETSON & STEELE
Matthew L. Garretson
Joseph W. Steele
Counsel for Plaintiff

RICHARDSON, PATRICK, WESTBROOK & BRICKMAN, LLC
H. Blair Hahn
Counsel for Plaintiff

Certificate of Service
I hereby certify that a true and correct copy of **Notice of Filing Plaintiff's Proposed Protective Order, and Protective Order** was served by messenger on:

Brewster H. Jamieson
Lane Powell LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648

By Peggy S. Crowe
Date 6/7/07

LAW OFFICES
FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

RINDNER

FILED
STATE OF ALASKA
THIRD DISTRICT
07 JUN -6 PM 1:19
CLERK, TRIAL COURTS
BY: _____ DEPUTY

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

NONOPPOSITION TO PLAINTIFF'S MOTION FOR EXTENSION OF TIME

COMES NOW, defendant, by and through counsel, and files its nonopposition to plaintiff's Motion for Extension of Time to File Opposition to Motion for Protective Order to Bar the Deposition of Sidney Taurel, dated June 5, 2007.

DATED this 6th day of June, 2007.

LANE POWELL LLC
Attorneys for Defendant

By _____
Brewster H. Jamieson, ASBA No. 8411122

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

I certify that on June 6, 2007, a copy of the foregoing was served by mail on:

Eric T. Sanders, Esq.
Feldman Orlansky & Sanders
500 L. Street, Suite 400
Anchorage, Alaska 99501-591

_____
Nanci L. Biggerstaff, CPS, PLS
009867.0038/460856.1

000351

A B C D E

RINDNER

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, vs. ELI LILLY AND COMPANY, Defendant.	Case No. 3AN-06-5630 CIV

MOTION FOR EXTENSION OF TIME TO FILE OPPOSITION TO MOTION FOR PROTECTIVE ORDER TO BAR THE DEPOSITION OF SIDNEY TAUREL

Plaintiff, State of Alaska, by and through its counsel, Feldman Orlansky & Sanders, requests that this Court grant it a three-day extension to Friday, June 8, 2007, to file its opposition to Eli Lilly's Motion for Protective Order to Bar the Deposition of Sidney Taurel. This extension is needed because Eric Sanders was required to be in Washington DC between May 29 and June 1, 2007, on an unrelated legal matter.

DATED this 5 day of June, 2007.

FELDMAN ORLANSKY & SANDERS
Counsel for Plaintiff

BY _____
Eric T. Sanders
AK Bar No. 7510085

LAW OFFICES
FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK 99501
TEL: 907.272.3538
FAX: 907.274.0819

GARRETSON & STEELE
Matthew L. Garretson
Joseph W. Steele
Counsel for Plaintiff

RICHARDSON, PATRICK, WESTBROOK
& BRICKMAN, LLC
H. Blair Hahn
Counsel for Plaintiff

Certificate of Service
I hereby certify that a true and correct copy of **Motion for Extension of Time to File Opposition to Motion for Protective Order to Bar Deposition of Sidney Taurel** was served by messenger on:

Brewster H. Jamieson
Lane Powell LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648

By Peggy D. Crowe
Date 6/5/07

LAW OFFICES
FELDMAN ORLANSKY
& SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
AT ANCHORAGE

State of Alaska — Plaintiff/Petitioner

vs.

Eli Lilly & Co — Defendant/Respondent.

CASE NO. 3AN-06-05630CI

CALENDARING NOTICE

This case is scheduled for:

Date: 06/22/2007
Time: 4:00 pm
Event: Status Hearing: Superior Court
Judge: Mark Rindner
Court: 825 W 4th Ave , Anchorage, Alaska 99501
Location: Courtroom 403, Anchorage Courthouse

6/1/2007
Effective Date

Mark Rindner
Superior Court Judge

I certify that on 6/1/2007, a copy of this order was mailed to:
Brewster H Jamieson
Eric T Sanders

Secretary/Clerk: LShaw

Hearing/Event information for this case is also available online at http://www.courtrecords.alaska.gov/.

FILE COPY

CALNOTICE
CALENDARING ORDER

000354

A B C D E

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

ORDER

Defendant Eli Lilly and Company's request for oral argument is GRANTED. Oral argument on Plaintiff's Motion for Rule of Law Concerning Its Claims and Proofs is set for July 12, 2007, at 3:30 ~~am~~/pm. Each party is granted 30 minutes.

ORDERED this 1st day of June, 2007.

Mark Rindner

The Honorable Mark Rindner
Judge of the Superior Court

I certify that on May 29, 2007, a copy of the foregoing was served by mail on:

Eric T. Sanders, Esq.
Feldman Orlansky & Sanders
500 L. Street, Suite 400
Anchorage, Alaska 99501-5911

009867.0038/160789.1

I certify that on June 1, 2007 a copy of the above was mailed to each of the following at their addresses of record:

Sanders Jamieson

Administrative Assistant

000355

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

MAY 30 2007

RENDER

FILED
STATE OF ALASKA
THIRD DISTRICT
07 MAY 30 PM 3:34
CLERK, TRIAL COURTS
BY _____ DEPUTY

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

DEFENDANT'S REQUEST FOR ORAL ARGUMENT

COMES NOW, defendant Eli Lilly and Company, by and through counsel, and requests oral argument on Plaintiff's Motion for Rule of Law Concerning Its Claims and Proofs.

DATED this 29th day of May, 2007.

LANE POWELL LLC
Attorneys for Defendant

By _____
Brewster H. Jamieson, ASBA No. 8411122
Andrea E. Girolamo-Welp, ASBA No. 0211044

I certify that on May 29, 2007, a copy of the foregoing was served by mail on:

Eric T. Sanders, Esq.
Feldman Orlansky & Sanders
500 L. Street, Suite 400
Anchorage, Alaska 99501-5911

_____

009867.0038/160788.1

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

A B C D E

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Filed in the Trial Courts
STATE OF ALASKA, THIRD DISTRICT
MAY 25 2007
Clerk of the Trial Courts
By Deputy

Case No. 3AN-06-05630 CI

DEFENDANT ELI LILLY AND COMPANY'S MOTION FOR PROTECTIVE ORDER TO BAR THE DEPOSITION OF SIDNEY TAUREL AND MEMORANDUM IN SUPPORT

Defendant Eli Lilly and Company ("Lilly") hereby moves for a protective order, pursuant to Alaska Civil Rule 26(c), barring the deposition of its Chairman and Chief Executive Officer, Sidney Taurel. Lilly's memorandum in support follows.

INTRODUCTION

Sidney Taurel, Chairman and Chief Executive Officer of Indianapolis-based Eli Lilly and Company, does not possess unique information about any facts relevant to this case. The State of Alaska, however, demands that Mr. Taurel appear for a deposition, but refuses to identify one valid example of such unique knowledge that would justify such a deposition.

At the most recent hearing in this matter, the Court several times instructed plaintiff to confine its discovery to Alaska-specific issues. The State ignored that directive, and it refused Lilly's request that it complete less burdensome discovery of individuals with direct

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

knowledge of relevant facts before deciding whether to pursue Mr. Taurel's deposition. Accordingly, Lilly seeks a protective order under Rule 26(c) of the Alaska Rules of Civil Procedure to bar the deposition of Mr. Taurel.

FACTUAL BACKGROUND

Mr. Taurel serves as chief executive of Lilly, a pharmaceutical company with worldwide operations, approximately 41,500 employees, and revenues last year of about $15.69 billion. *See* Affidavit of James B. Lootens, ¶ 4, attached hereto as Exhibit A [hereafter, "Lootens Aff."]. Lilly conducts clinical research in more than 50 countries, performs research and development in nine countries, manufactures medicines in 13 countries, and markets products in 143 countries. *Id.* There is much more to Lilly than Zyprexa and this litigation.

Mr. Taurel has been Lilly's CEO since July 1998, and Chairman of the Board of Directors since January 1999. Lootens Aff., ¶ 2. As Lilly's Chairman and CEO, Mr. Taurel oversees all aspects of Lilly's operations. *Id.*, ¶ 5. His duties do not focus on Zyprexa. *Id.* In addition to his responsibilities at Lilly, Mr. Taurel serves on the boards of directors of IBM Corporation and of the McGraw-Hill Companies, Inc. *Id.*, ¶ 3.

After the State told Lilly that it wanted to take Mr. Taurel's deposition, Lilly informed the State that the deposition would be unnecessary and improper unless the State had some basis for believing that Mr. Taurel possesses unique knowledge of relevant facts unavailable

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

through less intrusive methods of discovery and from other witnesses. Exhibit B. Lilly's counsel therefore requested that the State pursue other, less burdensome avenues of discovery, before seeking Mr. Taurel's deposition. *Id.*

By electronic mail on April 30, 2007, the State asserted that "it is obvious that Mr. Taurel has unique personal knowledge of matters that are critical to this litigation…." *Id.* Accordingly, the State's counsel stated, "[w]e will notice Mr. Taurel's deposition for a time of our convenience." *Id.* On May 2, 2007, the State served a notice of deposition setting Mr. Taurel's deposition for June 1, 2007, in Indianapolis, Indiana. Exhibit C. The parties agreed to postpone Mr. Taurel's deposition until the Court rules on this motion.

ARGUMENT

I. DEPOSITIONS OF TOP-LEVEL EXECUTIVES ARE IMPROPER UNLESS THE EXECUTIVE HAS UNIQUE KNOWLEDGE OF RELEVANT FACTS UNAVAILABLE FROM LESS INTRUSIVE DISCOVERY.

This Court has emphasized that the parties should focus their discovery on Alaska-specific issues, especially in view of the massive discovery that has been completed across the country in other Zyprexa-related matters. As the Court stated during the most recent hearing:

> I've given you ten depositions … and they're limited to Alaska stuff. … [Y]ou're going to focus on the Alaska issues that wouldn't have been covered in the MDL and you've got ten depositions to do that. Beyond that, depositions need to be coordinated with the MDL unless you come

> back to me and say, we want to take this witness, Judge, and here's why we don't think it should be coordinated.[1]

Just as this Court has instructed the parties to concentrate on state-specific concerns, the Alaska Rules of Civil Procedure further empower it to bar discovery from Lilly's top executive and order the State instead to seek discovery from Lilly's lower-level employees with direct knowledge of the relevant facts.

Indeed, Rule 26 requires the Court to limit unreasonably burdensome and harassing discovery. Rule 26(b)(2) provides that "use of the discovery methods otherwise permitted under these rules *shall* be limited by the court if … (i) the discovery sought is unreasonably cumulative or duplicative, or is obtainable from some other source that is more convenient, less burdensome, or less expensive; … or (iii) the burden or expense of the proposed discovery outweighs its likely benefit…." *Id.* (emphasis added). Rule 26(c) provides for entry of a protective order "[u]pon motion by a party … from whom discovery is sought … and for good cause shown." Alaska R. Civ. P. 26(c). The Court has "broad discretion to determine the scope and extent of discovery and to craft protective orders." *DeNardo v. Box*, 147 P.3d 672, 676 (Alaska 2006).

The Court may bar depositions of witnesses with limited first-hand knowledge, where the burdensomeness of the depositions outweighs their likely benefit, as the Alaska Supreme

[1] Transcript of Hearing on April 6, 2007, at pp. 31-33, attached hereto as Exhibit D.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

Court recently affirmed in *Gibson v. GEICO General Ins. Co.*, 153 P.3d 312 (Alaska 2007). In *Gibson*, the trial court entered a protective order barring the depositions of two individuals who lacked first-hand knowledge of the determinative facts. The Alaska Supreme Court held that the trial court acted within its discretion by prohibiting two such depositions:

> Civil Rule 26(b)(2) permits the court to limit the scope of discovery pursuant to a motion for a protective order like the one brought by GEICO. Discovery may be limited because evidence is "unreasonably cumulative or duplicative, or . . . obtainable from some other source that is more convenient, less burdensome, or less expensive" or because "the burden or expense of the proposed discovery outweighs its likely benefit, taking into account . . . the importance of the proposed discovery in resolving the issues." Even if deposing the claims adjustors might have led to some information on damages, the likely benefit of such information seems small given the availability of medical records and testimony. Gibson does not assert that the adjustors possessed personal knowledge about her damages. Since the relevant information the adjusters had was obtainable from other sources and the bulk of their testimony was likely to be tangential to the issue of damages, a conclusion that the burden of the discovery outweighed its likely benefit would have been within the court's discretion.[2]

Although Alaska courts have not yet had the opportunity to apply this Rule 26 analysis to the proposed deposition of a top-level executive, courts elsewhere applying similar rules have overwhelmingly concluded that such a deposition is improper unless the executive

[2] *Gibson*, 153 P.3d 312, 316-17 (quoting Alaska R. Civ. P. 26(b)(2)). *See also, e.g.*, *Mullin v. State*, 2003 WL 22208506, *4 (Alaska App. 2003) (holding that trial court did not abuse its discovery under Rule 26(b)(2)(i) and (iii) by restricting discovery where "there were other ways for [proponent] to prove the same thing").

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

possesses unique personal knowledge of relevant facts that cannot be discovered through less intrusive methods. In *Celerity, Inc. v. Ultra Clean Holding, Inc.*, 2007 WL 205067 (N.D. Cal. 2007), the court recently summarized this case law:

> Virtually every court that has addressed deposition notices directed at an official at the highest level or "apex" of corporate management has observed that such discovery creates a tremendous potential for abuse or harassment. Where a high-level decision maker removed from the daily subjects of the litigation has no unique personal knowledge of the facts at issue, a deposition of the official is improper. This is especially so where the information sought in the deposition can be obtained through less intrusive discovery methods (such as interrogatories) or from depositions of lower-level employees with more direct knowledge of the facts at issue.[3]

Recognition of the need to police harassing deposition practices aimed at top-level employees extends to state courts as well. For example, in *Liberty Mutual Ins. Co. v. Superior Court*, 13 Cal. Rptr. 2d 363, 365 (Cal. App. 1992), the California Court of Appeals held that "it amounts to an abuse of discretion to withhold a protective order when a plaintiff seeks to depose a corporate president, or corporate officer at the apex of the corporate hierarchy,

[3] *Celerity*, 2007 WL 205067, *3 (emphasis added; citations & quotation marks omitted). *See also*, *e.g.*, *Thomas v. IBM*, 48 F.3d 478, 483 (10th Cir. 1995) (affirming order precluding deposition of chairman of IBM's board of directors); *Lewelling v. Farmers Ins. Co. of Columbus, Inc.*, 879 F.2d 212, 218 (6th Cir. 1989) (affirming order precluding deposition of CEO); *Salter v. Upjohn Co.*, 593 F.2d 649, 650-51 (5th Cir. 1979) (affirming order precluding deposition of CEO unless proponent could demonstrate that the information sought was unavailable from lower-level employees); *Evans v. Allstate Ins. Co.*, 216 F.R.D. 515, 519 (N.D. Okla. 2003) (precluding depositions of Allstate executives where the information sought could "be obtained from other sources without deposing these 'apex' officers"); *Harris v. Computer Assocs. Int'l, Inc.*, 204 F.R.D. 44, 46-47 (E.D.N.Y. 2001) ("When a vice president can contribute nothing more than a lower level employee, good cause is not shown to take the deposition."); *Baine v. General Motors Corp.*, 141 F.R.D. 332, 334 (M.D. Ala. 1991); *Mulvey v. Chrysler Corp.*, 106 F.R.D. 364 (D.R.I. 1985) (precluding deposition of Chrysler CEO).

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

absent a reasonable indication of the officer's personal knowledge of the case and absent exhaustion of less intrusive discovery methods." *Id.* Similarly, in *Crown Cent. Petroleum Corp. v. Garcia*, 904 S.W.2d 125, 128 (Tex. 1995), the Texas Supreme Court held that "[i]f the party seeking the deposition cannot show that the official has any unique or superior personal knowledge of discoverable information, the trial court should grant the motion for protective order and first require the party seeking the deposition to attempt to obtain the discovery through less intrusive methods." *Id.* Other state appellate courts have reached similar conclusions.[4]

In short, the proponent of an executive's deposition must show more than that the executive merely has some knowledge of relevant facts. Rather, the executive's knowledge of relevant facts must be both (1) "unique," *i.e.*, non-cumulative, and (2) unavailable from less intrusive discovery. "This is an essential component of the standard for an apex deposition – unique personal knowledge by the high corporate official, unavailable from less intrusive discovery, including interrogatories and the depositions of lower-level employees."

[4] *E.g.*, *Ford Motor Co. v. Messina*, 71 S.W.3d 602, 607 (Mo. 2002) ("A protective order should issue if annoyance, oppression, and undue burden and expense outweigh the need for discovery. For top-level employee depositions, the court should consider: whether other methods of discovery have been pursued; the proponent's need for discovery by top-level depositions; and the burden, expense, annoyance and oppression to the organization and the proposed deponent."); *Shields v. Morgan Financial, Inc.*, 125 P.3d 164, 169 (Wash. App. 2005) (holding under Washington's Rule 26 that "a protective order barring the deposition of [defendant]'s high level corporate executives was appropriate").

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

Celerity, 2007 WL 205067, *4. Further, as with any deposition, the overall "likely benefit" of the deposition must outweigh its burdensomeness. *Gibson*, 153 P.3d 312, 317.

II. THE STATE CANNOT ESTABLISH THAT MR. TAUREL HAS UNIQUE KNOWLEDGE OF RELEVANT FACTS UNAVAILABLE THROUGH LESS INTRUSIVE DISCOVERY.

The State has neither shown that Mr. Taurel is likely to have any unique knowledge of facts relevant to the parties' claims and defenses here, nor that the information it seeks to obtain from Mr. Taurel cannot be gotten through less intrusive methods of discovery, such as interrogatories and depositions of others. The State's *entire* justification for seeking Mr. Taurel's deposition is set forth in an e-mail to Lilly's counsel, as follows:

> As CEO and Chairman of Lilly's Policy and Strategy Committee which met to discuss Zyprexa safety issues it is obvious that Mr. Taurel has unique personal knowledge of matters that are critical to this litigation and the decisions Lilly made to not warn physicians and consumers about the risks of the drug. In addition, as Chairman of the Board, he would have unique knowledge as to what safety information regarding Zyprexa was passed on to the Board of Directors and what was not provided to them. Moreover, since John Lechleiter testified he was unable to recall whether Mr. Taurel was even present at a particular meeting of the Policy and Strategy Committee in April of 2002 and testified he was unable to recall whether he passed certain safety information on to Mr. Taurel and other members of the Policy and Strategy Committee that he was informed of in July of 2002, it is necessary and appropriate for plaintiffs to depose Mr. Taurel for that reason as well. Exhibit B.

With respect to Mr. Taurel's role on the Policy and Strategy Committee, the State has identified two specific areas of inquiry that it would like to raise with Mr. Taurel, neither of

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
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which justifies the burden of a deposition. First, the State claims it needs to depose Mr. Taurel to learn "whether Mr. Taurel was even present at a particular meeting of the Policy and Strategy Committee in April of 2002." *Id.* Second, the State claims that it needs to depose Mr. Taurel to ask him whether John Lechleiter passed certain information to Mr. Taurel and other members of the Policy and Strategy Committee in July 2002. *Id.* Assuming for the sake of argument that this information is relevant to the claims or defenses of the parties, it is neither unique to Mr. Taurel (*i.e.*, he is not the only possible source), nor is it the type of information that cannot be sought by less intrusive methods of discovery.

Beyond these two specific questions, the State does not even attempt to explain what unique knowledge of facts relevant to this Alaska litigation that it believes Mr. Taurel has that no other Lilly employee has. Instead, the State simply asserts it is "obvious" that Mr. Taurel has such knowledge, by virtue of the fact that he is Lilly's Chairman and CEO and chair of its Policy and Strategy Committee. The State ignores its burden to demonstrate that Mr. Taurel has unique knowledge, *i.e.*, non-cumulative knowledge unavailable from other sources. "[U]nique personal knowledge must be truly unique – the deposition [will] not be allowed where the information could be had through interrogatories, deposition of a designated spokesperson, or deposition testimony of other persons." *Baine v. General Motors Corp.*, 141 F.R.D. 332, 334 (M.D. Ala. 1991). Information that Mr. Taurel obtained

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Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

from others at Lilly is not unique to him, but cumulative of the knowledge of the individuals from whom he obtained the information.

It is not enough for the State to argue merely that Mr. Taurel may have been present at meetings where he may have participated in policy discussions regarding Zyprexa. Indeed, the State has not even taken the trouble of confirming that Mr. Taurel actually was present at the April 2002 meeting of the Policy and Strategy Committee before noticing his deposition to ask him questions about that meeting. The fact that an executive helped formulate a policy or draft a memorandum relevant to the litigation does not necessarily subject that executive to deposition. *See, e.g., Baine*, 141 F.R.D. 332; *Thomas v. IBM*, 48 F.3d 478, 483 (10th Cir. 1995) (affirming order precluding deposition of chairman of IBM's board of directors even though he had drafted a policy relevant to the plaintiff's claim, where others had more direct knowledge of the facts of the case). In *Baine*, for example, the plaintiff sought to depose the head of General Motors' Buick Division, who had previously drafted a memorandum describing his observations of the performance of a prototype of the vehicle restraint system that allegedly failed in an accident. *Id.* at 333-34. Noting that "[t]he legal authority is fairly unequivocal in circumstances such as these," the court precluded the executive's deposition because the plaintiff had not shown that the executive possessed "any superior or unique personal knowledge of the restraint system" or "that the information necessary cannot be had from [other witnesses], interrogatories, or the corporate deposition." *Id.* at 334-35.

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Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

Here, too, the State speculates that Mr. Taurel, and Mr. Taurel alone, possesses significant, heretofore unknown facts about Zyprexa or Lilly's actions regarding Zyprexa, as well as unique information about the sale of Zyprexa in Alaska specifically. Although discovery in this action is at an early stage, extensive discovery has already been completed in the Zyprexa MDL. To further the Zyprexa MDL's goal of efficient discovery,[5] Judge Weinstein has ordered the Plaintiff's Steering Committee ("PSC") to make its collection of documents, depositions and other Zyprexa MDL discovery materials "available free of charge to litigants in state cases." *See* Memorandum on Cooperation Between Federal and State Judges at 1, MDL 1596-JBW (filed 1/22/2007) (attached hereto as Exhibit E). Consequently, all of the Zyprexa MDL discovery is available to the State in this case and need not be duplicated. Indeed, the State's counsel was present at, and took many of, these depositions.

In the Zyprexa MDL, more than 15 million pages of documents have been produced, and dozens of current and former Lilly employees have been deposed on a wide range of topics, including employees intimately familiar with the development, safety, labeling, and marketing of Zyprexa. Although the PSC at one point sought to depose Mr. Taurel, at Lilly's request, it instead pursued depositions of Lilly employees with more direct knowledge of the relevant facts. The PSC ultimately did not find it necessary to pursue Mr. Taurel's

[5] *See In re Zyprexa Products Liability Litigation*, MDL 1596, 314 F. Supp. 2d 1380 (J.P.M.L. 2004) (establishing Zyprexa MDL).

deposition, and Mr. Taurel has never been deposed in connection with Zyprexa litigation. The State has no greater need for Mr. Taurel's deposition in this case, which is limited to Alaska, than the PSC did in the Zyprexa MDL, which is national in scope.

Lilly employees with more direct knowledge of relevant facts who were deposed in the Zyprexa MDL include the following individuals, among many others:

- President and Chief Operating Officer, John Lechleiter, who is a member of Lilly's Board of Directors and is Lilly's second-ranking executive after Mr. Taurel. Mr. Lechleiter has been a member of Lilly's Policy and Strategy Committee since 1998.
- Vice President and Chief Medical Officer, Alan Breier, M.D. Dr. Breier was head of the Zyprexa Product Team from 1999 to 2002, and was responsible for medical and marketing aspects of the Zyprexa product, including label modifications.
- Gary Tollefson, M.D. Dr. Tollefson was head of the Zyprexa Product Team from 1994 until 1999, and was responsible for the clinical development and commercial launch of Zyprexa and for medical and marketing aspects of the Zyprexa product.
- Chief Scientific Officer for Global Product Safety, Charles Beasley, M.D.
- Manager of U.S. Regulatory Affairs, Michele Sharp. From 1999 through 2005, Ms. Sharp had direct responsibility for the Zyprexa label and package insert.
- Former Marketing Director for the Zyprexa Product Team, Denice Torres.

The depositions of these individuals alone yielded thousands of pages of detailed testimony covering the range of issues relevant to this litigation – including the development, safety, labeling, marketing and distribution of Zyprexa – by individuals with direct

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Telephone 907.277.9511 Facsimile 907.276.2631

knowledge of those issues. Although these individuals, and others, report through the chain of command to Mr. Taurel, the responsibilities of the CEO and Chairman do not include direct involvement with clinical research, adverse event reporting or marketing for Zyprexa or other medications. Lootens Aff. ¶ 6. Any specific knowledge Mr. Taurel may have with respect to Zyprexa's development, clinical trials, and adverse event reporting would have been relayed to him by others at Lilly. *Id.* Additionally, Mr. Taurel is not a medical doctor or clinical researcher, and relies on the professional judgment of other Lilly employees who have particular expertise in those areas. *Id.*, ¶ 7. Thus, any relevant information that Mr. Taurel may be able to provide in a deposition could be – and, in fact, likely already has been – obtained from other sources. In view of the extensive discovery already conducted in the Zyprexa MDL, it is not plausible for the State to speculate that Mr. Taurel's deposition will reveal any significant new information relevant to the parties' claims and defenses in this case, which deals specifically with the sale of Zyprexa in Alaska.

Absent a showing that there remains relevant information not covered by the broad discovery in the Zyprexa MDL, which is known only to Mr. Taurel himself and which cannot be obtained by less intrusive methods of discovery, the State cannot establish the unique personal knowledge required to justify Mr. Taurel's deposition.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

CONCLUSION

For the foregoing reasons, Lilly respectfully requests that the Court issue a protective order barring the deposition of Sidney Taurel.

DATED this 25th day of May, 2007.

Attorneys for Defendant

PEPPER HAMILTON LLP
Andrew R. Rogoff, admitted *pro hac vice*
3000 Two Logan Square
18th & Arch Streets
Philadelphia, PA 19103
(215) 981-4000

LANE POWELL LLC

By _____
Brewster H. Jamieson, ASBA No. 8411122
Andrea E. Girolamo-Welp, ASBA No. 0211044

I certify that on May 25, 2007, a copy of the foregoing was served by hand-delivery, on:

Eric T. Sanders, Esq., Feldman Orlansky & Sanders
500 L. Street, Suite 400, Anchorage, Alaska 99501-5911

_____

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LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT

STATE OF ALASKA, Plaintiff, vs. ELI LILLY AND COMPANY, Defendant.	) Case No. 3AN-06-5630CIV

AFFIDAVIT OF JAMES B. LOOTENS IN SUPPORT OF MOTION FOR PROTECTIVE ORDER TO BAR THE DEPOSITION OF SIDNEY TAUREL

I, James B. Lootens, being duly sworn, state as follows:

1. I am Secretary of Eli Lilly and Company ("Lilly"), and make this affidavit based on my own personal knowledge and my investigation of the facts stated herein.

2. Sidney Taurel is the Chairman of the Board of Directors and Chief Executive Officer ("CEO") of Lilly. He has been Lilly's CEO since July 1998, and has been Chairman of Lilly's Board of Directors since January 1999.

3. In addition to Mr. Taurel's responsibilities at Lilly, he serves on the boards of directors of IBM Corporation and of the McGraw-Hill Companies, Inc.

4. Lilly is a pharmaceutical company with worldwide operations, approximately 41,500 employees, and revenues last year of about $15.69 billion. Lilly conducts clinical research in more than 50 countries, performs research and development in nine countries, manufactures medicines in 13 countries, and markets products in 143 countries.

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EXHIBIT A
PAGE 1 OF 2

B C D E

5. As Lilly's Chairman and CEO, Mr. Taurel is responsible for overseeing all aspects of Lilly's operations, in the United States as well as internationally. Zyprexa is one of many products manufactured and sold by Lilly, and Mr. Taurel's duties and responsibilities are not limited to or focused solely on issues related to Zyprexa.

6. Mr. Taurel's responsibilities as Lilly's Chairman and CEO do not include direct involvement with clinical research, adverse event reporting or marketing for Zyprexa or other medications. He has no unique knowledge with respect to clinical research, adverse event reporting, safety, or marketing for Zyprexa, and he would not have personal knowledge about these issues beyond the knowledge that has been relayed to him.

7. Mr. Taurel is not a medical doctor or clinical researcher. With respect to matters that require expertise in medicine or clinical research, he relies on the professional judgment of Lilly employees who have particular expertise in those areas.

James B. Lootens

SWORN TO AND SUBSCRIBED
BEFORE ME, NOTARY, this
23 day of May, 2007
Marie A. Thomas
Notary Public

NOTARY PUBLIC SEAL INDIANA

Marie A. Thomas, Notary Public
Resident of Marion County
My Commission Expires:
February 10, 2009

Lehner, George A.

From: David Suggs [dsuggs@attglobal.net]
Sent: Monday, April 30, 2007 11:24 AM
To: Lehner, George A.
Subject: RE: Alaska AG Action

George –

As CEO and Chairman of Lilly's Policy and Strategy Committee which met to discuss Zyprexa safety issues it is obvious that Mr. Taurel has unique personal knowledge of matters that are critical to this litigation and the decisions Lilly made to not warn physicians and consumers about the risks of the drug. In addition, as Chairman of the Board, he would have unique knowledge as to what safety information regarding Zyprexa was passed on to the Board of Directors and what was not provided to them. Moreover, since John Lechleiter testified he was unable to recall whether Mr. Taurel was even present at a particular meeting of the Policy and Strategy Committee in April of 2002 and testified he was unable to recall whether he passed certain safety information on to Mr. Taurel and other members of the Policy and Strategy Committee that he was informed of in July of 2002, it is necessary and appropriate for plaintiffs to depose Mr. Taurel for that reason as well.

We will notice Mr. Taurel's deposition for a time at our convenience.

From: Lehner, George A. [mailto:lehnerg@pepperlaw.com]
Sent: Thursday, April 26, 2007 5:30 PM
To: dsuggs@attglobal.net
Subject: Alaska AG Action

David -

You have asked us to consider providing a date for the deposition of Sidney Taurel in connection with the on-going discovery in the Alaska AG case. After considerable review, we do not believe it is appropriate for plaintiff to take Mr. Taurel's deposition in this case. As you surely appreciate, Mr. Taurel, as Lilly's CEO, has an extensive schedule and company-wide responsibilities. But more importantly for this case, he does not have unique, first-hand knowledge of the facts at issue in the Alaska AG action. It is our understanding that the law requires plaintiff to exhaust more direct and less burdensome avenues of discovery before pursuing Mr. Taurel's deposition: "Virtually every court that has addressed deposition notices directed at an official at the highest level or 'apex ' of corporate management has observed that such discovery creates a tremendous potential for abuse or harassment. Where a high-level decision maker removed from the daily subjects of the litigation has no unique personal knowledge of the facts at issue, a deposition of the official is improper." *Celerity, Inc. v. Ultra Clean Holding, Inc.*, 2007 WL 205067, *3 (N.D. Cal. 2007).

Unless you can first establish a high likelihood of "unique personal knowledge by the high corporate official, unavailable from less intrusive discovery, including interrogatories and the depositions of lower-level employees," we do not see a basis for this deposition. *Id.* at *4. *See also Gibson v. GEICO General Ins. Co.*, 153 P.3d 312 (Alaska 2007) (affirming protective order barring depositions of witnesses where "the relevant information the [witnesses] had was obtainable from other sources and ... the burden of the discovery outweighed its likely benefit").

Accordingly, we request that you pursue other, less burdensome avenues of discovery (consistent with the Court's direction on the nature of the discovery to be conducted in this case) at this time, rather than seeking Mr. Taurel's deposition. If you nevertheless believes there is a basis for taking Mr. Taurel's deposition now, then, please set out in detail the unique knowledge that Mr. Taurel possesses and the reasons why it is necessary to take his deposition at this

Alaska AG Action

point.

George

George A. Lehner
Pepper Hamilton LLP

600 14th Street N.W.
Washington D.C. 20005-2004
Tele: 202-220-1416
Fax: 202-220-1665
lehnerg@pepperlaw.com

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, vs. ELI LILLY AND COMPANY, Defendant.	Case No. 3AN-06-5630 CIV

NOTICE OF VIDEOTAPED DEPOSITION

PLEASE TAKE NOTICE that pursuant to Rules 26, 30 and 30.1 of the Alaska Rules of Civil Procedure, Plaintiff will take the deposition upon oral examination of SIDNEY TAUREL on June 1, 2007, at 9:00 A.M. at a place to be determined in Indianapolis, Indiana. The deposition will be taken before a Notary Public or some other person authorized by Rule 28 of the Alaska Rules of Civil Procedure to administer oaths and it will be recorded stenographically and videotaped.

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LAW OFFICES
FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK 99501
TEL: 907.272.3538
FAX: 907.274.0819

D E

DATED this 2 day of May, 2007.

FELDMAN ORLANSKY & SANDERS
Counsel for Plaintiff

By _____
Eric T. Sanders
AK Bar No. 7510085

GARRETSON & STEELE
Matthew L. Garretson
Joseph W. Steele
Counsel for Plaintiff

RICHARDSON, PATRICK,
WESTBROOK & BRICKMAN, LLC
H. Blair Hahn
Counsel for Plaintiff

Certificate of Service
I hereby certify that a true and correct copy the foregoing Notice of Videotaped Deposition (Sidney Taurel) was served by mail / messenger / facsimile on:

Brewster H. Jamieson
Lane Powell LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648

By Peggy S. Crowe
Date 5/2/07

LAW OFFICES
FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK 99501
TEL: 907.272.3538
FAX: 907.274.0819

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,
Plaintiff,
vs.
ELI LILLY AND COMPANY,
Defendant.

Case No. 3AN-06-05630 Civil

TRANSCRIPT OF PROCEEDINGS

April 6, 2007 - Pages 1 through 45

A-P-P-E-A-R-A-N-C-E-S

For Plaintiff: FELDMAN ORLANSKY & SANDERS
500 L Street, Suite 400
Anchorage, Alaska 99501-5911
BY: ERIC T. SANDERS
(907) 272-3538

For Defendant: LANE POWELL LLC
301 West Northern Lights Boulevard
Suite 301
Anchorage, Alaska 99503-2648
BY: ANDREA E. GIROLAMO-WELP
(907) 264-3322

For Defendant Telephonically: MR. ANDREW ROGOFF
MR. ERIC ROTHSCHILD

THE COURT: Please be seated. We're on the record in Case No. 3AN-06-5630 Civil, State of Alaska versus Eli Lilly and Company. Representing the plaintiff is Mr. Sanders. Present in the courtroom for the defendant is Ms. --

MS. GIROLAMO-WELP: Girolamo-Welp.

THE COURT: Girolamo-Welp. Sorry. And I understand Mr. Rogoff is on the telephone for the defendant and maybe somebody else?

MR. ROGOFF: Yes, Your Honor. Eric Rothschild is with me, one of my colleagues.

THE COURT: Mr. Rothschild is also there.

This is a status hearing that I believe was requested by the defendant. What are the issues that we need to deal with?

MR. ROGOFF: Your Honor, if I may. This is Andrew Rogoff. I think it's really something that both the parties, even if we requested it technically, both the parties would need Your Honor's assistance in this. You

any problems with the coordination issues that Mr. Rogoff has raised?

MR. SANDERS: Yes, I do. Because, I mean, I'm not part of the MDL and so if they notice up --

THE COURT: You keep on saying that, Mr. Sanders, but part of what I'm going to do here is try to make everything efficient and whether or not you're part of the MDL or not, there are issues of efficiency and nonduplication. And a concern that I raised at the very first hearing where you told me I shouldn't worry about it, but I still do and continue to worry about it every time these issues come up, that this is an effort by co-counsel and other plaintiff's things to get second bites at the apple, and I'm going to resist that as much as I'm going to resist them limiting your depositions. And I don't understand if you're going to be narrow and focused and there's a limited number of Alaska-specific things, that if you go beyond that why you shouldn't coordinate with everybody else on the same subject matters and the same non-Alaska specific kinds of things.

MR. SANDERS: And, Your Honor, I guess what I would say is that when you see me in here and I'm being obstreperous and I'm causing problems in this case, then you get to chew me out, okay. Then the rubber meets the road here. What I'm saying is, why am I being forced to get in bed on a case I'm not involved in unless I'm causing a problem? And what you're saying is, well, I know you haven't caused any problems yet, but I just want to make sure you don't cause any problems in the future by requiring you to do these things. And what I'm saying is, don't -- don't parade -- assume that I'm going to be a problem, because I haven't been a problem yet and I don't anticipate I'm going to be. But I don't want to have to worry about what's going on in MDL. I'm going to worry about what's going on on behalf of the State of Alaska, and that's my --

THE COURT: Right, but I've given you ten depositions that I'm -- you're correct in terms of what I ruled before -- that are sort of noncoordinated and you're free to pick your ten witnesses and depose them and they're limited to Alaska stuff. What I'm asking,

though, is what are all these other ones and why shouldn't they be coordinated? I mean, once you start getting into a lot of depositions, I'm trying to avoid having deponents be deposed five times.

MR. SANDERS: I don't know if it's a problem or not because I don't have any idea what's going on in MDL. I've never done any work in the MDL. For all I know there's a deposition being taken today in the MDL. I have no --

THE COURT: But don't you have co-counsel -- I mean, I've got -- I just signed orders for about six or seven plaintiff's attorneys that are co-counseling this case with you, and I assume a few of them have something to do with MDL.

MR. SANDERS: To be honest with you, I have enough work to do without being involved in the MDL, and I am not involved in the MDL. So, I mean, if you want to say to me today -- I'll live with your orders, Judge, if your position is, Sanders, whether you like it or not you're getting involved in the MDL, I'll live with your order. My position is, I don't

want to be involved in it; I'm going to resist it, you know, but if you make me do it, I guess I'll do it. I don't want to do it.

THE COURT: What I'm ordering is you've got ten depositions that you can notice up without coordination. I assume, until it's proven otherwise, that as to those ten witnesses you're going to focus on -- you're not going to try to duplicate things and it's not going to be second bites at the apple about things that have previously been covered by people's depositions, and I'm not going to get a lot of stuff about people questioning people about things they've said in other -- when the deposition was taken in the MDL, since you don't care about the MDL, so I assume you won't need their depositions for that purpose, that you're going to focus on the Alaska issues that wouldn't have been covered in the MDL and you've got ten depositions to do that. Beyond that, depositions need to be coordinated with the MDL unless you come back to me and say, we want to take this witness, Judge, and here's why we don't think it should be coordinated.

MR. SANDERS: Well, let me just

say you're changing your initial order in this case by your -- I just want to make sure that that's clear. Because we were entitled -- we are entitled today to take ten depositions, any ten we want --

THE COURT: Right.

MR. SANDERS: -- in this case.

THE COURT: Right.

MR. SANDERS: No limits on what we can ask, no question about what the scope of the depositions are; we get --

THE COURT: Right, other than I have expressed more than once about a concern have that people not use these things -- use this case as a stalking horse to get second bites of the apple for the MDL case.

MR. SANDERS: Not for the MDL, okay, that's -- okay, I understand that.

THE COURT: I'm going to -- that's my concern.

MR. SANDERS: Now, let me ask you a question, though. I notice up a deposition of a Lilly employee or a former Lilly employee for June 1st. Do I have to worry about MDL lawyers come in and saying, wait a minute, we want to

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK
----------x

In re: ZYPREXA
PRODUCTS LIABILITY LITIGATION
----------x

MEMORANDUM ON
COOPERATION BETWEEN
FEDERAL AND STATE
JUDGES

THIS DOCUMENT RELATES TO:

ALL ACTIONS

04-MD-1596 (JBW)

----------x

JACK B. WEINSTEIN, Senior United States District Judge:

To: All state judges handling "Zyprexa-diabetes" cases
Re: Plaintiffs' Attorneys' Fees in "Zyprexa-diabetes" Cases

1. Before me are hundreds of cases against Eli Lilly & Company involving claims of diabetes-related injuries allegedly arising from the use of the antipsychotic drug Zyprexa. These cases were transferred to my court for discovery and other pretrial purposes by the federal Judicial Panel on Multidistrict Litigation from federal district courts in all of the states. Some of those cases were removed from state courts. There are motions to remand pending in this court. A number of "Zyprexa-diabetes" cases are pending in state courts.

2. Federal MDL plaintiffs' steering committees have assembled large collections of documents produced by Eli Lilly and conducted many depositions. These documents, deposition exhibits, and deposition transcripts are maintained by the current plaintiffs' steering committee in a depository in Mount Pleasant, South Carolina. In order to reduce transactional costs and the burdens on state courts, I have ruled that these materials shall be made available free of charge to litigants in state cases . *See In re Zyprexa Prods. Liab. Litig.*, No. 04-MD-1596, 2006 WL 3495667 *3 (E.D.N.Y. Dec. 5, 2006) ("All materials obtained by PSC I and PSC II in pretrial discovery . . . . have been available free of charge to state and federal plaintiffs who agree to adhere to the terms of the protective, case management, and other orders that have been issued by

this court"). Many of the state plaintiffs' attorneys have taken advantage of the federal depository in preparing their state cases.

3. Plaintiffs' steering committees are presently being compensated for their work in assembling documents and conducting depositions through mechanisms that to date do not impose any costs for this work on state plaintiffs or their attorneys. *See id.* at *8 ("The issue of assessing state cases with the costs of a discovery process that benefits all cases, state and federal, should, in the first instance, be left to state court judges.").

4. Some twenty thousand federal cases have been settled. The settlement agreements that have been reached by Eli Lilly & Company and the federal plaintiffs' steering committees include all or most of the state "Zyprexa-diabetes" cases.

5. Because of the enormous savings in transaction costs due to work by the plaintiffs' steering committees, and for other reasons, I have limited the fees available to plaintiffs' attorneys in federal MDL cases. *See In re Zyprexa Prods. Liab. Litig.*, 424 F. Supp. 2d 488 (E.D.N.Y. 2006) ("Limiting fees is particularly appropriate in the instant litigation since much of the discovery work the attorneys would normally have done on a retail basis in individual cases has been done at a reduced cost on a wholesale basis by the plaintiffs' steering committee."). I believe that those fee limits should, if possible, be applied in the state cases for a number of reasons:

A) Much of the preparatory work in state cases has already been done on a national basis, by the federal plaintiffs' steering committees, leaving less justification for high fees in individual state cases.

B) As part of the process of settlement, extensive liens from Medicare and Medicaid have been limited and controlled through national negotiations in this court involving the cooperation of all fifty states and the federal

government. *See In re Zyprexa Prods. Liab. Litig.*, No. 04-MD-1596, 2006 WL 3501263 (E.D.N.Y. Dec. 4, 2006) ("In compliance with this court's instructions . . . all fifty states as well as the federal government have resolved their Medicare and Medicaid liens."); *In re Zyprexa Prods. Liab. Litig.*, 451 F. Supp. 2d 458 (E.D.N.Y. 2006) (Memorandum Order & Judgment Regarding Liens and Disbursement Procedures). These negotiated lien settlements will probably accrue to the benefit of the state plaintiffs without the need for individual negotiations by state attorneys.

C) The nature of the plaintiffs in these state and federal cases, who allegedly are schizophrenics suffering from diabetes, places them in sad and difficult situations. It is desirable that as much of the recovery as practicable go to the plaintiffs themselves.

6. Despite my strong sense that similar fee limitations in state and federal cases is a fair and equitable result for all Zyprexa-diabetes plaintiffs and their attorneys, I have decided not to impose any fee limitations in state cases. I leave this question to your esteemed discretion.

7. I believe that the relevant fee decisions have been furnished to you, but in case you do not have copies on hand I am attaching them to this memorandum. You will note that in the Memorandum & Order on Common Benefit Fund and Continuing Applicability of Orders of Court and Special Masters of December 5, 2006, the suggestion is made that the MDL court in this case can limit fees in some, if not all, cases pending in state courts. *In re Zyprexa*, 2006 WL 3495667 at *13-15. A cooperative arrangement among state and federal judges limiting fees would be desirable.

8. Fees have been capped at 35%, though they can be varied upward to a maximum of 37.5% and downward to 30% in individual cases on the basis of special circumstances. *In re Zyprexa*, 424 F. Supp. 2d at 491. When individual matrices were provided by type of case, fees

were limited to 20% in certain small, lump-sum claims. *Id.*

9. I believe that a reasonable solution to the fee problem can be arranged for cases that have been and will be settled by negotiation among counsel with the supervision and consent of the concerned state and federal judges.

10. Evidentiary hearings at the state and national level may be desirable.

11. I should very much appreciate your views. I would be happy to visit with you by a telephone conference, at your convenience.

12. This memorandum is being filed and docketed so that judges, parties, and attorneys can respond.

Hon. Jack B. Weinstein

Dated: January 18, 2007
Brooklyn, New York

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff, vs. ELI LILLY AND COMPANY, Defendant.	)	Case No. 3AN-06-5630 CIV

ORDER GRANTING EXTENSION OF TIME

IT IS HEREBY ORDERED that plaintiff's Motion for Extension of Time is GRANTED. Plaintiff shall have until Friday, May 25, 2007, to file its Reply to Eli Lilly's Response to Plaintiff's Motion Concerning Claims and Proofs.

DATED this 24 day of May, 2007.

BY THE COURT

Mark Rindner
Superior Court Judge

I certify that on May 24, 2007 a copy of the above was mailed to each of the following at their addresses of record:
Sanders Jamieson

Administrative Assistant

MAY 22 2007

LAW OFFICES
FELDMAN ORLANSKY
& SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

RINDNER

FILED
STATE OF ALASKA
THIRD DISTRICT
07 MAY 22 PM 4:07
CLERK OF COURTS
BY _____ DEPUTY

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,	)	
	)	
Plaintiff,	)	
	)	
vs.	)	
	)	
ELI LILLY AND COMPANY,	)	
	)	Case No. 3AN-06-5630 CIV
Defendant.	)	
	)	

UNOPPOSED MOTION FOR EXTENSION OF TIME

Plaintiff, State of Alaska, by and through counsel, hereby requests an extension of time until Friday, May 25, 2007, to file its Reply to Eli Lilly's Response to Plaintiff's Motion Concerning Claims and Proofs. The parties have conferred and defendant's counsel does not object to this extension.

DATED this 22 day of May, 2007.

FELDMAN ORLANSKY & SANDERS
Attorneys for Plaintiff

BY _____
Eric T. Sanders
AK Bar No. 7510085

LAW OFFICES
FELDMAN ORLANSKY
& SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

GARRETSON & STEELE
Matthew L. Garretson
Joseph W. Steele
Counsel for Plaintiff

RICHARDSON, PATRICK, WESTBROOK
& BRICKMAN, LLC
H. Blair Hahn
Counsel for Plaintiff

Certificate of Service
I hereby certify that a true and correct
copy of **Unopposed Motion for Extension**
was served by messenger on:

Brewster H. Jamieson
Lane Powell LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648

By Peggy S Crowe
Date 5/22/07

LAW OFFICES
FELDMAN ORLANSKY
& SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK
99501
TEL: 907.272.3538
FAX: 907.274.0819

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA, Plaintiff,	)	
v.	)	Case No. 3AN-06-05630 CI
ELI LILLY AND COMPANY, Defendant.	)	

PLAINTIFF'S PRELIMINARY WITNESS LIST

Pursuant to the Court's Standard Pre-trial Scheduling Order entered in this action, Plaintiff hereby advises it may call the following witnesses to testify at the trial in this matter. Plaintiff specifically reserves the right to supplement and or amend this list of trial witnesses in accordance with the applicable Alaska Rules of Civil Procedure as discovery has just begun in this matter. Retained expert witnesses will be identified at a later date.

1. Robert W. Baker, M.D.
   c/o Eli Lilly and Company
   Lilly Corporate Center
   Indianapolis, IN 46285
   (317) 276-2000

LAW OFFICES
FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK 99501
TEL: 907.272.3538
FAX: 907.274.0819

Dr. Baker may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

2. Michael Edwin Bandick
Former employee of Eli Lilly and Company
l/k/a: Carmel, IN

Mr. Bandick may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

3. Charles M. Beasley, M.D.
c/o Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

Dr. Beasley may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

4. Alan Breier, M.D.
c/o Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

Dr. Breier may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

5. David Campana
c/o State of Alaska's Dept. of Health and Social Services
Division of Health Care Services
4501 Business Park Blvd., Suite 24
Anchorage, AK 99503

LAW OFFICES
FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK 99501
TEL: 907.272.3538
FAX: 907.274.0819

Mr. Campana may be asked to testify as to interactions between the State of Alaska and Eli Lilly and Company relating to Alaska's Medicaid program and the drug Zyprexa.

6. Patrizia Cavazzoni, M.D.
c/o Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

Dr. Cavazzoni may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

7. Jerry D. Clewell , Pharm D., MBA., BCPS
Former employee of Eli Lilly and Company
l/k/a Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

Mr. Clewell may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

8. Jack E. Jordan
Former employee of Eli Lilly and Company
l/k/a Bremen, IN

Mr. Jordan may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

9. Jared G. Kerr, M.P.H.
Former employee of Eli Lilly and Company
l/k/a Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

LAW OFFICES
FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK 99501
TEL: 907.272.3538
FAX: 907.274.0819

Mr. Kerr may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

10. Bruce Kinon, M.D.
c/o Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

Dr. Kinon may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

11. John Anthony Krueger
c/o Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

Mr. Krueger may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

12. Kenneth C. Kwong, M.D., Ph. D.
Former employee of Eli Lilly and Company
l/k/a Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

Dr. Kwong may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

13. John Clifford Lechleiter, Ph.D.
c/o Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

LAW OFFICES
FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK 99501
TEL: 907.272.3538
FAX: 907.274.0819

Dr. Lechleiter may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

14. Cassandra Mehlman, MBA
c/o Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

Ms. Mehlman may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

15. Matthew Pike
Former employee of Eli Lilly and Company
l/k/a Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

Mr. Pike may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

16. Thomas J. Porter, M.D.
3600 Mathews Drive
Anchorage, AK 99516-3523

Dr. Porter may be asked to testify as to interactions between the State of Alaska and Eli Lilly and Company relating to Alaska's Medicaid program and the drug Zyprexa.

17. Michelle Sharp
c/o Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

LAW OFFICES
FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK 99501
TEL: 907.272.3538
FAX: 907.274.0819

Ms. Sharp may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

18. Gary Tollefson
Former employee of Eli Lilly and Company
l/k/a Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

Mr. Tollefson may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

19. Denise Torres
Former employee of Eli Lilly and Company
l/k/a Lilly Corporate Center
Indianapolis, IN 46285
(317) 276-2000

Ms. Torres may be asked to testify as to the acts and/or omissions of Eli Lilly and Company as they relate to the matters alleged in Plaintiff's Complaint.

20. Lynda Walsh
c/o State of Alaska's Dept. of Health and Social Services
Division of Health Care Services
4501 Business Park Blvd., Suite 24
Anchorage, AK 99503

Ms. Walsh may be asked to testify as to interactions between the State of Alaska and Eli Lilly and Company relating to Alaska's Medicaid program and the drug Zyprexa.

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LAW OFFICES
FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK 99501
TEL: 907.272.3538
FAX: 907.274.0819

Respectfully SUBMITTED and DATED this 11 day of May, 2007

FELDMAN, ORLANSKY & SANDERS
Counsel for Plaintiff

BY _____
Eric T. Sanders
Alaska Bar No. 7510085

GARRETSON & STEELE
Matthew L. Garretson
Joseph W. Steele
5664 South Green Street
Salt Lake City, UT 84123
(801) 266-0999
Counsel for Plaintiff

RICHARDSON, PATRICK, WESTBROOK & BRICKMAN, LLC
H. Blair Hahn
Christiaan A. Marcum
P.O. Box 1007
Mt. Pleasant, SC 29465
(843) 727-6500
Counsel for Plaintiff

Certificate of Service
I hereby certify that a true and correct copy of **Plaintiff's Preliminary Witness List** was served by messenger on:

Brewster H. Jamieson
Lane Powell LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648

By Peggy J. Crowe
Date 5/11/07

LAW OFFICES
FELDMAN ORLANSKY & SANDERS
500 L STREET
FOURTH FLOOR
ANCHORAGE, AK 99501
TEL: 907.272.3538
FAX: 907.274.0819

FILED
STATE OF ALASKA
THIRD DISTRICT
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CLERK - TRIAL COURTS
BY _____ DEPUTY

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,
Plaintiff,

v.

ELI LILLY AND COMPANY,
Defendant.

Case No. 3AN-06-05630 CI

STIPULATION FOR EXTENSION OF TIME

COME NOW the parties, by and through counsel of record, and stipulate that defendant shall have an extension of time until May 7, 2007, to file its response to Plaintiff's Memorandum Describing Its Claims and Proofs.

FELDMAN ORLANSKY & SANDERS
Attorneys for Plaintiff

Dated: May 1, 2007

By _____
Eric T. Sanders, ASBA No. 75100085

LANE POWELL LLC
Attorneys for Defendant

Dated: May 1, 2007

By _____
Brewster H. Jamieson, ASBA No. 8411122
Andrea E. Girolamo-Welp, ASBA No. 0211044

ORDER

IT IS SO ORDERED this 7 day of May, 2007.

_____
The Honorable Mark Rindner

I certify that on May 7, 2007 a copy of the above was mailed to each of the following at their addresses of record:
Sanders Jamieson

_____
Administrative Assistant

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LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

Appendix

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

ELI LILLY'S RESPONSE TO PLAINTIFF'S MOTION CONCERNING CLAIMS AND PROOFS

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

Appendix

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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Appendix

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

I. INTRODUCTION

Since Zyprexa® entered the market in 1996, it has been prescribed by Alaska physicians to beneficiaries of Alaska's Medicaid program to treat their serious mental illnesses, such as schizophrenia and bipolar disorder, and the State of Alaska has paid for those prescriptions without restrictions. The State has sued Zyprexa's manufacturer, Eli Lilly and Company ("Lilly"), alleging that Zyprexa is defective, and that fraudulent representations and improper marketing by Lilly caused physicians to prescribe Zyprexa to Medicaid beneficiaries, resulting in medical injuries. The State seeks to recover the costs incurred to treat these patients allegedly injured by Zyprexa, and some undefined portion of the cost of the medication itself. But today, just as it did before the lawsuit, the State continues to pay for Zyprexa, without restrictions. The State has not bothered to explain why it takes one position as a matter of public policy and another, irreconcilable posture in this litigation.

The gap between the actual facts in Alaska and the State's "litigation facts" extends beyond its reimbursement practices. The facts necessary to determine whether the State's allegations of product defect and company misconduct are actionable include: what prescribing doctors were told by Lilly; from what additional or independent sources they obtain information about Zyprexa; why they prescribed the medication; how long patients took the medication; what other medications the patients were taking before, during, and after the time they were taking Zyprexa; how they fared; whether patients suffer from one of the medical conditions that the State alleges is caused by Zyprexa; what other risk factors for each individual might explain

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Appendix

the condition; and what medical costs have been incurred as a result of any supposed wrongdoing. The State, however, has represented to the Court that it will not present any evidence on these subjects, and it opposes Lilly discovering these facts.

In place of actual facts, the State proposes to prove its claims using aggregate data and statistical analyses only. This Court has required the State to file a pleading explaining how this method of proof can satisfy its legal burden. The methodology described by the State fails to sustain this lawsuit.

At a minimum, this aggregate analysis must satisfy the element of proximate causation, an element of each of the State's causes of action. To prove its case, the State must show that: (1) Zyprexa is defective; (2) Lilly's improper marketing caused physicians to write Zyprexa prescriptions that otherwise would not have been written; and (3) the use of Zyprexa by patients who received Zyprexa prescriptions caused medical injuries that the State must pay to treat. Failure to demonstrate causation in any respect dooms the State's case. Statistics will not suffice.

Statistics do not explain why a doctor prescribed a life-saving medication. Statistics do not demonstrate what a company communicated to its customers. Statistics do not prove why an individual has diabetes. The State has not provided any explanation for how it will use statistical evidence to prove a defect or to show that improper marketing caused inappropriate prescriptions to be written. It proposes to use epidemiological evidence to show that use of Zyprexa caused medical injuries, but admits that epidemiological evidence is reliable to show

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

general causation only. Legal causation in a product liability case requires proof of specific causation. The State has identified no authority for its assertion that a court should discard this requirement when the injuries allegedly caused by the product are aggregated under the banner of a single, indirectly affected party.

These deficiencies in the State's offer of proof provides sufficient basis for the Court to dismiss the case.

The State's claims also fail for independent reasons. Its demand for damages based on physical injuries suffered by non-parties (the Medicaid recipients) enjoys no legal support, no matter how the State proposes to prove its case. The State's common law tort claims fail under the remoteness and economic loss doctrines. Alaska's Unfair Trade Practices Act has never been, and should not be, applied to prescription drug transactions, which are separately regulated. Moreover, the State does not have standing under the Act to seek the money damages it has demanded.

II. BACKGROUND

A. Description of Zyprexa

Zyprexa, or olanzapine, belongs to a class of medications known as "atypical" or "second generation" antipsychotics.[1] The federal Food and Drug Administration ("FDA") approved Zyprexa for sale on September 30, 1996, after review of Lilly's New Drug

[1] *See* Lilly's Zyprexa Backgrounder ("Backgrounder"), which was filed with the Court on October 6, 2006, as Exhibit A to Lilly's Scheduling and Planning Conference Memorandum.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

Application ("NDA") and additional information provided by Lilly in response to FDA requests. In so doing, the FDA determined that Zyprexa was safe and effective for "treatment of the manifestations of psychotic disorders."[2] After reviewing additional data and clinical trials, the FDA also approved Zyprexa as safe and effective for maintenance treatment of schizophrenia (November 2000);[3] treatment of acute mania associated with bipolar I disorder as monotherapy (March 2000),[4] or in combination with lithium or valproate (July 2003);[5] and maintenance treatment of manic episodes and mixed manic and depressive episodes associated with bipolar I disorder (January 2004).[6] Since its introduction to the market, Zyprexa has been prescribed for more than 20 million people worldwide.

Zyprexa continues to be approved by the FDA for the treatment of schizophrenia and bipolar disorder, and is a well established treatment for both conditions.[7] In addition to these FDA-approved indications, physicians may prescribe Zyprexa for any other "off-label" uses that, in their medical judgment, will best serve their patients, consistent with normal

[2] *See* FDA 9/30/96 approval letter. (Attached to Backgrounder).

[3] *See* FDA 11/9/00 approval letter. (Attached to Backgrounder).

[4] *See* FDA 3/17/00 approval letter. (Attached to Backgrounder).

[5] *See* FDA 7/10/03 approval letter. (Attached to Backgrounder).

[6] *See* FDA 1/14/04 approval letter. (Attached to Backgrounder).

[7] *See, e.g.*, Expert Consensus Guideline Series: Optimizing Pharmacologic Treatment of Psychotic Disorders, J. Clin. Psychiatry, vol. 64, supp. 12, pp. 21-94 (2003) (attached as Exhibit A).

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

medical practice and long-settled law. *See, e.g., Use of Approved Drugs for Unlabeled Indications*, 12 FDA Drug Bulletin 4, 5 (1982); *Washington Legal Foundation v. Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000).[8] Authoritative medical publications, relied upon by the federal and state governments in the administration of Medicare and Medicaid, support several "off-label" uses of Zyprexa, including treatment of Alzheimer's symptoms, dementia-related anxiety, depression, and certain pediatric developmental disorders.[9]

The State's theories revolve around the allegation that Lilly failed to disclose side effects of Zyprexa relating to weight gain and diabetes. But from the time Zyprexa was first marketed in October 1996, its labeling has advised doctors that weight gain was a commonly observed adverse event in clinical trials.[10] Likewise, Lilly has also always listed four diabetes-related adverse events (diabetes mellitus, hyperglycemia, ketosis, and diabetic acidosis) among the adverse reactions observed in patients during clinical trials.[11] Lilly monitors all post-marketing reports of adverse events, and it provides the FDA with regular periodic safety update reports based on post-marketing experience with Zyprexa.

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[8]The FDA has reaffirmed this policy on numerous occasions. *See, e.g.*, James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths & Misconceptions,* 53 FOOD & DRUG L.J. 71, 77-78 (1998). (Attached to Backgrounder).

[9]*See* DRUGDEX – Olanzapine §§ 4.5.C, 4.5.E, 4.5.O, 4.5.Y (attached as Exhibit B).

[10]*See* Zyprexa package insert (10/02/96). (Attached to Backgrounder).

[11]*See* Zyprexa package insert (10/02/96). (Attached to Backgrounder).

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

FDA oversight of drug safety does not end with the approval of a medication. In the case of all second generation antipsychotics, the agency undertook a three-year review of all manufacturers' data and, on September 11, 2003, asked that a warning regarding diabetes-related adverse events be included in the product labeling for *every* atypical antipsychotic.[12] Lilly complied within days.[13] Rather than stating that atypical antipsychotic use causes diabetes, the FDA-approved label notes that "the relationship between atypical antipsychotic use and diabetes mellitus adverse events has not been completely described."[14] As discussed in more detail in Lilly's Backgrounder, scientists recognized an association between schizophrenia, affective disorders and diabetes long before the introduction of medications for the treatment of schizophrenia and bipolar disorder. Thus, the mere fact that a patient who took Zyprexa develops a diabetes-related condition does not mean that Zyprexa caused it, especially in light of what some have termed a recent "epidemic" of obesity and diabetes in the population at large.[15]

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[12] *See* FDA 9/11/03 letter. (Attached to Backgrounder).

[13] *See* Zyprexa package insert (revised 9/16/03). (Attached to Backgrounder).

[14] *See* FDA 9/11/03 letter. (Attached to Backgrounder).

[15] Richard Perez-Pena, *One in Eight Adults in New York City has Diabetes, a Study Finds*, N.Y. Times, Jan. 31, 2007, at B2; Alan D. Aviles, President of N.Y.C. Health & Hosp. Corp., *Letter to the Editor*, N.Y. Times, Feb. 3, 2007, at A14.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

B. The State's Coverage of Zyprexa Prescriptions Under Alaska's Medicaid Program

The State seeks to recover payments for Zyprexa made by its Medicaid program. Under the federal Medicaid program, participating states, such as Alaska, receive money from the federal government to cover all or part of the cost of medical assistance that the states provide to their low income residents, provided that the states comply with federally imposed standards. *Wilder v. Virginia Hosp. Assn.*, 496 U.S. 498, 502 (1990). Alaska complies by, among other things, paying for such benefits as medical services and prescription medications.[16] For such medications, Alaska may (i) exclude coverage for certain uses; (ii) require prior authorization for certain uses; (iii) designate the medication as non-preferred under a formulary system, covering it through an exception process, such as by requiring prior authorization; and (iv) impose prescription limitations.[17]

Federal Medicaid regulations govern the coverage of "off-label" prescriptions, about which the State raises various claims.[18] Doctors write such prescriptions to treat illnesses that are not specified in the FDA-approved label, and Medicaid regulations authorize payments for such uses. As defined in the Medicaid Drug Rebate Statute, a "covered outpatient drug" is one that (i) "is approved for safety and effectiveness as a

[16] *See* 42 U.S.C. §§ 1396(a)(1), 1396a(10) (2007).

[17] *See* 42 U.S.C. § 1396r-8(d)(1)-(6) (2007).

[18] *See supra* at 4; Comp. ¶¶ 12-13, 20, 22, 26, 32; Plaintiff's Memorandum Describing Its Claims and Proofs ("Memorandum" at 4-5, 7, 18).

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

prescription drug" by the FDA and (ii) is prescribed for outpatient use (subject to some exceptions) for a "medically accepted indication."[19] A "medically accepted indication" includes any FDA-approved use (*i.e.*, "on label") *or* a use identified in any of the three compendia identified in the Covered Outpatient Drug Statute: (1) the American Hospital Formulary Service Drug Information, (2) the United States Pharmacopeia-Drug Information, or (3) the DRUGDEX Information System.[20] Although "off-label," such uses for a covered outpatient medication that are supported by one or more of these compendia are deemed "medically accepted indications" and are covered under the Medicaid program.[21] Numerous "off-label" uses of Zyprexa are supported by the Medicaid compendia. Finally, a state may elect to cover uses that are not supported by any of these compendia.

Although Alaska claims Lilly made a variety of misrepresentations that supposedly led to excessive or inappropriate prescriptions for Zyprexa, the State has yet to impose a *single* restriction on reimbursement for Zyprexa.[22]

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[19] *See* 42 U.S.C. § 1396r-8(k)(2), (k)(3)(A)-(H) (2007).

[20] *See* 42 U.S.C. § 1396r-8(k)(6), (g)(1)(B)(i) (2007).

[21] *See* Letter from Edward C. Gendron to State Medicaid Directors, Release #141 (May 4, 2006), *available at* http://www.cms.hhs.gov/DeficitReductionAct/Downloads/rel141.pdf; Letter from Sally K. Richardson to State Medicaid Directors (June 19, 1996), *available at* http://www.cms.hhs.gov/smdl/downloads/smd061996.pdf; Letter from Sally K. Richardson to State Medicaid Directors (Dec. 5, 1994), *available at* http://www.cms.hhs.gov/smdl/downloads/smd120594.pdf.

[22] *See* Pl.'s Resp. to Def.'s First Set of Interrog. Nos. 1.c., 2.c. ("There are no rules, regulations and/or restrictions on the prescription of Zyprexa except the general requirement that it be 'medically necessary.'") (attached as Exhibit C).

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

III. PROCEDURAL BACKGROUND OF THE CASE

A. The Causes of Action Pleaded

Although the State's Complaint alleges a variety of wrongdoing under several labels, including products liability, varieties of misrepresentation and violations of the Unfair Trade Practices and Consumer Protection Act, it principally claims that:

> As a result of ingesting Zyprexa, Alaska Medicaid patients have suffered serious health effects, which now require further and more extensive medical treatment and health-related care and services. For these individuals, the State is the financially responsible party of these services. The State has thus suffered and will continue to suffer additional financial loss in the care of those Medicaid recipients who consumed prescriptions which were ineffective, unsafe, and actively harmful. In addition, the State has paid for Zyprexa prescriptions for uses which were not approved.

Compl. ¶ 26. According to the Complaint, Lilly misled numerous actors about the safety and efficacy of Zyprexa, including the State, the FDA, physicians, patients, and the public in general. Compl. ¶¶ 7, 20, 24-25, 43. In addition, the State alleges that Lilly promoted Zyprexa for off-label use as part of a concerted effort to boost sales. Compl. ¶¶ 12, 20. The State seeks "damages and penalties arising from the marketing and sale of the prescription drug Zyprexa" that it suffered and will continue to suffer as the payor of health benefits for beneficiaries of the Alaska Medicaid program. Compl. ¶ 6.

The Complaint requests four distinct forms of relief:

- Payment of Zyprexa-related damages for past, present, and future medical expenses of recipients of the Alaska Medicaid program.

- Restitution for the cost of all Zyprexa prescriptions paid by the State.
- Civil penalties.
- Costs, interest and actual attorneys' fees.

Compl. Prayer for Relief. The Complaint does not allege that it is brought in subrogation or on behalf of the beneficiaries of the Alaska Medicaid program, nor does it seek injunctive relief.

Lilly has answered the Complaint, denying the material allegations.

B. The Pleading Required by the Court

At the initial pretrial conference on January 8, 2007, the Court recognized that the question that had to be resolved in this case is how causation gets proven. The State represented that it intended to prove causation through aggregate statistical evidence presented by expert witnesses. By contrast, Lilly advised the Court that to rebut this claim, it needed individualized discovery regarding the prescriptions covered in Alaska and the diabetes-related illnesses, if any, that resulted from Zyprexa use. To resolve these divergent approaches, the Court directed the State to file a motion for rule of law to articulate its burdens of poof and describe how it intends to meet such burdens without individualized evidence. The Court advised the parties that it would dismiss the case if it found the State's proposed evidence insufficient. Finally, the Court stated that it would use the motion as a vehicle to rule on the scope of permissible discovery.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

The Court permitted the parties to begin discovery, and both parties served and responded to written discovery requests. The State has begun to take depositions of Lilly personnel.

In its response to Lilly's document requests, the State refused to identify the individuals that the State contends were injured by Zyprexa. Pl.'s Resp. to Def.'s First Set of Interrog. Nos. 10, 12, 24.[23] The State further refused to respond to discovery requests from Lilly seeking such information as the age, diagnosis, length of time on Zyprexa, and alternative treatments for Alaska Medicaid recipients, on relevancy grounds. *Id.*, Nos. 11, 13. For the same reason, the State also refused to identify physicians who wrote Zyprexa prescriptions that the State alleges would not have been written but for Lilly's alleged wrongdoing, *id.*, No. 16, despite the State's contention "that Lilly's wrongful conduct increased the number of" on-label and off-label Zyprexa prescriptions written by Alaska physicians. *Id.*, Nos. 19, 21. And the State has refused to identify what physicians were allegedly deceived by Lilly, or disclose what false or misleading statement was made to them. *Id.*, Nos. 15-17.

C. The State's Methodology for Proving Its Claims

The State's Memorandum Describing Its Claims and Proofs ("Memorandum") advises that it seeks "damages proximately caused to the State by Lilly's introduction of the

[23] Pl.'s Resp. to Interrog. (attached as Exhibit C); *see also* Pl.'s Resp. to Def.'s First Set of Req. for Produc. of Docs. Nos. 5, 6, 8 (attached as Exhibit D).

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

defective drug Zyprexa into the State's Medicaid population," but it disclaims any interest in bringing a subrogation action. Memorandum at 1-2. The recovery sought includes the present and future costs of medical treatment for diabetes-related illnesses that resulted from individual patients' use of Zyprexa and civil penalties for deceptive marketing. *Id.* The State mentions in passing that it "paid for thousands of prescriptions of a defective medication," *id.* at 6, but never states that it is seeking reimbursement of the prescription price, and certainly never describes how it will prove entitlement to that remedy.

The State provides a "Background" section that sets forth an abbreviated version of the same partisan facts alleged in the Complaint. Memorandum at 2-5. It describes in general terms the manner in which Lilly marketed Zyprexa and the various ways Lilly allegedly communicated Zyprexa's safety and efficacy to physicians and the FDA. *Id.* The State alleges that prescriptions grew because of Lilly's "aggressive overpromotion of Zyprexa," *id.* at 5, but it never explains how it will demonstrate the causal connection between its general allegations of misconduct and the doctors' behavior in prescribing Zyprexa to Medicaid recipients. Notably, the State discards any suggestion that Lilly made actionable misrepresentations to the State.

The State proposes to use statistical evidence, derived from its Medicaid database, to prove that Zyprexa caused injury to beneficiaries, through experts who will compare the records in the database to what it refers to as "similar, properly controlled groups." *Id.* at 7. These experts will then use these comparative statistics to "show the extent to which diabetes

and diabetes-related illnesses increased among Zyprexa users in Alaska's Medicaid population." *Id.* at 11. The State claims that this type of epidemiological evidence is "routinely used to prove generic causation of injuries in tort litigation." *Id.* at 9.[24] It also claims that generic causation, defined as "proof that an agent . . . can or does cause a particular injury or condition in a population of individuals," is all that is required. *Id.* at 8. It dismisses the need to demonstrate "proof that the agent proximately caused an injury or condition in a specific individual" with the mystifying comment that the State "is responsible for all Medicaid patients who developed diabetes." *Id.* at 8-9.

IV. ARGUMENT

A. The Evidence Proffered by Alaska Is Not Sufficient to Prove Its Claims

Although all of the State's causes of action require proof of proximate causation,[25] its proposed proof does not include evidence of any causal relationship between Lilly's

[24]The State's definitions of the different types of causation come from a publication discussing the role of epidemiology in toxic tort cases. *See* Michael D. Green, D. Michael Freedman & Leon Gordis, *Reference Guide on Epidemiology*, *in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 336 (2d ed. 2000).

[25]The State admits as much for its common law counts. *See* Memorandum at 13 (Strict Products Liability-Design Defect), 19 (Strict Products Liability – Failure to Warn), 23 (Negligence), 26 (Fraudulent and Negligent Misrepresentation); s*ee also* Shanks *v. The Upjohn Co*., 835 P.2d 1189, 1198 (Alaska 1992) (strict liability); *DeNardo v. GCI Comm. Corp*., 983 P.2d 1288, 1290 (Alaska 1999) (negligence); *Anchorage Chrysler Ctr., Inc. v. DaimlerChrysler Corp*., 129 P.3d 905, 914 (Alaska 2006) (fraud); *Reeves v. Alyeska Pipeline Servs*., 56 P.3d 660, 670-71 (Alaska 2002) (negligent misrepresentation).

The State incorrectly suggests that there is no causation requirement for its UTP claim. Memorandum at 20. This issue is addressed at note 36, *infra*.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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alleged misconduct and the (i) writing of one prescription, or (ii) the development of one case of diabetes. Instead, the State proposes to prove Lilly's misconduct through statistical evidence, presented through experts. According to the State, this is permissible because "[t]he state's claim does not rest in the experience of the many individual Zyprexa users, but in the aggregate effect upon the state's Medicaid program." Memorandum at 6. But if the State has experienced increased Medicaid costs because of Zyprexa, this occurred only because *individual* doctors wrote Zyprexa prescriptions for *individual* Medicaid recipients as a result of Lilly's alleged misconduct, and because those prescriptions caused medical injuries to *individual* Medicaid recipients that they otherwise would not have experienced.

In the absence of individualized evidence about the patients, the State must explain how statistical evidence proves two essential facets of causation. First, it must demonstrate that wrongful marketing caused prescriptions to be written that otherwise would not have been written. Second, it must prove that the exposure to Zyprexa from these "extra" prescriptions caused the medical injuries to Medicaid recipients that the State is paying for.

1. The State Has Not Explained How It Will Prove That Lilly's Marketing Caused Zyprexa Prescriptions to Be Written for Alaska Medicaid Recipients That Otherwise Would Not Have Been Written

The State does not explain how it can prove that improper marketing caused prescriptions to be written that otherwise would not have been using only statistical evidence. This deficiency dooms the State's case, whether or not it can prove that Zyprexa caused injuries to Medicaid recipients.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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Tort law across this country in any misrepresentation or unlawful marketing case involving a prescription medication requires that the plaintiff demonstrate what information was communicated to individual prescribers, what other sources of information affected the prescriber's decision, and how the prescriber made his or her treatment decision. *See, e.g., Heindel v. Pfizer, Inc.*, 381 F. Supp. 2d 364, 383-84 (D.N.J. 2004); *Flynn v. Am. Home Prods. Corp.*, 627 N.W.2d 342, 349-50 (Minn. Ct. App. 2001). "[I]n absence of evidence that [the doctor] relied on defendant's misrepresentations, plaintiff's clams for failure to warn…must be dismissed." *Huntman v. Danek Med., Inc.*, No. 97-2155, 1998 U.S. Dist. LEXIS 13431, at *19 (S.D. Cal. July 27, 1998).

A statistical or economic model cannot take the place of an oral or written exchange between two people to prove fraud or individual reliance. Thus, in the class action context, courts consistently hold that, because reliance is based on the individual's "knowledge, motivations and expectations," it is not susceptible to aggregate class treatment. *Poulos v. Caesars World, Inc.*, 379 F.3d 654, 665 (9th Cir. 2004); *see also, e.g., Sikes v. Teleline, Inc.*, 281 F.3d 1350, 1361-64 (11th Cir. 2002) (reversing certification where there was no basis for presumption of reliance); *Sprague v. General Motors Corp.*, 133 F.3d 388, 398 (6th Cir. 1998) (denying certification where a claim "requires proof of what statements were made to a particular person, how the person interpreted these statements and whether the person justifiably relied on those statements to his detriment."); *Rodriguez v. McKinney*, 156 F.R.D. 112, 116 (E.D. Pa. 1994) (reliance should not be presumed where there are "various factors"

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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involved in plaintiff's decision). While the State's claim is not a class action, it is based on the aggregation of many alleged individual misrepresentations, acts of reliance, and injuries, giving it the same practical dynamic.

The challenge the State faces in meeting its burden of proof is particularly acute in the context of its claim regarding a prescription medication, as a physician's prescribing decision is based on a combination of factors that is unique to doctor and patient. *See Makvipodis v. Merrell-Dow Pharm., Inc.*, 523 A.2d 374, 377 (Pa. Super. Ct. 1987) ("[E]ach individual for whom [prescription medications] are prescribed is a unique organism who must be examined by a physician who is aware of the nature of the patient's condition as well as the medical history of the patient."); *Heindel*, 381 F. Supp. 2d at 372, 382 (same).

Innumerable variables affect the writing of a prescription: a doctor will consider the patient's age, race, dosage level, length of hospitalization, prior medications, compliance history, predisposition to disease, shared interest in the prescription decision and severity of illness; and the doctor will be influenced by his or her own propensity for prescribing multiple medications, perception of the patient's condition, approved guidelines and personal experience using the medication. Jennifer Hoblyn, *et. al*, *Factors in Choosing Atypical Antipsychotics: Toward Understanding the Bases of Physicians' Prescribing Decisions*, J. OF PSYCH. RESEARCH 40, 160-166 (2006); James D. Arden & Peter C. Brensilver, *A Bitter Pill For Plaintiffs: Obstacles to Market Theories of Causation in Prescription Drug Consumer*

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

Fraud Cases, 61 FOOD & DRUG L.J. 539, 543 (2006). No statistical model can ever account for the complex tapestry of a physician's decision-making processes.

The analysis of whether representations by Lilly caused physicians to write Zyprexa prescriptions they otherwise would not have is further complicated by the fact that the information available to both Lilly and physicians changed over time, as the State acknowledges in its Complaint and Memorandum. *See also* Backgrounder.

Furthermore, the nature of Lilly's marketing communications changed over time. *See, e.g.*, Memorandum at 4. This heterogeneity of information and communications makes any aggregate case for how marketing affected prescribing behavior an unreliable endeavor. *See Moore v. Painewebber, Inc.*, 306 F.3d 1247, 1253 (2d Cir. 2002) ("fraud claims based on individualized misrepresentations" are not susceptible to "generalized proof").

2. The State's Statistical Evidence Cannot Establish That Exposure to Zyprexa From the "Extra" Prescriptions Written as a Result of Lilly's Marketing Caused Diabetes-Related Illnesses in Alaska Medicaid Recipients

The second causation burden the State must carry is proof that Zyprexa exposure caused injuries to Medicaid recipients who were prescribed Zyprexa because of Lilly's alleged improper marketing. The State proposes to prove this through epidemiological evidence of the incidence of particular medical injuries experienced by Medicaid beneficiaries who used Zyprexa compared to an unspecified control group.

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301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

The State's proposed epidemiological study does not even start at the right place. The relevant group of patients is not all Alaska Medicaid recipients who used Zyprexa, but rather the subset of Alaska Medicaid recipients who allegedly used Zyprexa because of alleged improper conduct by Lilly. Again, the alleged harm to Zyprexa users must be connected to the alleged misconduct, but the State has not explained how it will identify that subset of users for its proposed epidemiological study.

That consideration aside, the State's proposal to prove that a prescription medication caused recipients' injuries solely through epidemiological evidence enjoys no support in the case law. The State acknowledges that epidemiological evidence has been accepted by courts only to establish "general causation," then incorrectly states that its burden in this case is limited to general causation. Courts have consistently held that a plaintiff must prove both general and specific causation to recover damages in a product liability case.[26]

The State cannot evade these well established elements of proof by aggregating multiple alleged anonymous personal injuries. As stated above, the injuries giving rise to the

[26] *See In re Fibreboard Corp.*, 893 F.2d 706, 712 (5th Cir. 1990) (holding that the plaintiffs' use of statistical estimates fails to address the required element of individualized causation); *see also Amorgianos v. Amtrak*, 303 F.3d 256, 268 (2d Cir. 2002); *Sterling v. Velsicol Chem. Corp.*, 855 F.2d 1188, 1200 (6th Cir. 1998); ("[G]eneralized proofs will not suffice to prove individual damages."); *Barasich v. Columbia Gulf Transmission Co.*, 467 F. Supp. 2d 676, 694 (E.D. La. 2006); *Wade-Greaux v. Whitehall Lab.*, 874 F. Supp. 1441, 1485 (D.V.I. 1994) ("[P]laintiff must prove not only that [product] can cause [the injury] (general causation), but also that they did so in this case (specific causation).")

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damages claim remain individual injuries suffered by individual people. Even assuming that the State can prove what is not established in the medical literature – that there is a causal connection between Zyprexa and diabetes – whether or not the injuries were caused by Zyprexa would depend on the circumstances of each case: whether and to what extent the patient was exposed to Zyprexa; what other exposures and risk factors (weight, body mass index, family history of diabetes) existed for the patient; and when diabetes was diagnosed relative to the use of Zyprexa.

Epidemiological evidence cannot, and has never been permitted to, displace these individualized aspects of causation. Indeed, the very publication that the State relies upon concedes that epidemiology only identifies an "association," or a relationship between two events, but associations are not necessarily "causal" in nature. *See* Michael D. Green, D. Michael Freedman & Leon Gordis, *Reference Guide on Epidemiology*, in REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, 336 n.8 (2d ed. 2000) ("Epidemiologic methods cannot deductively prove causation; indeed, all empirically based science cannot affirmatively prove a causal relation."). An entire section of this authority relied upon by the State asks "What Role Does Epidemiology Play in Providing Specific Causation?" *Id.* at 381-86. The answer: "[t]his question is not a question that is addressed by epidemiology." *Id.* at 382. The best that epidemiological evidence can do is look at whether an agent is capable of causing

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

disease. *Id.* at 386.[27] It never establishes that an exposure *did* cause an injury. *Id.* at 382; *see also Merrell Dow Pharm., Inc. v. Havner*, 953 S.W.2d 706, 715 (Tex. 1997) (finding "epidemiological studies cannot establish the actual cause of an individual's injury or condition....").

The idea that specific causation evidence can be ignored for claims based on multiple personal injuries has been tried – and rejected – in the class certification context. *See In re Fibreboard Corp.*, 893 F.2d 706, 712 (5th Cir. 1990); *Georgine v. Amchem Prod., Inc.*, 83 F.3d 610, 617 (3d Cir. 1996) (declining to certify a class in order to protect the judicial system's "institutional values" rather than attempt to solve "a major social problem"). In *Fibreboard*, the Court rejected as insufficient proof of specific causation an offer of proof that included test cases along with epidemiological evidence, a more substantial presentation than proposed by Alaska in this case. Its words ring true here: "[T]he precision-like mesh of numbers tends to make fits of social problems when I intuitively doubt such fits. I remain wary of the siren call of the numerical display . . . ." 893 F.2d at 710. The "numerical display" described by the State in this case can not establish that Lilly marketing conduct caused extra prescriptions, or that those extra prescriptions caused patients to be injured.

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[27] *See also In re "Agent Orange" Prods. Liab. Litig.*, 818 F.2d 145, 165 (2d Cir. 1987); Vern R. Walker, *Restoring the Individual Plaintiff to Tort Law by Rejecting "Junk Logic" About Specific Causation*, 56 ALA. L. REV. 381, 383 (2004).

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LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

B. **The State Cannot Recover Damages Under Its Common Law Tort Claims for the Injuries Alleged**

1. **The State's Injuries Are Too Remote as a Matter of Law to Allow the State to Recover Under Its Common Law Causes of Action**

The State's attempt to recover directly from Lilly for the costs of treating beneficiaries' medical costs fails under the remoteness doctrine, which has been applied consistently to dismiss claims against third-party tortfeasors by parties obligated to pay the medical expenses of another. In particular, claims almost identical to those set forth in this case have been dismissed by numerous courts in tobacco litigation.[28] Almost uniformly, courts considering this issue found that "plaintiffs who are obligated to pay the medical expenses of another may not recover against the tortfeasor who caused the damage, because their injuries are indirect since they derive wholly from the injuries sustained by the third party." *Laborers Local 17 Health & Benefit Fund v. Philip Morris*, 191 F.3d 229, 233-34, 242 (2d Cir. 1999), *cert. denied*, 528 U.S. 1080, 145 L. Ed. 2d 673, 120 S. Ct. 799 (2000). This principle is applied to public as well as private payors. *Washington v. Am. Tobacco,*

[28] *See, e.g., Laborers Local 17 Health & Benefit Fund v. Philip Morris*, 191 F.3d 229, 233-34, 242 (2d Cir. 1999), *cert. denied*, 528 U.S. 1080, 145 L. Ed. 2d 673, 120 S. Ct. 799 (2000); *Oregon Laborers-Employers Health & Welfare Trust Fund v. Philip Morris, Inc.*, 185 F.3d 957, 969 (9th Cir. 1999), *cert. denied*, 528 U.S. 1075, 145 L. Ed. 2d 666, 120 S. Ct. 789 (2000); *Steamfitters Local Union 420 Welfare Fund v. Philip Morris*, 171 F.3d 912, 921 (3d Cir. 1999); *Williams & Drake, Inc. v. Am. Tobacco Co.*, No. 98-553, 1998 U.S. Dist. LEXIS 21917, at *2 (W.D. Pa. Dec. 21, 1998); *Texas Carpenters Health and Benefit Fund v. Philip Morris, Inc.*, 21 F. Supp. 2d 664, 668 (E.D. Tex. 1998), *affirm'd*, 199 F.3d 788 (5th Cir. 2000); *Blue Cross and Blue Shield of N.J. v. Philip Morris, Inc.*, 818 N.E.2d 1140, 1143 (N.Y. 2004); *Steamfitters Local Union 614 Health and Welfare Fund v. Philip Morris, Inc.*, No. W1999-01061, 2000 Tenn. App. LEXIS 644, at *28 (Tenn. Ct. App. Sept. 26, 2000).

Inc., No. 15056-8, 1997 WL 714842, at *4 (Wash. Sup. Ct. June 6, 1997) (applying common law rule to dismiss State's claim for increased Medicaid costs where the State sought "damages caused by defendants' breach of duty to third party tobacco users").[29]

The State has a well established, straightforward method for recovering its indirect costs: subrogation. 42 U.S.C. § 1396a(a)(25)(A), (B) (2007). Here, the State chose not to bring an action in subrogation. Memorandum at 2. This is no accident. A party bringing a subrogation claim stands in the shoes of the injured party, and must prove its case with the same evidence that the injured party would. *State v. McKinnon*, 667 P.2d 1239, 1243 (Alaska 1983) (holding a subrogee under Alaska law has "no more rights than were held by the [subrogor]"); *Dierks v. Alaska Air Trans., Inc.*, 109 F. Supp. 695, 697 (D. Alaska 1953) ("[T]he same defenses are available against the [subrogee] as against the plaintiff, with the right of recovery depending on essentially the same proof."). The State must elect whether it is standing in its own shoes, in which case its damages claim is too remote from the misconduct alleged, or its beneficiaries' shoes, in which case its evidentiary proposal is deficient.

[29] *See also Iowa v. Philip Morris, Inc.*, 577 N.W.2d 401, 406 (Iowa 1998); *Maryland v. Philip Morris, Inc.*, No. 96-122107, 1997 WL 540913, at *14 (Md. Cir. Ct. May 21, 1997); *Minnesota v. Philip Morris, Inc.*, 551 N.W.2d 490, 495 (Minn. 1996) (ruling where state of Minnesota was nominal plaintiff). *But see Texas v. Am. Tobacco Co.*, 14 F. Supp. 2d 956 (E.D. Tex. 1997).

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

2. The State's Strict Product Liability Claims Are Barred by the Economic Loss Doctrine Because the State Has Suffered Neither Property Damage Nor Personal Injury

The State seeks only the economic losses it has allegedly suffered or will suffer from paying for Zyprexa prescriptions, and from paying to treat injuries allegedly suffered by non-party Alaska Medicaid recipients. In Alaska, however, a plaintiff may not recover economic losses in strict liability in the absence of any property damage or personal injury suffered by the plaintiff itself. "Economic loss" does not suffice. *Kodiak Elec. Ass'n v. Delaval Turbine, Inc.*, 694 P.2d 150, 153 (Alaska 1984); *see also Northern Power & Eng'g v. Caterpillar Tractor Co.*, 623 P.2d 324, 329 (Alaska 1981); *Pratt & Whitney Canada, Inc. v. Sheehan*, 852 P.2d 1173, 1177-81 (Alaska 1993).

Alaska has never recognized a strict liability claim for purely economic loss by a party who neither used the product at issue nor suffered any non-economic loss from it. And courts elsewhere that have considered the question have held that "plaintiffs cannot rely on harm to property belonging to other people to show a non-economic injury." *See, e.g., In re Starlink Corn Prods. Liab. Litig.*, 212 F. Supp. 2d 828, 840 (N.D. Ill. 2002). Accordingly, the economic loss rule bars its strict liability claims.

C. Alaska's Unfair Trade Practices and Consumer Protection Act Does Not Apply to Prescription Medication Transactions

1. The Unfair Trade Practices Acts Do Not Apply to Prescription Medication Transactions

Alaska's Unfair Trade Practices and Consumer Protection Act (UTP) prohibits "[u]nfair methods of competition and unfair or deceptive acts or practices in the conduct of

trade or commerce." AS 45.50.471(a). No published decision by an Alaska Court has ever applied the UTP to product liability claims against prescription medication manufacturers. Because of (i) Alaska's deference to the Federal Trade Commission Act ("FTCA"); (ii) the absence of any application of the UTP to prescription medication manufacturers; and (iii) the historical development of other states' similar consumer protection statutes, the Court should be guided by the federal analog to Alaska's UTP (the FTCA, 15 U.S.C. §§ 41-77 (2007)) and by other states' practices.

The FTCA does not apply to prescription medications, and neither should Alaska's UTP. The Drug Amendments, enacted in 1962, long before Alaska's UTP became law, eliminated the FTC's jurisdiction over prescription medication advertising as it relates to safety and efficacy and transferred this responsibility to the FDA. *See id.*; 21 U.S.C. § 352(n) (2007).

State UTPs are commonly called "little FTC acts" because they were modeled on the FTC Act, and designed to accomplish the same purpose.[30] Victor E. Schwartz & Cary Silverman, *Common-Sense Construction of Consumer Protection Acts,* 54 KAN. L. REV. 1, 16 (2005). Alaska's UTP, enacted in 1970, requires courts to give "due consideration and great weight" to the interpretation of the FTCA when determining what constitutes an unfair trade

[30] *See, e.g.*, Ohio Rev. Code Ann. § 1345.05(B)(2) (2007); Texas Bus. & Com. Code § 17.46(c)(1) (2006); Idaho Code § 48-604(2) (2007); La. Rev. Stat. Ann. §§ 51:1401-1425 (2007); Ga. Code Ann. § 10-1-391(b) (2007); Miss. Code Ann. § 75-24-3(c) (2007); Vt. Stat. Ann. tit. 9, § 2453(b) (2007); W. Va. Code § 46-A-6-103 (2007).

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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practice. AS 45.50.545; *see also State v. O'Neill Investigations*, 609 P.2d 520, 524, 532 (Alaska 1980). The Supreme Court of Alaska has relied upon FTC precedent to define the types of commercial transactions subject to Alaska's UTP. *Id.* at 534.

Nothing in the legislative history of Alaska's UTP, its language, or any court decision interpreting it suggests it should be applied differently from its FTC model to cover prescription medications. The fact that the "little FTC acts" have been in effect for decades without being applied to prescription medication manufacturers demonstrates that the UTPs are not, and have been understood not to be, a source of product liability law.

The historical understanding that UTPs do not apply to prescription medications is supported by sound policy reasons. Prescribers of prescription medications are not the unsophisticated consumers that consumer protection law seeks to protect. In addition, the interests of prescription medication consumers are protected by the FDA and available tort causes of action.

Finally, allowing the UTP to be used by the State to bring product liability claims would trespass on the FDA's jurisdiction. The type of claim brought by the State here, aggregating hundreds or thousands of prescriptions and medical claims, and pursuing quasi-criminal civil penalties, *O'Neill Investigations, Inc.*, 609 P.2d at 525-26, would, if permitted, impose such substantial coercive effect on pharmaceutical manufacturers that it would interfere with the FDA's regulation of the industry. That problem would only be exacerbated by multiple state suits under this theory, each with its own variation on manufacturer liability.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

2. The Acts and Practices at Issue in This Litigation Are Exempt From the UTP

The fact that Alaska's UTP is not intended to apply to prescription medication transactions is reinforced by an exemption in the statute that is so apt that it might have been written with those transactions in mind. UTP section 45.50.481 states:

> Nothing in AS 45.50.471 - 45.50.561 applies to … an act or transaction regulated under laws administered by the state, by a regulatory board or commission … or officer acting under statutory authority of the state or of the United States, unless the law regulating the act or transaction does not prohibit the practices declared unlawful in AS 45.50.471.

AS 45.50.481(a)(1). This provision prevents a party from suing where the alleged unlawful practices at issue are already prohibited by an ongoing regulatory scheme, whether administered by Alaska or the federal government.

Interpreting the Act, the Alaska Supreme Court has applied a simple test to decide whether an act or practice is exempt under AS 45.50.481(a)(1): "[W]here the business is both regulated elsewhere and the unfair acts and practices are prohibited therein," the exemption applies. *O'Neill Investigations, Inc.*, 609 P.2d 520, 528 (Alaska 1980).

The sales of an FDA-approved pharmaceutical such as Zyprexa are exempt under the test because both prongs are met: 1) the FDA regulates the industry, and 2) the alleged unlawful practices at issue here – off-label promotion and making false claims regarding safety and efficacy – are prohibited by FDA regulations.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

a. The FDA maintains a regulatory framework that is both ongoing and careful as required under Alaska Statute § 45.50.481

The federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-399 (2007), provides the national regulatory framework for the pharmaceutical industry, and satisfies the first prong of the exemption: "ongoing, careful regulation." *Matanuska Maid, Inc. v. State*, 620 P.2d 182, 186 (Alaska 1980), *rev'd on other grounds*, *Rosen v. State Bd. of Pub. Accountancy*, 689 P.2d 478 (Alaska 1984). Enforcement by the FDA occurs before and after pharmaceuticals come to the market. The FDA's Center for Drug Evaluation and Research ("CDER") regulates, day to day, the safety and efficacy of pharmaceutical products. *See, e.g.*, Food and Drug Admin., Dept. of Health and Human Services, FDA and the Drug Development Process: How the Agency Ensures That Drugs Are Safe and Effective, FS 02-5 (2002), *available at* http://www.fda.gov/fdac/features/2002/402_drug.html. More important, the CDER continues to monitor products post-approval, requiring strict adherence by manufacturers to reporting and labeling regulations. *See* Ctr. for Drug Evaluation and Research, Food and Drug Admin., Dept. of Health and Human Services, *Post Drug Approval Process*, *in* The CDER Handbook, *available at* http://www.fda.gov/cder/handbook/index.htm. Indeed, the 2003 label change for Zyprexa and other second generation antipsychotics provides a case in point of the ongoing regulatory oversight of prescription medicines.[31]

[31] *See* discussion at 3-4, *supra*.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

b. FDA regulations prohibit the alleged unfair practices at issue in this litigation

FDA regulations prohibit the specific unlawful practices set forth in the Complaint in a manner sufficient to satisfy the second prong of the exemption test. In the Complaint, the State sets forth five unlawful practices that it alleges Lilly engaged in. One allegation claims that Lilly violated the labeling and advertising provisions of Alaska's Food and Drug Act. Compl. ¶ 53. Nine separate parts of the Alaska Food and Drug Act deal with labeling or advertising that are applicable to Zyprexa.[32] As shown in the chart attached as Appendix 1, the thirteen allegedly improper practices cited by the State are regulated by the FDA, and the unlawful practices at issue are prohibited by those regulations.

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[32]The Alaska Food, Drug and Cosmetic Act regulates both advertising and labeling. AS 17.20.005-.380.

There are two false advertising sections, one general and one specific. The general provision states, "An advertisement of a food, drug, device or cosmetic is false if it is false or misleading in any particular." AS 17.20.160. The specific provision applies to advertising of products remedying illness enumerated within the provision, none of the enumerated illnesses are ones for which Zyprexa has ever been promoted. AS 17.20.170.

The Act also contains detailed labeling requirements. AS 17.20.90. However, Zyprexa, as a drug sold only on a prescription written by a medical professional, is exempt from the requirements found in sub-sections (2) and (5) pursuant to section 100 of the Act, which sets forth certain exemptions. AS 17.20.100. Moreover, some of the sub-parts of section 90 do not apply to Zyprexa because the drug does not contain particular ingredients, such as cocaine, heroin or marijuana. AS 17.20.090(4), (11)(A). Finally, Zyprexa does not contain "any quantity of aminopyrine, barbituric acid, cincohophen, pituitary, thyroid, or their derivatives." AS 17.20.090(11)(A).

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

D. The State Cannot Recover Money Damages, Restitution or Civil Penalties Pursuant to Its UTP Claim

Even if this Court extends the UTP to cover prescription medicine transactions, the State has no authority under the UTP to seek the remedies it demands in the Complaint – money damages for the cost of medical treatment for Medicaid beneficiaries allegedly injured by Zyprexa, restitution for the purchase price of Zyprexa prescriptions, and civil penalties. In fact, the State seeks every remedy except the one provided by statute: injunctive relief. In addition, it fails to set forth any method for calculating the amount of money it would be entitled to in restitution or for civil penalties. For all of these reasons, the State's UTP cause of action must be dismissed.

1. No Authority Exists Under the UTP That Allows the Attorney General to Recover Money Damages for Medical Treatment Expense

In its Memorandum, the State asserts that, if it proves violations of the Act, it "may collect three times actual damages" pursuant to section 531 of the Act. Memorandum at 23. This assertion ignores the statutory scheme, which confers different causes of action and different remedies on the State and private actors. The Attorney General derives his authority from section 501,[33] which provides for injunctive relief, and section 551,[34] which

[33] "When the attorney general has reason to believe that a person has used, is using, or is about to use an act or practice declared unlawful in AS 45.50.471, and that proceedings would be in the public interest, the attorney general may bring an action in the name of the state against the person *to restrain by injunction* the use of the act or practice." AS 45.50.501(a) (emphasis added).

[34] "In an action brought under AS 45.50.501, if the court finds that a person is using or has used an act or practice declared unlawful by AS 45.50.471, the attorney general, upon petition to the court, may recover, on behalf of the state, a civil penalty of not less than $1,000 and not more than $25,000 for each violation." AS 45.50.551(b).

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provides for civil penalties. Section 531 of the statute,[35] which permits for the recovery of three times actual damages, is limited to "private and class actions." The statute nowhere provides for actual damages, treble or otherwise, for the State.

The Alaska Supreme Court has recognized this distinction between the remedies available to the State from those available to private litigants:

> The Attorney General is charged with enforcement of the Act: he may adopt interpretive regulations subject to the strictures of the Administrative Procedure Act; he has broad investigatory powers in connection with ferreting out the use of deceptive trade practices; and he is empowered *to seek injunctive relief* when he has reason to believe "that a person has used, is using or is about to use an act or practice declared unlawful in § 471…and…[such] proceedings would be in the public interest." AS 45.50.501(a). Where injunctive relief is sought, the court has available broad equitable remedies to redress violations of the Act. AS 45.50.501(b). Private and class actions are also authorized by the act for recovery of actual damages incurred as a result of proscribed acts and practices, including treble damages for willful violations. AS 45.50.531(a) and (b).

O'Neill Investigations, Inc., 609 P.2d at 524 (emphasis added); *see also Casciola v. F.S. Air Service, Inc.*, 120 P.3d 1059, 1066 n.24 (Alaska 2005) (describing attorney general's authority to seek civil penalties, before stating "[i]n addition, injured *private parties* in this chapter are statutorily authorized to seek treble damages") (emphasis added).

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[35] "A person who suffers an ascertainable loss of money or property as a result of another person's act or practice declared unlawful by AS 45.50.471 may bring a civil action to recover for each unlawful act or practice three times the actual damages or $500, whichever is greater. The court may provide other relief it considers necessary and proper." AS 45.50.531(a).

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

Accordingly, the Court should strike the State's claim for money damages under its UTP claim.[36]

2. The State May Not Recover Civil Penalties

The Attorney General may recover civil penalties only if it achieves injunctive relief under section 501, AS 45.50.551(b), but it has not sought injunctive relief under section 501.

The requirement that civil penalties (and restitution, as discussed below) can be awarded only ancillary to, not separate from, an injunction is not simply a procedural formality. Instead, it underscores the fundamental illogic at the core of the State's case against Lilly. Requiring an injunction as a condition precedent for other relief constitutes a policy judgment by the State that any monetary consequences to the defendant should flow only from behavior that the State has determined *must stop*. Here, quite the contrary, the State has decided that Zyprexa sales to Medicaid recipients *should continue* when their

[36]To the extent that actual damages were available to the State in this lawsuit pursuant to section 531, it has misrepresented the elements of proof necessary to satisfy such a claim. The State claims that it must prove only that the defendant is engaged in trade or commerce, and committed an unfair or deceptive act, and not that there was actual injury or causation. Memorandum at 20. The State derives that standard from *O'Neill*, which described the proof required for an *injunctive* action by the state, not a claim for damages. Under Alaska case law, a party seeking damages under section 531, which expressly applies only to "[a] person who suffers *an ascertainable loss of money or property as a result* of another person's act or practice declared unlawful" by the Act, AS 45.50.531(a) (emphasis added), must show causation and reliance in order to establish alleged injuries resulted from the defendant's conduct. *Garrison v. Dixon*, 19 P.3d 1229, 1235 (Alaska 2001); *Western Star Trucks, Inc. v. Big Iron Equip. Serv., Inc.*, 101 P.3d 1047, 1048 (Alaska 2004) (approving recovery under UTP where reliance is established).

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

physicians determine that it is the best treatment for their mental health conditions, and that such sales *should continue* to be reimbursed by the State, without restriction.

3. The State May Not Recover Restitution

The State seeks recovery of its payment for Zyprexa because, "without the misrepresentations and other unfair acts" by Lilly "there would have been less direct cost to the state, as the drug would have been used only for the very limited indications for which it is approved." Memorandum at 23. Alaska's UTP does not provide for the restitution remedy sought by the State. To the extent that it is available, it arises by implication from section 501(b), which states:

> The court may make *additional* orders or judgments that are necessary to restore to any person in interest any money or property, real or personal, which may have been acquired by means of an act or practice declared to be unlawful by AS 45.50.471.

AS 45.50.501(b) (emphasis added). In *O'Neill Investigation, Inc.*, the Alaska Supreme Court stated, "*Where injunctive relief is sought*, the court has available broad equitable remedies to redress violations of the Act." *O'Neill Investigations, Inc.*, 609 P.2d at 524 (emphasis added).

As with civil penalties, the language of section 501(b) demonstrates that it is not meant to provide authority for a stand-alone cause of action or remedies, but rather for additional remedies that the court may order when the State has brought a proper action for injunctive relief. *See id.* at 524. Absent a proper action for injunctive relief under section

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

501(a), which has not been brought here, there are no grounds for seeking or awarding restitution under the UTP.

Even if the Attorney General had properly pleaded restitution, such a remedy would be improper because the State does not intend to offer any evidence that Zyprexa was not effective for the Medicaid recipients who used it. Under the State's theory of the case, it would be reimbursed for prescriptions that benefited the Alaska citizens that used it.

Under Alaska law, as elsewhere, where no money or property has been lost, there are no grounds for restitution. *See, e.g., Old Harbor Native Corp. v. Afognak Joint Venture*, 30 P.3d 101, 107 (Alaska 2001) (describing restitution in general terms as "When a party unjustly receives, retains or appropriates property or a benefit, [and] the party should repay the source of the property or benefit.").

In the prescription medication context, absent an allegation that a medication failed to perform as advertised for *the individual patient*, the patient "has received the benefit of his bargain and has no basis to recover purchase costs." *Williams v. Purdue Pharma Co.*, 297 F. Supp. 2d 171, 176 (D.D.C. 2003). If the medication has not failed to perform for the individual patient, the manufacturer has not unjustly benefited from the sale of the medication. For this reason, courts have consistently rejected the sufficiency of a "deception plus payment" claim. *Heindel v. Pfizer, Inc.*, 381 F. Supp. 2d 364, 381 (D.N.J. 2004). The Fifth Circuit described such a plaintiff's inadequate injury by stating:

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

> Rivera's claim to injury runs something like this: Wyeth sold Duract; Rivera purchased and used Duract; Wyeth did not list enough warnings on Duract, and/or Duract was defective; other patients were injured by Duract; Rivera would like her money back.

Rivera v. Wyeth-Ayerst Labs., 283 F.3d 315, 319 (5th Cir. 2002). Such claims, the court held, "cannot constitute an injury in fact." *Id.* at 320. For this reason as well, the State's restitution claim fails.

4. The State Has Not Set Forth How Restitution Damages or Civil Penalties Will Be Determined

The State articulates no method for how an award of restitution or civil penalties should be determined. Thus, both of these remedies should be stricken.

E. Discovery by Lilly

1. Even if the State May Present Its Case Using Only Statistical Evidence, Lilly Is Entitled to Build and Present a Defense Using Non-Statistical Evidence

The State claims for itself a right to prove its complex case with a package of statistical evidence, and, at the same time, seeks to handicap Lilly's defense by barring Lilly from discovery of direct evidence of the actual experiences of Zyprexa prescribers and patients in Alaska. Because the claims made by the State grow out of individual prescribing decisions and individual patient experiences, Lilly seeks to rebut the State's claims with the real-life experiences of the people comprising the State's statistical package. Much to the State's consternation, this requires the use of the discovery tools provided by Rules 26, 33 and 34 of the Alaska Rules of Civil Procedure.

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LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

The State argues that "the court should not allow defendants to offer" testimony from any "ordinary physicians" to contradict the opinions of the State's designated experts on the issue of whether Zyprexa performed as safely as an ordinary physician would expect. Memorandum at 15. The State has refused to respond to Lilly's written discovery requests seeking specific, individualized information about Alaska prescribers and Zyprexa patients.[37] In fact, the State has announced in Court that it will simply abandon this lawsuit if the Court allows individualized discovery about Zyprexa prescribers and patients.

Regardless of whether the Court permits the State to present its case by statistics, the State's effort to block Lilly's discovery and use of direct evidence offends Rules 26, 33 and 34.

The test for whether information is discoverable by Lilly is whether it "is relevant to the subject matter involved in the pending action." Alaska R. Civ. P. 26(b)(1). To be discoverable, information "need not be admissible at trial," but only "reasonably calculated to lead to discovery of admissible evidence." *Id.* "[R]elevancy at trial and relevancy for purposes of discovery are two different matters," and relevancy for purposes of discovery is "to be construed liberally." *Doe v. Alaska Superior Court, Third Judicial Dist.*, 721 P.2d 617, 620-21 (Alaska 1986). Applying this standard here, there are two reasons why Lilly is

[37] *See* Pl.'s Resp. to Def.'s First Set of Interrog. Nos. 10-13, 16-17, 24 (attached as Exhibit C); *see also* Pl.'s Resp. to Def.'s First Set of Req. for Produc. Nos. 5-8 (attached as Exhibit D).

entitled to discovery of the actual experiences of individual Zyprexa prescribers and patients in Alaska.

First, Lilly requires discovery of the facts essential to its case-in-chief. The State may not dictate how Lilly will prepare its defense or present its case to the jury. Lilly may discover and gather evidence in support of those defenses, consistent with Rule 26 and related discovery rules. Contrary to what the State suggests, its intended method of proving causation or damages should not hamper Lilly's defense nor its pretrial discovery. As another court stated, applying the analogous federal Rule 26(b)(1),

> [Defendants are] entitled to relevant discovery of damages data in order to formulate defendants' own theory on the computation of … damages. By the interrogatories here in dispute, [Defendant] seeks … to enable its experts to put forth a distinct, competing theory of damages…. *While plaintiffs may disagree with the theory, there is no precedent which permits the plaintiffs to refuse to provide discovery based on their lack of agreement with defendants' theory of damages.* Similarly, defendants, in conducting damages discovery, are not limited by the documents considered by plaintiffs' experts. . . .

Fox v. Cheminova, Inc., No. 00-5145, 2006 WL 508087, at *7 (E.D.N.Y. Mar. 1, 2006) (emphasis added). Particularly where highly individualized, professional decisions (such as the decision whether to prescribe medicine) are at issue, rebuttal evidence can include "challenge[s to] the ability of statistical evidence . . . to approximate the actual determinative factors" that governed the decisions at issue. *Penk v. Oregon State Bd. of Higher Ed.*, 816 F.2d 458, 464 (9th Cir. 1987). Similarly, where the alleged injuries may be associated with

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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many possible factors, as is true of diabetes, recourse to individual medical records and patient histories is relevant to Lilly's defense.

Here, Lilly is entitled to build and present its defense on the theory that the best evidence for evaluating the State's allegations is not statistical modeling, but individualized consideration of the numerous factors – including the unique information that each prescriber relied on, patients' unique medical histories and experiences with other medicines, balancing of side effects, and individual preferences – that led physicians to prescribe Zyprexa. Only by examining patient-specific medical information can one determine when patients developed diabetes and identify confounding factors, such as the patient's use of other medications, obesity, diet, sedentary lifestyle, and family history.

Second, Lilly is entitled to discovery of all evidence necessary to test the accuracy and reliability of the State's data and theories, including discovery of individual prescriber and patient information. Lilly need not accept, on faith, the State's assurances that its Medicaid database represents an accurate and complete compilation of the experiences of Zyprexa prescribers and patients in Alaska, or that Medicaid patients who took Zyprexa can properly be compared with Medicaid patients who did not take Zyprexa. Lilly is entitled to test the accuracy and reliability of the information in the State's Medicaid database by checking those data against external sources, including the physicians who actually wrote the prescriptions identified in the database, and the medical records and histories of the patients whose information the database purports to record.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

Further, if the State seeks to present its case in the manner described in its Claims Memorandum, it will rely almost entirely on expert testimony derived from statistical analyses of the State's Medicaid database to prove causation and damages. Such expert testimony will only be admissible at trial if it satisfies all the requirements of the Alaska Rules of Evidence, including the requirements of Rule 702 and the *Daubert-Coon* standard. *See* Alaska R. Evid. 702; *State v. Coon*, 974 P.2d 386, 394 (Alaska 1999). Without full discovery of actual prescriber and patient information, Lilly will be deprived of information necessary to mount effective evidentiary challenges to the State's expert evidence.

2. Lilly's Discovery of Prescriber and Patient Information

Lilly has already served discovery requests addressing some of these issues, but the State has refused to provide the information Lilly requested. It sought – but the State refused to provide – information about the identity of any prescriber who wrote a prescription that the State claims was the result of wrongful conduct by Lilly.[38] It also denied Lilly access to patient and control group medical records and histories.[39]

[38] *See* Pl.'s Resp. to Interrog. Nos. 11, 13, 16-17, 24 (attached as Exhibit C).

[39] *See* Pl.s Resp. to Interrog. Nos. 10-13, 24 (attached as Exhibit C); *see also* Pl.'s Resp. to Def.'s First Set of Req. for Produc. of Docs. Nos. 5- 8, 32-37 (attached as Exhibit D). The State indicates that it will provide some additional information upon entry of a protective order "which does not identify individuals." (*E.g.*, Pl.'s Resp. to Interrog. Nos. 10-14, 24; Pl.'s Resp. to Req. for Produc. Nos. 5-8, 35). The State has also stated that it will produce information "related to the State's damages" as part of its expert disclosures. (*E.g.*, Pl.'s Resp. Interrog. Nos. 11, 13, 24; Pl.'s Resp. to Req. for Produc. Nos. 5-8, 32-35). Lilly is entitled to production of factual information now, without awaiting preparation of the State's experts' analysis of that underlying factual information.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

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Despite the vagueness of the State's description of its intended method of proving causation and damages, numerous questions that require individualized consideration of patient medical records and histories are already apparent, including the following:

- How will the State determine what is a "similar, properly controlled" group of non-Zyprexa users? For example, how will the State control for predisposing factors, including family history, height, weight, diet, physical activity or history of blood-sugar-related conditions? Detailed medical histories of the individuals in each group are necessary for the State's experts to answer these questions and for Lilly to assess whether the State's experts have appropriately answered these questions.

- How will the State account for whether another medication should have or could have been prescribed instead of Zyprexa for any given patient? This determination cannot be made without knowledge of, among other things, that patient's prior responses to potential alternatives medications, and other aspects of the patient's medical history.

- For patients who received Zyprexa prescriptions to treat "off-label" conditions, how will the State determine whether Zyprexa was effective and medically appropriate? The State's position cannot be that *all* "off-label" uses of Zyprexa are medically inappropriate. In fact, the State continues to reimburse such uses without restriction. The only way to distinguish between allegedly medically inappropriate "off-label" uses and those the State agrees were medically appropriate is by consideration of the individualized factors that led the patient's physician to determine that Zyprexa was an appropriate treatment.

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

To answer questions such as these, Lilly must obtain medical histories and records for each of the Medicaid recipients who are included in the State's claim or in its control group, as well as individual information about each physician who wrote an allegedly inappropriate Zyprexa prescription to an Alaska Medicaid recipient. Lilly intends to pursue such discovery, which is reasonably calculated to lead to admissible evidence.

3. Discovery Regarding Lilly's Alleged Misrepresentations and the State's Reliance

In addition to prescriber and patient information, Lilly needs full discovery of facts relating to the State's knowledge about Zyprexa and the actions it took based on that knowledge. Lilly is entitled to take discovery directly from the State to support its statute of limitations defense, and to demonstrate the State's failure to take any different action regarding Zyprexa after its alleged shortcomings were exposed. Lilly addresses this issue here briefly, in compliance with the Court's directive that the parties describe the types of discovery required to prepare this case for trial.

For example, Lilly intends to take discovery regarding what information the State had available to it regarding Zyprexa and alleged adverse events, and when the State had such information. Similarly, Lilly's discovery will address what efforts, if any, the State has undertaken to review the relative benefits of Zyprexa and other antipsychotic medications through "pharmacy and therapeutics committees" or drug review boards. Lilly is entitled to know if the State's own medical review efforts have yielded conclusions that are contrary to

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the State's litigation position in this case. As with patient and prescriber discovery, these areas of discovery are central to Lilly's ability to prepare for trial and defend against the State's claims, and the Court should not permit the State to obstruct Lilly's ability to obtain the discovery it needs in order to adequately prepare its defense.

V. CONCLUSION

For the foregoing reasons, Eli Lilly and Company requests that the Court enter an Order dismissing the State's claims with prejudice because the State of Alaska may not prove proximate cause using statistical evidence only. Lilly also requests that the Court dismiss the State's claims on the independent legal grounds set forth in this memorandum.

In the alternative, Lilly requests an Order permitting it to take discovery of individual patients, physicians, and prescriptions.

DATED this 7th day of May, 2007.

Attorneys for Defendant

PEPPER HAMILTON LLP
Andrew R. Rogoff, admitted *pro hac vice*
3000 Two Logan Square
18th & Arch Streets
Philadelphia, PA 19103
(215) 981-4000

LANE POWELL LLC

By _____
Brewster H. Jamieson, ASBA No. 8411122
Andrea E. Girolamo-Welp, ASBA No. 0211044

LANE POWELL LLC
301 West Northern Lights Boulevard, Suite 301
Anchorage, Alaska 99503-2648
Telephone 907.277.9511 Facsimile 907.276.2631

I certify that on May 7, 2007, a copy of the foregoing was served by hand-delivery, on:

Eric T. Sanders, Esq., Feldman Orlansky & Sanders
500 L Street, Suite 400, Anchorage, Alaska 99501-5911

009867.0038/160607.1

APPENDIX 1

Alleged Unlawful Practice	Corresponding FDA Regulation
Defendant represented that Zyprexa had characteristics, uses, benefits, and/or qualities that it did not have, in violation to [sic] AS 45.50.471(b)(4).	"A drug is drug or device shall be deemed to be misbranded if its labeling is false or misleading in any particular" 21 U.S.C. § 352(a) (2007); *see also* 21 U.S.C. § 352(n) (2007); 21 C.F.R. § 202.1(e)(3)(i)-(iii) (2007); 21 C.F.R. § 202.1(e)(6)(i)-(xx) (2007).
Defendant represented that Zyprexa was of a particular standard, quality, and grade suitable for consumption when in fact it was not, in violation of AS 45.50.471(b)(6).	"An advertisement does not satisfy the requirement that it present a 'true statement' of information in brief summary relating to side effects, contraindications, and effectiveness if it is false or misleading with respect to side effects, contraindications, or effectiveness." 21 C.F.R. § 202.1(e)(5)(i) (2007); *see also* 21 C.F.R. § 202.1(e)(5)(ii), (iii) (2007).
Defendant advertised Zyprexa with an intent not to sell it as advertised, in violation of AS 45.50.471(b)(8).	"An advertisement for a prescription drug is false, lacking in fair balance, or otherwise misleading, or otherwise violative of section 502(n) of the act, among other reasons, if it uses literature, quotations or references for the purpose of recommending or suggesting conditions of drug use that are not approved or permitted in the drug package label." 21 C.F.R. § 202.1(e)(6)(xi) (2007); *see also* 21 C.F.R. § 202.1(e)(6)(i)-(x), (xii)-(xx) (2007).
Defendant used misrepresentations or omissions of material facts with the intent that others rely on the misrepresentations or omissions in connection with the sale of Zyprexa, in violation of AS 45.50.471(b)(12).	"If any part or theme of the advertisement would make the advertisement false or misleading by reason of the omission of appropriate qualification or pertinent information, that part or theme shall include the appropriate qualification or pertinent information …. 21 C.F.R. § 202.1(e)(3)(i) (2007); *see also* 21 C.F.R. § 201.6 (2007); 21 C.F.R. § 202.1(e)(3)(ii),(iii) (2007); 21 C.F.R. § 202.1(e)(5)(i)-(iii) (2007); 21 C.F.R. § 202.1(e)(6)(i)-(xx) (2007); 21 C.F.R. § 202.1(e)(7)(i)-(xiii) (2007).

Alleged Unlawful Practice	Corresponding FDA Regulation
"A drug or device is misbranded if its labeling is false or misleading in any particular." AS 17.20.090(1).	"A drug or device shall be deemed to be misbranded if its labeling is false or misleading in any particular." 21 U.S.C. § 352(a) (2007); *see also* 21 C.F.R. § 201.6 (2007).
"A drug or device is misbranded if a word, statement, or other information required by or under authority of this chapter to appear on the label is not prominently placed …." AS 17.20.090(3).	"A drug or device shall be deemed to be misbranded if any word, statement, or other information required by or under authority of this Act to appear on the label or labeling is not prominently placed thereon …." 21 U.S.C. § 352(c) (2007); *see also* 21 C.F.R. § 201.15 (2007).
"A drug or device is misbranded unless its labeling bears adequate directions for use." AS 17.20.090(6)(A).	"A drug or device shall be deemed to be misbranded unless its labeling bears adequate directions for use." 21 U.S.C. § 352(f)(1) (2007); *see also* 21 C.F.R. 201.5(a)-(g)(2007).
"A drug or device is misbranded unless its labeling bears adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health …." AS 17.20.090(6)(B).	"A drug or device shall be deemed to be misbranded unless its labeling bears such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health …." 21 U.S.C. § 352(f)(2) (2007).
"A drug or device is misbranded if it purports to be a drug of which is recognized in an official compendium, unless it is packaged and labeled as prescribed in the compendium …." AS 17.20.090(7).	"A drug or device shall be deemed to be misbranded if it purports to be a drug the name of which is recognized in an official compendium, unless it is packaged and labeled as prescribed therein..." 21 U.S.C. § 352(g) (2007).
"A drug or device is misbranded if it has been found by the commissioner to be a drug liable to deterioration, unless it is packaged in the form and manner and its label bears a statement of precautions the department by regulation requires as necessary for the protection of public health …." AS 17.20.090(8).	"A drug or device shall be deemed to be misbranded if it has been found by the Secretary to be a drug liable to deterioration, unless it is packaged in such form and manner, and its label bears a statement of such precautions." 21 U.S.C. § 352(h) (2007).

Alleged Unlawful Practice	Corresponding FDA Regulation
"A drug or device is misbranded if it is a drug and its container is made, formed, or filled so as to be misleading or if it is an imitation of another drug; or it is offered for sale under the name of another drug." AS 17.20.090(9).	"A drug or device shall be deemed to be misbranded if it is a drug and its container is so made, formed, or filled as to be misleading, or (2) if it is an imitation of another drug; or if it is offered for sale under the name of another drug." 21 U.S.C. § 352(i) (2007).
"A drug or device is misbranded if it is dangerous to health when used in the dosage, or with the frequency or duration prescribed, recommended, or suggested in its labeling." AS 17.20.090(10).	"A drug or device shall be deemed to be misbranded if it is dangerous to health when used in the dosage, or manner or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. § 352(j) (2007).
"An advertisement of a food, drug, device, or cosmetic is false if it is false or misleading in any particular." AS 17.20.160.	"An advertisement for a prescription drug is false, lacking in fair balance, or otherwise misleading, or otherwise violative of section 502(n) of the act, among other reasons, if it: contains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is better, more effective, useful in a broader range of conditions or patients …, safer, has fewer, or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience …." 21 C.F.R. § 202.1(e)(6)(i) (2007); *see also* 21 C.F.R. § 202.1(e)(6)(ii)-(xx) (2007); 21 C.F.R. § 202.1(e)(7)(i)-(xiii) (2007).
"A drug or device is misbranded if it is a drug or device sold at retail and its label as originally packed bears a statement that it is to be dispensed or sold only by or on the prescription of a physician, dentist, or veterinarian, unless it is sold on a written prescription signed by a member of the medical, dental, or veterinary profession licensed by law to administer the drug or device, and its label as dispensed bears the name and place of business of the seller, the serial number and date of the prescription, and the name of the member of the medical, dental, or veterinary profession, and the prescription shall not be refilled except on the written authorization of the prescribing physician, dentist, or veterinarian." AS 17.20.090(11)(B).	"A pharmacist may dispense directly a controlled substance listed in Schedule II, which is a prescription drug as determined under the Federal Food, Drug, and Cosmetic Act, only pursuant to a written prescription signed by the practitioner ...." 21 C.F.R. § 1306.11(a) (2007); "The drug label bears: [t]he statement 'RX Only.'" 21 C.F.R. 201.100(b)(1) (2007); "All labeling described in paragraph (d) of this section bears conspicuously the name and place of business of the manufacturer, packer, or distributor, as required for the label of the drug under § 201.1." 21 C.F.R. § 201.100(e) (2007); *see also* 21 U.S.C. § 353(b)(2) (2007).

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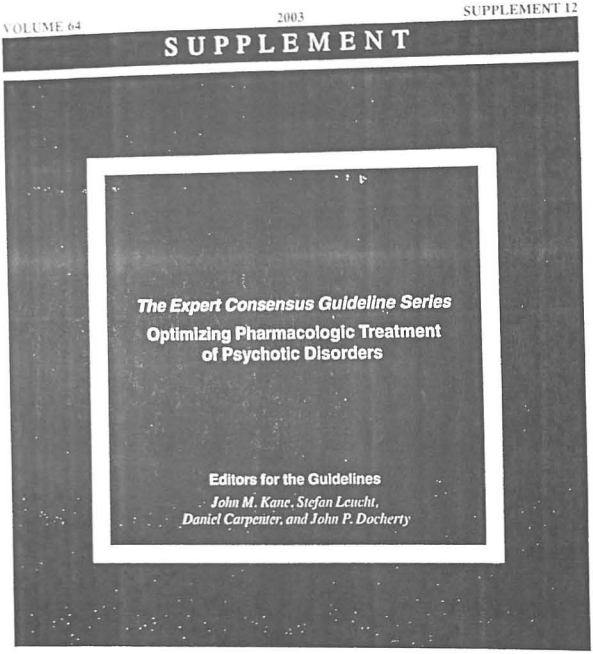

THE JOURNAL OF
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VOLUME 64 2003 SUPPLEMENT 12

OPTIMIZING PHARMACOLOGIC TREATMENT OF PSYCHOTIC DISORDERS

GUIDELINES

SURVEY RESULTS

CME SECTION

The Expert Consensus Panel for Optimizing Pharmacologic Treatment of Psychotic Disorders

The following participants in the Expert Consensus Survey were identified from several sources: recent research publications and funded grants, the DSM-IV advisers for psychotic disorders, the Task Force for the American Psychiatric Association's *Practice Guideline for the Treatment of Patients with Schizophrenia*, those who have worked on other schizophrenia guidelines, and participants in previous Expert Consensus Surveys on psychotic disorders. Of the 50 experts to whom we sent the schizophrenia survey, 47 (94%) replied. The recommendations in the guidelines reflect the aggregate opinions of the experts and do not necessarily reflect the opinion of each individual on each question.

Jorge L. Armanteros, M.D.
University of Miami

Ross J. Baldessarini, M.D.
Harvard Medical School

Nigel Bark, M.D.
Bronx Psychiatric Center

Robert Buchanan, M.D.
University of Maryland & Maryland Psychiatric Research Center

Peter F. Buckley, M.D.
Medical College of Georgia

William Carpenter, M.D.
University of Maryland & Maryland Psychiatric Research Center

Daniel E. Casey, M.D.
Oregon Health & Science University

Guy Chouinard, M.D.
Hopital L-H Lafontaine

Robert R. Conley, M.D.
University of Maryland Baltimore

John G. Csernansky, M.D.
Washington University School of Medicine

David G. Daniel, M.D.
Bioniche Development, Inc.

Michael Davidson, M.D.
Tel-Aviv University

John M. Davis, M.D.
University of Illinois

Lisa Dixon, M.D., M.P.H.
University of Maryland & VA Capitol Health Care Network MIRECC

Michael A. Flaum, M.D.
Iowa Consortium for Mental Health

Rohan Ganguli, M.D.
Western Psychiatric Institute, University of Pittsburgh Medical Center

David L. Garver, M.D.
University of Louisville

Steven Geisler, M.D.
The Zucker Hillside Hospital

John H. Gilmore, M.D.
University of North Carolina

Donald C. Goff, M.D.
Massachusetts General Hospital

Rona J. Hu, M.D.
Stanford University School of Medicine

Paul E. Keck, Jr., M.D.
University of Cincinnati College of Medicine

Samuel Keith, M.D.
University of New Mexico

Matcheri S. Keshavan, M.D.
University of Pittsburgh

John Krystal, M.D.
Yale University School of Medicine

John Lauriello, M.D.
University of New Mexico

Robert Paul Liberman, M.D.
UCLA School of Medicine

Jean-Pierre Lindenmayer, M.D.
NYU School of Medicine

Stephen Marder, M.D.
West LA Healthcare Center

Joseph McEvoy, M.D.
Duke University Medical Center

Alan Mendelowitz, M.D.
The Zucker Hillside Hospital

Alexander Miller, M.D.
University of Texas Health Science Center at San Antonio

Del D. Miller, M.D, Pharm.D.
University of Iowa

Henry A. Nasrallah, M.D.
University of Cincinnati

John Newcomer, M.D.
Washington University School of Medicine

Gary Remington, M.D.
University of Toronto

Samuel C. Risch, M.D.
University of California at San Francisco

Del Robinson, M.D.
Albert Einstein College of Medicine

Nina Schooler, M.D.
The Zucker Hillside Hospital

George Simpson, M.D.
University of Southern California at Los Angeles

Samuel B. Siris, M.D.
The Zucker Hillside Hospital

Thomas E. Smith, M.D.
Columbia University College of Physicians & Surgeons

Rajiv Tandon, M.D.
University of Michigan

Jan Volavka, M.D.
New York University

Peter J. Weiden, M.D.
SUNY Downstate Medical Center

Donna Wirshing, M.D.
UCLA School of Medicine

William C. Wirshing, M.D.
UCLA School of Medicine

Introduction: Methods, Commentary, and Summary

John M. Kane, M.D., Stefan Leucht, M.D., Daniel Carpenter, Ph.D., John P. Docherty, M.D.

ABSTRACT

Objectives. A growing number of atypical antipsychotics are available for clinicians to choose from in the treatment of psychotic disorders. However, a number of important questions concerning medication selection, dosing and dose equivalence, and the management of inadequate response, compliance problems, and relapse have not been adequately addressed by clinical trials. To aid clinical decision-making, a consensus survey of expert opinion on the pharmacologic treatment of psychotic disorders was undertaken to address questions not definitively answered in the research literature.

Method. Based on a literature review, a written survey was developed with 60 questions and 994 options. Approximately half of the options were scored using a modified version of the RAND 9-point scale for rating the appropriateness of medical decisions. For the other options, the experts were asked to write in answers (e.g., average doses) or check a box to indicate their preferred answer. The survey was sent to 50 national experts on the pharmacologic treatment of psychotic disorders, 47 (94%) of whom completed it. In analyzing the responses to items rated on the 9-point scale, consensus on each option was defined as a non-random distribution of scores by chi-square "goodness-of-fit" test. We assigned a categorical rank (first line/preferred choice, second line/alternate choice, third line/usually inappropriate) to each option based on the 95% confidence interval around the mean rating. Guideline tables indicating preferred treatment strategies were then developed for key clinical situations.

Results. The expert panel reached consensus on 88% of the options rated on the 9-point scale. The experts overwhelmingly endorsed the atypical antipsychotics for the treatment of psychotic disorders. Risperidone was the top choice for first-episode and multi-episode patients, with the other newer atypicals rated first line or high second line depending on the clinical situation. Clozapine and a long-acting injectable atypical (when available) were other high second line options for multi-episode patients. The experts' dosing recommendations agreed closely with the package inserts for the drugs, and their estimates of dose equivalence among the antipsychotics followed a linear pattern.

The experts considered 3–6 weeks an adequate antipsychotic trial, but would wait a little longer (4–10 weeks) before making a major change in treatment regimen if there is a partial response. The experts recommended trying to improve response by increasing the dose of atypical and depot antipsychotics before switching to a different agent; there was less agreement about increasing the dose of conventional antipsychotics before switching, probably because of concern about side effects at higher doses. If it is decided to switch because of inadequate response, risperidone was the experts' first choice to switch to, no matter what drug was initially tried. Although there was some disparity in the experts' recommendations concerning how many agents to try before switching to clozapine, the experts' responses suggest that switching to clozapine should be considered after failure to respond to two atypical antipsychotics. Clozapine was also the antipsychotic of choice for patients with suicidal behavior. When switching oral antipsychotics, the experts considered cross-titration the preferred strategy. When switching to an injectable antipsychotic, the experts stressed the importance of continuing the oral antipsychotic until therapeutic levels of the injectable agent are achieved.

The experts considered psychosocial interventions the first choice strategy for partially compliant patients, with pharmacologic interventions the first choice for patients with clear evidence of noncompliance. However, because it can be difficult to distinguish partially compliant from noncompliant patients, the editors recommended combining psychosocial and pharmacologic interventions to improve compliance whenever possible. When patients relapse because of compliance problems or if there is any doubt about compliance, the experts recommended the use of a long-acting injectable antipsychotic and would select an injectable atypical when this option becomes available. The experts would also consider using an injectable atypical antipsychotic (when available) in many clinical situations that do not involve compliance problems.

The experts stressed the importance of monitoring for health problems—especially obesity, diabetes, cardiovascular problems, HIV risk behaviors, medical complications of substance abuse, heavy smoking and its effects, hypertension, and amenorrhea—in patients being treated with antipsychotics.

Although many patients are prescribed adjunctive treatments, multiple antipsychotics, and combinations of different classes of drugs (e.g., antipsychotics plus mood stabilizers or antidepressants) in an effort to enhance response, the experts gave little support to any of these strategies, with the exception of antidepressants for patients with dysphoria/depression, antidepressants or ECT for patients with suicidal behavior, and mood stabilizers for patients with aggression/violence.

When asked about indicators of remission and recovery, the experts considered acute improvement in psychotic symptoms the most important indicator of remission, whereas they considered more sustained improvement in multiple outcome domains (e.g., occupational/educational functioning, peer relationships, independent living) important in assessing recovery.

Conclusions. The experts reached a high level of consensus on many of the key treatment questions in the survey. Within the limits of expert opinion and with the expectation that future research data will take precedence, these guidelines provide direction for addressing common clinical dilemmas that arise in the pharmacologic treatment of psychotic disorders. They can be used to inform clinicians and educate patients regarding the relative merits of a variety of interventions. Clinicians should keep in mind that no guidelines can address the complexities involved in the care of each individual patient and that sound clinical judgment based on clinical experience should be used in applying these recommendations.

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WHY ARE NEW GUIDELINES ON THE USE OF ANTIPSYCHOTICS NEEDED?

Now that the new generation of antipsychotics has been in widespread use for several years, it is important to provide guidelines reflecting this experience. In addition, despite considerable activity in clinical trials, clinicians continue to struggle with a number of very important practical issues concerning the treatment of psychotic disorders that are not adequately addressed by clinical trial data. We were interested in determining how the atypical antipsychotics are perceived by experts in the field with regard to questions such as drug choice, use in different clinical situations, dose equivalencies, duration of adequate trials, and preferences for switching. We were also very interested in the best strategies for managing poor or partial response to treatment. We therefore asked the experts about the number of trials of different types of agents that they would recommend before going to clozapine and the role of adjunctive pharmacologic treatment strategies in enhancing response in a number of different domains. Since the first long-acting formulation of a newer atypical antipsychotic is expected to be marketed in the near future, we wanted to determine what role the experts believe this new formulation will play in the treatment of patients with psychotic disorders. We also asked what role psychosocial interventions play in improving compliance and promoting better functional outcomes. Finally, given increasing expectations for treatment outcomes, we were particularly interested in how experts in the field conceptualize and evaluate remission and recovery in their patients.

METHOD OF DEVELOPING EXPERT CONSENSUS GUIDELINES

The contribution of expert consensus to practice guideline development continues to evolve throughout medicine, alongside the "gold standard" of meta-analysis of clinical trials and other experimental data. The sheer number of possible combinations and sequences of available treatments for many diseases makes it difficult to provide comparative recommendations based entirely on clinical trial data.[1,2] A method for describing expert opinion in a quantitative, reliable manner to help fill some of the gaps in evidence-based guidelines has been developed. This method has been applied to a variety of psychiatric disorders.[3–14]

Creating the Surveys

We first created a skeleton algorithm based on a literature review. We sought to identify key decision points in the use of antipsychotics to treat psychotic disorders as well as a list of feasible options for intervention. We highlighted important clinical questions that had not yet been adequately addressed or definitively answered in the literature.[15] A written questionnaire was developed with 60 questions and 994 options. We asked about medication selection, dosing, and dose equivalence, compliance issues, the most appropriate way to use long-acting atypical antipsychotics when they become available, and how best to define the concepts of remission and recovery in schizophrenia.

The Rating Scale

For approximately half the options in the survey, we asked raters to evaluate appropriateness using a 9-point scale slightly modified from a format developed by the RAND Corporation for ascertaining expert consensus.[16] For the other questions, we asked respondents to write in answers (e.g., target dose of a drug). We asked the experts to draw on their knowledge of the research literature (we did not provide a literature review) and their best clinical judgment in making their ratings, but not to consider financial cost. We presented the rating scale to the experts with the anchors shown in figure 1. Figure 2 shows an excerpt from Survey Question 26 as an example of our question format.

Figure 1. The Rating Scale

Extremely Inappropriate ← 1 2 3 4 5 6 7 8 9 → Extremely Appropriate

9 = Extremely appropriate: this is your treatment of choice
7–8 = Usually appropriate: a first line treatment you would often use
4–6 = Equivocal: a second line treatment you would sometimes use (e.g., patient/family preference or if first line treatment is ineffective, unavailable, or unsuitable)
2–3 = Usually inappropriate: a treatment you would rarely use
1 = Extremely inappropriate: a treatment you would never use

Composition of the Expert Panel

We identified 50 leading American experts in the treatment of schizophrenia. The experts were identified from several sources: recent research publications and funded grants, the DSM-IV advisors for psychotic disorders, the Task Force for the American Psychiatric Association's *Practice Guideline for the Treatment of Patients With Schizophrenia*,[17] those who worked on the Patient Outcomes Research Team (PORT guidelines),[18] and participants in previous Expert Consensus surveys on psychotic disorders.[4,7] We provided a $500 honorarium. Panelists reported taking 2 or more hours to complete the survey. This project was supported by an unrestricted grant from Janssen Pharmaceutica, L.P. However, the experts were kept blind to the sponsorship for this project while they completed the survey to reduce the chance of possible bias.

We received responses from 47 of the 50 experts (94%) to whom the survey was sent. All of the respondents held an MD degree and 1 also held an MPH and 1 a PharmD degree. Of the respondents, 6 (13%) were female and 41 (87%) male. Their mean age was 52 years, with a mean of 24 years in practice or research; 40% reported spending at least half their work time and 43% about a quarter of their work time seeing patients. The majority of the experts worked in an academic clinical or

Figure 2. Sample Survey Question

26. Rate the appropriateness of each of the following types of antipsychotic medications for a patient with suicidal behavior. Give your highest ratings to the medications you consider most appropriate for this problem.

Oral formulations			
1) Aripiprazole	1 2 3	4 5 6	7 8 9
2) Clozapine	1 2 3	4 5 6	7 8 9
3) Olanzapine	1 2 3	4 5 6	7 8 9
4) Quetiapine	1 2 3	4 5 6	7 8 9
5) Risperidone	1 2 3	4 5 6	7 8 9
6) Ziprasidone	1 2 3	4 5 6	7 8 9
7) High-potency conventional	1 2 3	4 5 6	7 8 9
8) Mid-potency conventional	1 2 3	4 5 6	7 8 9
9) Low-potency conventional	1 2 3	4 5 6	7 8 9
Injectable formulations			
10)Long-acting injectable atypical	1 2 3	4 5 6	7 8 9
11)Long-acting depot conventional	1 2 3	4 5 6	7 8 9

research setting, while 19% were in private practice and 17% in the public sector. Of the 47 respondents, 98% had participated in a research project involving antipsychotics during the past 5 years, 87% had held a federal (NIMH or NIH) research grant as a principal investigator, and 96% had been principal investigator for an industry-sponsored grant. Respondents had received grants, speaking fees, and funding for studies from a wide variety of sources. The pharmaceutical companies from whom at least 30% of respondents reported receiving support included Eli Lilly (83% of respondents), Janssen (77%), Pfizer (72%), Bristol-Myers Squibb (57%), AstraZeneca (57%), Abbott (30%), and Novartis (32%).

Data Analysis for Options Scored on the Rating Scale

For each option, we first defined the presence or absence of consensus as a distribution unlikely to occur by chance by performing a χ^2 test ($p < 0.05$) of the distribution of scores across the 3 ranges of appropriateness (1–3, 4–6, 7–9). Next we calculated the mean and 95% confidence interval (C.I.). A categorical rating of first, second, or third line was designated based on the lowest category in which the C.I. fell, with boundaries of 6.5 or greater for first line, and 3.5 up to 6.5 for second line. Within first line, we designated an item as "treatment of choice" if at least 50% of the experts rated it as 9.

Data Analysis for Write-In Options

For many questions concerning dosing, we asked respondents to write in their answers. This kind of question typically produces a number of extreme outlier responses. In analyzing the results of this type of question in this survey, we subjected these write-in responses to a Winsorizing(1) process,[19] which involved replacing the highest and lowest responses to a given question with the next highest and next lowest responses, respectively. Practically speaking, Winsorizing has an impact on a distribution only if there is a single extreme outlier in either direction from the mean; in such situations, that extreme value is replaced with the next most extreme value. Our rationale for using this process was that a single extreme outlier might have interpreted the question differently than his or her peers—but that two extreme outliers would be less likely to have done so. Using the Winsorized data, means and standard deviations were calculated for each dosing question. The aggregate dosing values given in the guidelines are based on those means and standard deviations adjusted based on available pill strengths to the nearest available dosage for each drug.

Displaying the Survey Results

The results of the section of Question 26 asking about choice of antipsychotics for a patient with suicidal behavior (figure 2) are presented graphically in figure 3. The C.I.s for each treatment option are shown as horizontal bars and the numerical values are given in the table on the right.

The Ratings

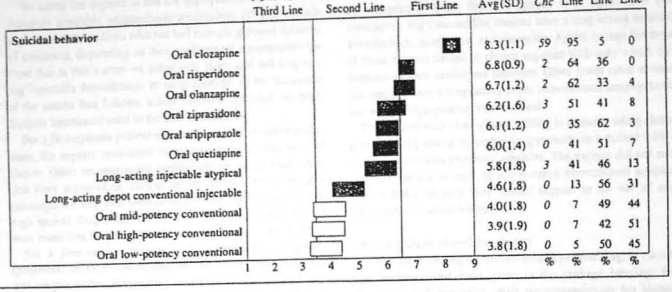
- Treatment of choice
- First line
- Second line
- Third line
- No consensus

First line treatments are those strategies that came out on top when the experts' responses to the survey were statistically aggregated. These are options that the panel feels are usually appropriate as initial treatment for a given situation. Treatment of choice, when it appears, is an especially strong first line recommendation (having been rated as "9" by at least half the experts). In choosing between several first line recommendations, or deciding whether to use a first line treatment at all, clinicians should consider the overall clinical situation, including the patient's prior response to treatment, side effects, general medical problems, and patient preferences.

Second line treatments are reasonable choices for patients who cannot tolerate or do not respond to the first line choices. A second line choice might also be used for initial treatment if the first line options are deemed unsuitable for a particular patient (e.g., because of poor previous response, inconvenient dosing regimen, particularly annoying side effects, general medical contraindication, potential drug interaction, or if the experts do not agree on a first line treatment). For some questions, second line ratings dominated, especially when the experts did not reach any consensus on first line options. In such cases, to differentiate among the alternatives, we label those items whose C.I.s overlap with the first line category as "high second line."

Figure 3. Graphic Results of Survey Question 26 (Section on Suicidal Behavior)

26 **Complicating problems.** Rate the appropriateness of each of the following types of antipsychotic medications for a patient with a psychotic disorder who has suicidal behavior. Give your highest ratings to the medications you consider most appropriate.



	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
			%	%	%
Oral clozapine	8.3(1.1)	59	95	5	0
Oral risperidone	6.8(0.9)	2	64	36	0
Oral olanzapine	6.7(1.2)	2	62	33	4
Oral ziprasidone	6.2(1.6)	3	51	41	8
Oral aripiprazole	6.1(1.2)	0	35	62	3
Oral quetiapine	6.0(1.4)	0	41	51	7
Long-acting injectable atypical	5.8(1.8)	3	41	46	13
Long-acting depot conventional injectable	4.6(1.8)	0	13	56	31
Oral mid-potency conventional	4.0(1.8)	0	7	49	44
Oral high-potency conventional	3.9(1.9)	0	7	42	51
Oral low-potency conventional	3.8(1.8)	0	5	50	45

Third line treatments are usually inappropriate or used only when preferred alternatives have not been effective.

No consensus. For each item in the survey, we used a χ^2 test to determine whether the experts' responses were randomly distributed across the 3 categories, which suggests a lack of consensus. These items are indicated by an unshaded bar in the survey results.

Statistical differences between treatments. While we did not perform tests of significance for most treatments, the reader can readily see whether C.I.s overlap (roughly indicating no significant difference between options by *t*-test). The wider the gap between C.I.s, the smaller the *P* value would be (i.e., the more significant the difference). In some questions there are striking and important differences within levels, which we occasionally point out. Often, however, differences within levels are not significant from a statistical perspective. Also, there are sometimes no statistical differences between choices at the bottom of first line and those at the top of second line.

From Survey Results to Guidelines

After the survey results were analyzed and ratings assigned, the next step was to turn these recommendations into user-friendly guidelines. We generally present three levels of recommendations: first line, high second line (options for which the confidence interval bar crosses or touches the boundary with first line), and other second line. For some guidelines, we present just preferred (first line) options and also consider (second line) options. Whenever the guideline lists more than one option in a rating level, we list the options in the order of their mean scores.

As an example, the full results of the question presented above are shown on pages 75–76 and are used in Guideline 10A. For a patient with suicidal behavior, clozapine was rated the treatment of choice. High second line options were oral risperidone, olanzapine, and ziprasidone.

Degree of Consensus

Of the 474 options rated on the 9-point scale, consensus was reached on 418 options (88%) as defined by the χ^2 test. When there was no first line recommendation, we chose the highest-rated second line option as the "preferred" treatment and indicated this in the guideline.

RESULTS AND COMMENTARY

In the following sections, we summarize the key recommendations from the guidelines and consider how the experts' recommendations relate to the available research literature. The complete set of data from the survey is presented on pages 52–94. The guidelines derived from the data are presented on pages 21–51.

Initial Medication Selection

An increasingly wide range of medications is available for the treatment of schizophrenia. While the growing number of options increases the chances of a positive treatment outcome for patients, clinicians are faced with ever more complex choices in trying to select the best medication for each specific patient. Recommendations in current textbooks state that, with the exception of clozapine, all available antipsychotics have similar efficacy when given at optimum doses.[20] However, at least con-

cerning the traditional conventional antipsychotics, this statement may have been biased by the use of small studies without enough power to detect modest to moderate differences in treatment effects. Furthermore, there are important differences in side-effect profiles that may influence treatment choices.[21,22]

We asked the experts to rate the appropriateness of all of the currently available antipsychotic medications for first-episode patients and for patients who had had multiple previous episodes of psychosis, depending on their predominant symptomatology. Note that in this survey we asked only about oral and long-acting injectable formulations of antipsychotics. In the discussion of the results that follows, unless otherwise specified, all medications mentioned refer to the oral formulations.

For a ***first-episode patient with predominantly positive symptoms***, the experts considered risperidone to be the treatment of choice. Other recommended medications for this clinical situation were aripiprazole, olanzapine, ziprasidone, and quetiapine (although the first two were rated first line and the second two high second line, these four options clustered together and all were rated first line by approximately two thirds of the experts).

For a ***first-episode patient with predominantly negative symptoms***, the experts recommended one of the newer oral atypical antipsychotics. Risperidone and aripiprazole received first line ratings, and the other three were rated high second line; however, all of the options clustered together with only small differences in their confidence intervals.

For a ***first-episode patient with both prominent positive and negative symptoms***, the experts preferred risperidone. Other recommended medications for this clinical situation are aripiprazole, ziprasidone, olanzapine, and quetiapine (again these four options clustered together with only small differences in their confidence intervals).

At the time of the survey, a long-acting injectable atypical antipsychotic was not available in the United States, although it was available in several other countries. We therefore asked the experts to tell us how they would use such a formulation if it were available. As a group, the experts varied in their ratings of using a long-acting injectable atypical antipsychotic for a first-episode patient to such an extent that there was no consensus on this item (with approximately a quarter of the experts rating it first line and approximately a third of the experts giving it third line ratings). The experts did not recommend the use of either oral or depot conventional antipsychotics for a first-episode patient (conventional antipsychotics received third line ratings in every case).

For a ***multi-episode patient with predominantly positive symptoms***, the experts considered risperidone treatment of choice. Other recommended first line medications for this clinical situation were aripiprazole, ziprasidone, olanzapine, and quetiapine and a long-acting atypical antipsychotic. Clozapine was rated high second line. Other lower rated second line options were a long-acting conventional antipsychotic (depot) and an oral high-potency conventional.

For a ***multi-episode patient with predominantly negative symptoms***, risperidone, aripiprazole, and ziprasidone were rated first line; high second line choices were olanzapine, quetiapine, a long-acting atypical antipsychotic, and clozapine. All these options tended to cluster together, with only small differences in their confidence intervals. A long-acting depot conventional antipsychotic was a lower rated second line option.

For a ***multi-episode patient with both prominent positive and negative symptoms***, the experts preferred risperidone, followed by aripiprazole. Other first line options were ziprasidone and olanzapine. High second line choices were a long-acting atypical antipsychotic, quetiapine, and clozapine. Again, ratings for most of these options tended to cluster together with only small differences in their confidence intervals. Other lower rated second line options were a long-acting depot conventional antipsychotic and an oral high-potency conventional.

The experts were clearly more willing to consider using clozapine or a long-acting injectable antipsychotic in a patient with a history of previous psychotic episodes. The experts did not recommend the use of mid- or low-potency conventional antipsychotics and gave only very limited support to the use of oral high-potency conventionals.

Adequate Dose of Antipsychotics

The experts' dosing recommendations generally agree closely with recommended doses given in the package labeling. For olanzapine and quetiapine, their recommendations for highest acute dose were somewhat higher than the highest doses for which safety data from clinical trials are available (20 mg of olanzapine and 800 mg of quetiapine). The panel would generally use higher doses for a patient who had had multiple episodes of psychosis than for a first-episode patient. The recommended dose ranges for maintenance treatment were also slightly lower than for acute treatment.

Use of Therapeutic Drug Monitoring

We asked the experts for which antipsychotics plasma level assays were available to them and whether and how they used such levels to adjust dosing. Over 50% of the experts reported that plasma levels were available to them only for clozapine, haloperidol, and haloperidol decanoate. Clozapine was the agent for which the experts considered plasma levels most clinically useful. Over half of the experts use plasma levels of clozapine and haloperidol to monitor compliance; 88% use clozapine levels to adjust dose, primarily if there has been an inadequate response or side effects are a problem; 50% of the experts use plasma levels of oral haloperidol and haloperidol decanoate to adjust dose levels if the patient has an inadequate response or problematic side effects.

Dose Equivalence

Dose equivalences of different antipsychotics are an important but tricky issue. For the conventional antipsychotics, certain estimates can be derived from their different affinities for dopamine receptors.[23] For the newer atypical antipsychotics, the issue is more complicated, because their effectiveness seems to be related not only to dopamine but also to other receptors, especially serotonin receptors. We therefore asked the experts to

write in doses of conventional and atypical antipsychotics that they would consider equivalent to a range of haloperidol doses. The goal was to obtain a better sense of the equivalency between the older conventional antipsychotics and the new generation of atypical antipsychotics. We also asked the experts to write in doses of conventional and atypical antipsychotics that they would consider equivalent to a range of risperidone doses. The goal here was to obtain a better sense of the equivalency of doses among the new generation of atypical antipsychotics. In general, the experts' responses followed a very linear pattern, indicating that it would probably be possible to use linear formulas to calculate dose equivalency. It is interesting to note that, in every case, the dose the experts considered equivalent to 30 mg of haloperidol is higher than the highest acute dose the experts indicated they would usually use (see Guideline 2). In addition, the doses the experts considered equivalent to 10 mg of risperidone were closest to those they considered equivalent to 20 mg of haloperidol (as would be expected since they indicated that they considered 10.5 mg of risperidone to be equivalent to 20 mg of haloperidol).

Dose Adjustment

Data indicate that there is a relationship between certain patient characteristics and necessary dose adjustments. For example, smoking can reduce the plasma levels of some antipsychotic drugs[24] and there is a constantly increasing literature on the effects of genetic polymorphisms involving cytochrome P450 enzymes and the metabolism of psychotropic drugs.[25] It has also been shown that elderly patients are more sensitive to the side effects of antipsychotic drugs.[26] However, the clinical relevance of individual factors is not always clear. We therefore asked the experts which factors they would consider in adjusting the acute antipsychotic dose. The experts considered the use of concomitant medications, the patient's age, and the presence of hepatic disease the most important factors to consider in adjusting the acute antipsychotic dose. The priority given to the use of concomitant medications reflects our expanding knowledge of drug-drug interactions and their potential consequences. Other important factors to consider are the presence of cardiovascular or renal disease, whether or not the patient smokes, and the patient's weight. There was no consensus about the importance of the patient's sex, with 30% of the experts saying they would nearly always consider the patient's sex in dose adjustment and 23% saying they would rarely or never consider it. It is surprising that many of the experts (45%) would only sometimes consider the patient's weight in adjusting the dose. This may reflect the fact that clinicians tend not to pay adequate attention to the weight of patients with schizophrenia and what impact it may have on blood levels of psychotropic drugs following specific doses.

Dose Selection for Special Populations

Dose selection for children and adolescents. A majority of the experts would not generally use the following medications in children with a psychotic disorder who are 12 years of age or younger: aripiprazole, clozapine, chlorpromazine, fluphenazine, perphenazine, thioridazine, thiothixene, trifluoperazine, fluphenazine decanoate, and haloperidol decanoate. A majority of the experts would not generally use the following medications in an adolescent (13–18 years old) with a psychotic disorder: chlorpromazine, perphenazine, thioridazine, thiothixene, trifluoperazine. The doses recommended for pediatric patients were generally much lower than those given for adult patients (see Guideline 2), while the doses recommended for adolescents were only somewhat lower than those recommended for adults. These results underscore the need for more data on optimum dosing for children and adolescents.

Dose selection for elderly patients. The experts generally recommended using lower doses in elderly patients than in younger adults. This probably reflects previous recommendations and concerns about slower metabolism and greater sensitivity to adverse effects in older patients.[26] Older patients are also more likely to have comorbid medical conditions and to be taking multiple medications, increasing the risk for adverse effects and drug-drug interactions. The experts generally recommended using much lower doses in elderly patients with dementia than in those with a psychotic disorder. The majority of the experts would not generally use the following medications in an elderly patient with a psychotic disorder or with dementia: chlorpromazine, thioridazine, thiothixene, trifluoperazine; 70% would also avoid haloperidol or fluphenazine decanoate in elderly patients with dementia.

Inadequate Response to Treatment

Adequate treatment trial. The time-course of the antipsychotic effect is poorly understood.[27] It has recently been shown that, in general, antipsychotic drugs do not have a delayed onset of action, but rather that their clinical effects begin to appear in the first week of treatment.[28] Patients then continue to improve over longer periods of time. We asked the experts about the appropriate duration of an antipsychotic trial. If a patient is having little or no response to the initial or to the second antipsychotic that was prescribed, the experts recommended waiting a minimum of 3 weeks and a maximum of 6 weeks before making a major change in treatment regimen. By a major change in treatment regimen, we mean either a significant dose increase or switching to a different agent. If the patient is showing a partial response to treatment, the experts would extend the duration of the trial somewhat to 4–10 weeks for the initial antipsychotic and 5–11 weeks for the second antipsychotic prescribed. Note that the experts would wait longer if the patient is having a partial response, especially in the second trial. Although the differences in the recommendations were not dramatic, they are interesting, particularly given the lack of data from controlled trials addressing these issues. It should also be noted that the results are similar to the recommendations given in the 1996 *Expert Consensus Guidelines on the Treatment of Schizophrenia*,[4] which recommended waiting 3–8 weeks if there is no response and 5–12 weeks if there is a partial response before switching to another pharmacologic strategy.

When to switch antipsychotics. For each antipsychotic, we asked the experts whether they would increase the dose or switch to another agent if a multi-episode patient was having an inadequate response to the average target dose of the medication (see Guideline 2 for recommended target doses). Over 90% of the experts would first increase the dose of clozapine and olanzapine before switching, going as high as 850 mg/day of clozapine and 40 mg of olanzapine. Over 80% would increase the dose of quetiapine and risperidone before switching, going as high as 950 mg/day of quetiapine and 10 mg/day of risperidone. Approximately 60% or more of the experts would also increase the dose of aripiprazole, ziprasidone, and the decanoate formulations of fluphenazine and haloperidol. The experts were divided fairly evenly as to whether increasing the dose or switching is the best strategy if a patient is having an inadequate response to the recommended target dose of one of the conventional oral antipsychotics, except for thioridazine, where 67% would switch to another agent. The experts may be less willing to increase the dose of the conventional oral medications because of concern about side effects, especially extrapyramidal side effects (EPS) and tardive dyskinesia (TD), at higher doses.

Switching antipsychotics: selecting the next agent and dose. We asked the experts to indicate the first and second antipsychotics they would try if there was an inadequate response to the initial medication. Guideline 7B lists those agents that were written in by 10% or more of the experts in response to Question 15. It should be noted that, after trials of two atypical antipsychotics, 30% or more of the experts would switch to clozapine; this was recommended as a first line strategy in this situation by 70% of the experts in Question 18. The discrepancy between the responses given in Questions 15 and 18 probably reflects differences in the way the question was posed as well as the lack of certainty in the field as to the most appropriate place for clozapine in the treatment algorithm. The editors note that they would endorse the response given in question 18, where approximately three quarters of the experts recommended switching to clozapine after inadequate response to two atypical antipsychotics. For patients who had started with a conventional antipsychotic, the experts were more likely to try two other atypical antipsychotics before moving to clozapine.

The recommended target doses for the second and third antipsychotics the experts would try were mostly consistent with the acute target doses shown in Guideline 2, although there was a tendency to consider using doses at the higher end of the range, especially for the third medication tried.

Switching strategies. Some recent studies compared different strategies for switching from one antipsychotic drug to another.[29,30] These studies did not usually show dramatic differences in outcomes between different strategies. However, only a small number of antipsychotics have been examined and there might be pragmatic reasons to prefer one strategy over another. We therefore asked the experts what strategy they would use in switching to each of the oral atypical antipsychotics, assuming the first antipsychotic does not require tapering before discontinuation. In switching to any of the oral atypicals except clozapine, the experts recommended using cross-titration (gradually tapering the dose of the first antipsychotic while gradually increasing the dose of the second) or overlap and taper (continuing the same dose of the first antipsychotic while gradually increasing the second to a therapeutic level and then tapering the first). Of the two strategies, cross-titration was rated first line by a higher percentage of the experts. In switching to clozapine, the experts' preferred strategy is cross-titration, probably reflecting the need for relatively slow titration of clozapine. They would also consider using overlap and taper in switching to clozapine (high second line).

Even fewer evidence-based data are available to determine the optimum method for switching to a long-acting injectable antipsychotic; we therefore asked the experts about strategies for this situation. In switching to a depot conventional antipsychotic, the experts recommended either continuing the oral antipsychotic at the same dose until therapeutic drug levels of the injectable antipsychotic are achieved and then gradually tapering the oral antipsychotic or else beginning to taper the oral antipsychotic gradually after giving the first injection, with a larger percentage of the experts favoring the first strategy. Some experts would consider discontinuing the oral antipsychotic immediately once therapeutic levels of the injectable antipsychotic are achieved. The experts' recommendations for switching to a long-acting atypical antipsychotic were similar, except that there was stronger support for continuing the oral antipsychotic at the same dose until therapeutic drug levels of the injectable antipsychotic are achieved and then gradually tapering the oral antipsychotic compared with the other options. It should be noted the experts definitely did not recommend stopping the oral antipsychotic when the first long-acting injection is given, since this would leave the patient without adequate antipsychotic coverage during the switchover and potentially increase the risk of relapse.

Strategies for enhancing a partial response. We asked the experts about the appropriateness of a number of strategies to try to improve response in a patient who is having a partial but still inadequate response (e.g., a patient with some persisting positive symptoms). The experts gave only limited support to any of the options and rated many of them third line. This probably reflects the lack of strong empirical data in the literature. For example, although mood stabilizers are frequently used in combination with antipsychotic drugs,[31] a recent meta-analysis found no benefits of carbamazepine augmentation in patients with schizophrenia.[32] Most of the trials in this field are underpowered. A noteworthy exception is a recent trial of valproate augmentation that clearly showed a more rapid onset of action; however, the superiority vanished over time.[33]

The experts considered adding a second oral atypical a low second line treatment for those patients who failed to respond adequately to an oral conventional or atypical antipsychotic. This is striking given the widespread use of combined antipsychotics in the field. This practice, which continues despite a lack of supportive data from clinical trials or guidance from expert opinion,

adds to the cost of treatment. It also increases the potential side-effect burden for patients, since studies suggest that those patients who are taking multiple antipsychotics are generally receiving a higher dose equivalence than patients receiving only one drug.[34]

Use of clozapine. Clozapine is indicated for treatment-refractory schizophrenia.[35] However, clinicians vary in how they define treatment-refractory illness and there are no universally accepted criteria for treatment-refractoriness in schizophrenia. We therefore asked the experts in what clinical situations they would be most likely to consider a switch to clozapine. The experts considered a trial of clozapine a strategy of choice for a patient who has failed to respond to adequate trials of one or more conventional antipsychotics and two atypical antipsychotics. They would also consider it a strategy of choice for a patient who had failed to respond to trials of one or more conventionals and all of the atypicals. However, 13% of the experts rated this option third line, probably reflecting the feeling that there would be no advantage in conducting trials of all of the other five atypicals before considering clozapine. The experts also considered a trial of clozapine a first line option for patients who have failed to respond to trials of two or three atypicals or trials of one or more conventionals and one atypical. Although some experts would consider clozapine for patients who have not responded to two conventionals or one atypical, there was much less support for these options. When it is appropriate to switch to clozapine remains an area of controversy and there are few data to inform clinical practice. We may in fact be doing our patients a disservice by trying multiple drugs before going to clozapine (see discussion on switching antipsychotics above).

Managing Relapse

Unfortunately, drug research often stops after determining whether an antipsychotic is efficacious in reducing positive symptoms. Hardly any data are available concerning sequential treatment steps, including strategies for managing relapse. Thus, expert opinions are relevant here.

Relapse when taking an oral antipsychotic. When relapse occurs in a patient whom the clinician believes to be compliant with medication based on all available evidence (e.g., family report, plasma levels), the experts recommended (high second line ratings) either switching to a different oral antipsychotic or increasing the dose of the current medication. The only study the editors are aware of is an inconclusive small pilot trial that did not find a difference between increasing the dose of fluphenazine and maintaining the same dose in 32 relapsed patients.[36] Another second line option the experts would consider is switching to a long-acting injectable antipsychotic. This probably reflects concerns that the patient may not actually be compliant, since studies have found that clinicians are often incorrect in their assessment of patients' compliance.[37]

When the clinician is unsure of the level of compliance or there is clear evidence of noncompliance, the experts' first line recommendation was to switch to a long-acting injectable atypical if available. They would also consider a long-acting conventional antipsychotic (high second line). If the clinician is unsure of the level of compliance, the experts would also consider adding a long-acting atypical to the oral antipsychotic.

Relapse on a long-acting injectable antipsychotic. If a patient relapses when receiving a long-acting conventional antipsychotic, the experts' first line recommendation was to switch to a long-acting injectable atypical antipsychotic. They would also consider increasing the dose or the frequency of injections of the long-acting conventional (high second line options).

If a patient relapses when receiving a long-acting injectable atypical antipsychotic, the experts' first line recommendation was to increase the dose of the injectable antipsychotic. They would also strongly consider adding the oral form of the injectable antipsychotic to try to boost response (very high second line). The experts did not recommend switching to a conventional depot antipsychotic (third line rating).

Dose Adjustment in Stable Patients

If the patient is being treated with an atypical antipsychotic or with fluphenazine or haloperidol decanoate, the majority of the experts would continue maintenance treatment with the same dose that was effective acutely, although over 40% would lower the dose of olanzapine or risperidone. A majority of the experts said they would lower the dose of an oral conventional antipsychotic for maintenance treatment; however, the percentages were very close, with 40% or more of the experts recommending continuing the acute dose of the conventional antipsychotic. The uncertainties shown in this area are consistent with a lack of information concerning optimum doses for maintenance treatment with both conventional and atypical antipsychotics.

Managing Complicating Problems

Choosing antipsychotics for patients with complicating problems. There has been increasing interest in the efficacy of the different atypical antipsychotics for symptoms and problems that are frequently associated with schizophrenia (e.g., cognitive dysfunction, depression, substance abuse) and often lead to significant functional impairment. For the most part, the experts' recommendations reflect findings in the literature. The experts considered clozapine the treatment of choice for patients who present with suicidal behavior. Clozapine was also the top choice for aggression and violence. Other highly rated options for aggression and violence were risperidone (rated first line), olanzapine, and a long-acting injectable atypical (both rated high second line). These recommendations reflect studies that have found clozapine to be more effective than other available antipsychotics in reducing rates of suicide[38] and moderating aggressive behavior.[39] There is a new indication for clozapine for "reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder."[40]

There were no first line recommendations for the other problems we asked about—dysphoria/depression, cognitive problems,

and substance abuse—for which all of the oral atypical antipsychotics as well as a long-acting injectable atypical received second line ratings. The experts would also consider a long-acting depot conventional for a patient with substance abuse problems. The lack of first line consensus on these items probably reflects the fact that, although an increasing number of studies have looked at the effects of the atypical antipsychotics on mood,[41,42] cognition,[43] and substance use,[44] there are few empirical data definitive enough to guide clinical practice. A good example are the studies on cognition by Kern et al.[45] and Green et al.[46] In an initial trial using high haloperidol doses (15 mg/day in the fixed dose phase), these researchers found that risperidone was superior on several domains of cognition,[45] but they could not confirm this in a subsequent trial using relatively low haloperidol doses (mean 5 mg/day).[46] It is interesting that the experts would not recommend oral conventional antipsychotics for patients with any of the problems we asked about, except aggression/violence, for which conventional orals were second line options.

It is possible that these complicating problems may be caused or exacerbated by noncompliance. Therefore, it is not surprising that a long-acting atypical antipsychotic was a prominent alternative, especially for aggression/violence and substance-abuse problems.

Selecting adjunctive treatments for patients with complicating problems. When we asked about a number of adjunctive medications that are commonly used in clinical practice to treat a variety of complicating problems in patients with schizophrenia, the experts as a group had few strong recommendations, probably reflecting the lack of decisive empirical data in this area. The only first line recommendation was a selective serotonin reuptake inhibitor (SSRI) for dysphoria/depression. The first line ratings given to the SSRIs probably reflect a concern to choose an antidepressant associated with few side effects. Venlafaxine was a very high second line for dysphoria/depression. The support given to the use of antidepressants probably reflects studies suggesting that antidepressants may be helpful for patients with comorbid depression, although the literature is conflicting in this area. For aggression and violence, valproate and lithium received high second line ratings. For suicidal behavior, the same two antidepressants recommended for dysphoria/depression received high second line ratings, with ECT another high second line option. The question of how to treat persisting negative symptoms has long been a difficult issue in the field. Although there was no consensus on any of the adjunctive treatments that were rated second line for negative symptoms, it should be noted that approximately a quarter of the experts or more rated the following options first line: a glutaminergic agent, an SSRI, another antipsychotic, or venlafaxine.

Obesity. There is increasing concern about long-term medical problems in patients with schizophrenia, especially obesity and its complications. It has been reported that over one-third of the adults in the United States are obese.[47] Obesity is a threat to health and longevity and has been associated with a number of diseases such as hypertension, type II diabetes, coronary heart disease, and stroke. Moreover, obesity is a common concomitant of schizophrenia,[48] and individuals with schizophrenia appear to be at increased risk for certain obesity-related conditions such as type II diabetes and cardiovascular disease.[49] Many psychotropic medications can contribute to weight gain[21] and clinicians face difficult clinical dilemmas when a patient with clinically significant obesity (BMI ≥ 30) responds well to a medication that is likely to be contributing to the patient's weight problem. If a patient with clinically significant obesity has responded to an antipsychotic other than clozapine, the experts recommended a trial of a different antipsychotic with less weight gain liability combined with nutritional and exercise counseling if possible. They would also consider (high second line) continuing the same antipsychotic and providing nutritional and exercise counseling to try to help the patient lose weight. However, reflecting the fact that most patients receiving clozapine have already failed to respond to other agents, the experts would continue clozapine in this situation and try to address the weight problem with nutritional and exercise counseling. Although the experts gave a high second line rating to lowering the dose of clozapine in this situation, clinical studies have found that weight gain does not appear to be a dose-related effect. It is interesting that the experts gave second line ratings to the addition of topiramate. Although there have been case reports of weight loss with this agent in schizophrenia, there are no controlled studies supporting this practice. The experts did not recommend the use of weight loss medications (orlistat, sibutramine) or surgical treatment of obesity in this population.

Monitoring for comorbid conditions and risk factors. Many patients with schizophrenia rely on their psychiatric care provider for general medical care. With the improving outcomes being achieved with the newer atypical antipsychotics, more attention is being focused on short- and long-term health and wellness in this population. We asked the experts which conditions and risk factors they felt it was most important to monitor. We also asked which ones it was feasible to monitor in a psychiatric treatment setting. The experts strongly felt that it was important to monitor for all the conditions we asked about, with obesity and diabetes considered the most important (rated 9 by 60% and 56% of the experts, respectively). Amenorrhea was included among these conditions, because many antipsychotics can lead to an increase in prolactin levels and associated problems.[50] The experts' ratings of feasibility reflect the relative difficulty of the assessments involved (e.g., it is relatively simple to monitor weight, blood pressure, and amenorrhea, but much harder to evaluate osteoporosis).

Although we did not ask about obtaining lipid profiles, the editors note that clinicians should obtain lipid levels on a regular basis, because some antipsychotics are associated with hyperlipidemia. At the Mount Sinai Conference on the Health Monitoring of Patients with Schizophrenia, held in 2002, a group of psychiatric and medical experts met to evaluate the existing literature and develop recommendations for improving the medical monitoring of patients with schizophrenia who are managed

in outpatient settings. A publication outlining the recommendations generated at this conference is in preparation.[51] The conference concluded that, as part of routine care, a lipid panel should be obtained if a recent panel is not available. Given that individuals with schizophrenia, as a group, are considered to be at high risk for coronary heart disease, lipid screening should be carried out at least once every 5 years and more often when there is evidence of lipid levels that approach those that would lead to treatment.[51] The conference also recommended that clinicians should be aware of, and monitor regularly for, symptoms of increased prolactin. If clinically indicated, prolactin should be measured, and, if elevated, a work-up for the cause of the elevation should be initiated. Consideration should also be given to switching to a prolactin-sparing medication—if the symptoms disappear and prolactin levels fall to normal, an endocrine work-up can then be avoided.[51] Recommendations on other complicating conditions, such as cardiac problems (QTc prolongation and myocarditis), cataracts, and EPS will also be included in the Mount Sinai guideline when it is published.

Compliance (Adherence)

Noncompliance is a frequent phenomenon in psychiatric disorders.[52] Studies have shown that continuous antipsychotic medication provides significantly better protection from psychotic relapse than no antipsychotic maintenance therapy[53] or so-called intermittent treatment.[54] Although it is clear that, below a certain degree of compliance, patients are at risk to relapse, thresholds have not been established. This is partly because the impact of partial compliance is difficult to study: schizophrenic relapses usually do not occur immediately after stopping medication but rather after a delay of several weeks to months (or even years).[55]

Levels of compliance. We provided the experts with the following definitions of compliance to use as benchmarks in answering a series of questions about the assessment and management of compliance problems:

- Compliant: misses < 20% of medication
- Partially compliant: misses 20%–80% of medication
- Noncompliant: misses > 80% of medications

We also asked the experts to tell us how they would define levels of compliance. On average, the expert panel would set a higher threshold for compliance, as shown below, and would consider a patient who missed more than 65% of his or her medication noncompliant:

- Compliant: misses < 25% of medication
- Partially compliant: misses 25%–65% of medication
- Noncompliant: misses > 65% of medications

Not surprisingly, the experts reported that their patients show higher levels of compliance than are generally reported in the literature.

Assessing compliance. The experts considered asking the caregiver or patient first line strategies for assessing compliance; they would also consider pill counts, obtaining blood levels, and using self-rating scales. They did not consider routine use of urine tests appropriate.

When to intervene for compliance problems. The experts would usually intervene if a patient is missing approximately 50% of prescribed medication (91% would usually intervene) and were unanimous about the need to intervene if a patient is missing more than 80% of medication. The majority of the experts (52%) would usually intervene when a patient is missing approximately 20% of medication. There was less agreement about whether to intervene if a patient is only missing occasional doses (13% would usually intervene, 39% would sometimes intervene, and 48% would generally not intervene).

Strategies for addressing compliance problems. We asked the experts about the appropriateness of three different types of strategies that have been used to address compliance problems:

- Pharmacologic interventions (e.g., switching to a long-acting medication)
- Psychosocial interventions (e.g., patient education, compliance therapy [focused cognitive-behavioral therapy targeting compliance issues])
- Programmatic interventions (e.g., intensive case management, assertive community treatment)

The experts gave first line ratings to all three types of interventions. The editors note that clinicians should generally employ a combination of strategies tailored to the specific needs of the patient. The experts gave the highest ratings to psychosocial interventions for patients who are partially compliant, probably reflecting findings that such interventions can improve compliance levels. Psychopharmacologic interventions received the highest ratings for noncompliant patients, probably reflecting the fact that patients who are not taking their medication are at the highest risk for relapse and it is especially important to try to get the patient back on medication as quickly as possible.

Psychosocial interventions to improve compliance. Among psychosocial interventions for improving compliance, the experts gave the highest ratings to patient/family education, medication monitoring, and compliance therapy. Their ratings agree with research findings concerning the efficacy of these strategies in improving compliance. Cochrane reviews[56,57] and other meta-analyses[58] have found a reduction in relapse rates associated with family interventions and psychoeducation. Compliance therapy is a new strategy for promoting medication compliance that has shown positive effects in one trial.[59] Findings concerning the efficacy of group and individual psychotherapy in improving compliance are equivocal, as shown by the lower ratings given to these options.

Programmatic interventions to improve compliance. Among programmatic interventions, the experts recommended assertive community treatment (ACT), ensuring continuity of treatment

provider across treatment settings, and intensive case management services. Studies have shown that the kind of assistance provided by ACT programs can significantly improve compliance levels.[60] Lack of continuity in care providers can lead to serious compliance problems, since patients may be continued on an ineffective or difficult-to-tolerate treatment regimen or may not receive continuing medication coverage after discharge. Although case management is considered to be effective by the experts, the scientific data are conflicting. A Cochrane review showed that, with this intervention, more people remain in contact with psychiatric services, but readmission rates increased.[61] The experts also considered supervised residential services, partial hospitalization, rehabilitation services, and involuntary outpatient commitment useful options for improving compliance.

Pharmacologic strategies for addressing compliance problems. The experts strongly agreed that the first line pharmacologic strategy for addressing compliance problems is to switch the patient to a long-acting injectable atypical antipsychotic once this option is available (first line for partially compliant patients and treatment of choice for noncompliant patients). High second line options were to switch to a long-acting depot conventional or add a long-acting injectable atypical. Although the advantages of long-acting injectable medication—assured compliance and immediate awareness of noncompliance—are obvious, they are difficult to prove in randomized, double-blind trials. This is partly because patients who are willing to participate in such trials may *per se* be compliant.[62] Despite this, meta-analyses that included only long-terms trials in outpatients showed superiority of long-acting agents; however, the database involved is old and small.[63,64] Large pragmatic trials in which patients are randomized to depot or oral medication and then followed in an open fashion are needed to further examine this issue. Another high second line option for a patient who is partially compliant was to continue the same pharmacotherapy and intensify psychosocial interventions to improve compliance. However, the experts did not recommend this strategy for a patient who is noncompliant.

Use of Long-Acting Injectable Antipsychotics

Benefits. The experts considered the greatest benefit of long-acting injectable antipsychotics to be assured medication delivery. Other important advantages are the ability to know immediately when a patient misses medication and the fact that the patient continues to have some medication in his or her system even after a missed dose. Additional advantages are the reduced risk of relapse associated with continuous medication and the ability to know that relapse, if it occurs, is not the result of compliance problems.

Potential disadvantages. The experts considered lack of patient acceptance the most important potential disadvantage of long-acting injectable antipsychotics. To some extent, this response probably reflects an assumption that patients will not accept the idea of continuing injections. However, once they try a long-acting medication, many patients are surprised to find how easy it is to tolerate receiving medication in this way. Although lack of patient autonomy is another potential concern that is sometimes mentioned, patient surveys do not support this as being a major factor.[65] Although the experts said that they considered inability to stop medication immediately should side effects become a problem somewhat important as a potential disadvantage, the editors were hard pressed to find examples of situations in which immediate discontinuation of a long-acting antipsychotic was a medical necessity. Even in neuroleptic malignant syndrome, there is no evidence that mortality rates are higher among patients receiving a long-acting injectable antipsychotic than in those receiving an oral medication (assuming the condition is identified and appropriately treated).[66]

Factors favoring the use of long-acting injectables. In deciding whether to use a long-acting injectable antipsychotic, 96% of the experts considered the availability of an atypical antipsychotic in such a formulation very important. This doubtless reflects concerns about the side effects associated with the conventional depot antipsychotics. Other factors that the experts considered very important in deciding to use a long-acting injectable are good patient acceptance of the injection, evidence that the rate of relapses and side effects will be lower than with oral equivalents, better quality of life for patients, and ease of administration.

Indications for switching to a long-acting injectable atypical antipsychotic. We asked the experts about the appropriateness of using a long-acting injectable atypical antipsychotic, when available, in a variety of clinical situations. The experts considered a long-acting atypical antipsychotic the treatment of choice for a patient who is taking an oral atypical and requests the long-acting formulation, for a patient who relapses because of noncompliance with an oral atypical antipsychotic, and for a patient who is experiencing EPS on a depot conventional antipsychotic. The experts considered a long-acting injectable atypical first line for a patient in involuntary outpatient commitment, for a patient who is chronically relapsing on an oral conventional, for a patient with lack of insight or denial of illness, for a patient taking an oral atypical antipsychotic who is relapsing for reasons that are unclear, and for a patient with a history of aggressive or violent behavior. It is interesting that the experts perceived a role for the use of long-acting injectable atypicals that goes well beyond treatment of patients with compliance problems (see the many other second line indications listed in Guideline 18). Of all the situations we asked about, the only ones in which the experts would not generally consider a long-acting injectable atypical are a patient taking an oral atypical or conventional who is stable and not experiencing EPS or a patient who has been newly diagnosed with schizophrenia and has had no previous antipsychotic treatment.

We then asked the experts how concern about the potential for TD would affect their decision to switch to an injectable atypical antipsychotic. The majority of the experts would definitely switch if there is concern about TD in a patient who is experiencing EPS on a depot or oral conventional antipsychotic (96%

and 73% first line, respectively). Even if the patient is not experiencing EPS, many of the experts would consider switching from a depot or oral conventional if there is concern about TD (49% and 38% first line, respectively). The editors were unsure on what basis a clinician would decide that there was in fact no or minimal risk of TD.

Beginning injections while hospitalized. We asked the experts about the appropriateness of beginning treatment with a long-acting injectable atypical while the patient is hospitalized, given shorter lengths of hospital stays. This strategy was rated high second line by the expert panel, in order to ensure continuing medication coverage when the patient is discharged and to facilitate acceptance of an injectable medication in outpatient treatment. The experts also noted that this strategy may be helpful because patients are most vulnerable to relapse soon after discharge.

Motivating patients to return for repeat injections. The experts consider the influence of family/caregivers and physician/treatment team to be most important in motivating patients to return for repeat injections.

Defining Remission and Recovery

With improving outcomes, research studies are now trying to evaluate the effectiveness of different antipsychotics not only in producing remission of symptoms but in promoting long-term recovery in patients with schizophrenia. However, as yet there is no general consensus on how best to define these terms. We therefore asked the experts to rate the appropriateness of a number of factors as indicators of remission and recovery. There was strong agreement that the level of positive symptoms is the single most important indicator of remission. High second line indicators were levels of cognitive/disorganized, negative, and depressive symptoms, reflecting studies showing that these associated symptoms contribute in a substantial way to the functional disability associated with schizophrenia.[67–73] In defining recovery, however, the experts gave almost equal weight to all of the indicators we asked about, indicating that recovery is a concept involving improvement in multiple domains.

Rank ordering of symptomatic indicators. When the experts were asked to rank four key indicators of remission and recovery, their responses agreed very closely with the responses described above: 89% considered level of positive symptoms the most important indicator of remission, followed by cognitive/disorganized, negative, and depressive symptoms, all three of which were ranked similarly. However, there was less agreement on the most important indicator of recovery, with 41% considering level of positive symptoms most important, 33% giving the highest ranking to level of cognitive/disorganized symptoms, and 28% ranking level of negative symptoms as most important.

Rank ordering of functional outcomes. When asked to rank three functional outcomes as indicators of remission, the experts were divided, with 45% considering independent living, 32% occupational/education functioning, and 20% peer relationships the most important functional indicator of remission. This division among the panel may reflect the fact that one is unlikely to see major changes in any of these areas in the shorter time frame usually used to measure remission (see Guideline 21). However, when asked about the same functional outcomes as indicators of recovery, the majority (64%) felt that occupational/educational functioning was the most important functional outcome in recovery, followed by peer relationships (rated most important by 20%) and independent living (rated most important by 18%). When asked about the most appropriate way of defining functional improvement in their patients, 86% of the experts considered relative rather than absolute change in the patient the most appropriate indicator.

Severity and duration of symptoms as indicators of remission and recovery. We asked the experts what levels of symptom severity were most appropriate to use in defining remission and recovery. Their ratings are summarized in the bar charts in Guideline 21. The majority of the experts would consider a patient in remission who had mild levels of positive, cognitive/disorganized, negative, and depressive symptoms (62%, 69%, 62%, and 73% of the experts, respectively). However, a third of the experts felt that no positive symptoms should be present for a patient to be considered in remission.

When asked about indicators for recovery, the experts said that they would look for greater reduction in positive symptoms, with a majority (62%) saying that there should be no positive symptoms present for a patient to be considered in recovery. In terms of negative symptoms, 62% of the panel would consider a patient in recovery who had mild negative symptoms while 33% would look for no negative symptoms. The panel was more evenly split as to whether a patient could have mild cognitive or depressive symptoms and still be considered in recovery.

In terms of duration of symptoms, the experts said that the improvement in symptomatic indicators should be maintained for at least 3 months for a patient to be considered in remission and for a year or more for a patient to be considered in recovery. The experts said that improvement in functional indicators (occupational/vocational functioning, independent living, peer relationships) needs to be maintained for somewhat longer, 15–17 months, for the patient to be considered in recovery.

SUMMARY OF KEY RECOMMENDATIONS

The experts overwhelmingly endorsed the atypical antipsychotics for the treatment of psychotic disorders. Risperidone was their top choice for first-episode and multi-episode patients, with the other newer atypicals rated first line or high second line depending on the clinical situation. Clozapine and a long-acting injectable atypical (when available) were other high second line options for multi-episode patients. The experts' dosing recommendations agreed closely with the package inserts for the drugs. The experts recommended using much lower doses for pediatric patients and somewhat lower doses for adolescent and elderly

patients. They also stressed the importance of considering concomitant medications and the presence of comorbid medical conditions (hepatic, renal, or cardiovascular disease) in selecting the most appropriate dose. The experts' estimates of dose equivalence among the different antipsychotics followed a linear pattern, suggesting that linear formulas could be used to calculate dose equivalency.

The experts considered 3–6 weeks an adequate antipsychotic trial, but would wait a little longer (4–10 weeks) before making a major change in treatment regimen if there is a partial response. The experts recommended trying to improve response by increasing the dose of atypical and depot antipsychotics before switching to a different agent; there was less agreement about increasing the dose of conventional antipsychotics before switching, probably because of concern about side effects at higher doses. If it is decided to switch because of inadequate response, risperidone was the experts' first choice to switch to, no matter what drug was initially tried. Although there was some disparity in the experts' recommendations concerning how many agents to try before switching to clozapine, the experts' responses suggest that switching to clozapine should be considered after failure to respond to two atypical antipsychotics. Clozapine was also the antipsychotic of choice for patients with suicidal behavior. When switching oral antipsychotics, the experts considered cross titration the preferred strategy. When switching to an injectable antipsychotic, the experts stressed the importance of continuing the oral antipsychotic until therapeutic levels of the injectable agent are achieved.

The experts considered psychosocial interventions the first choice strategy for partially compliant patients, with pharmacologic interventions the first choice for patients with clear evidence of noncompliance. However, because it can be difficult to distinguish partially compliant from noncompliant patients, the editors recommended combining psychosocial and pharmacologic interventions to improve compliance whenever possible. When patients relapse because of compliance problems or if there is any doubt about compliance, the experts recommended the use of a long-acting injectable antipsychotic and would select an injectable atypical when this option becomes available. The experts would also consider using an injectable atypical antipsychotic (when available) in many clinical situations that do not involve compliance problems.

The experts stressed the importance of monitoring for health problems—especially obesity, diabetes, cardiovascular problems, HIV risk behaviors, medical complications of substance abuse, heavy smoking and its effects, hypertension, and amenorrhea—in patients being treated with antipsychotics.

Although many patients are prescribed adjunctive treatments, multiple antipsychotics, and combinations of different classes of drugs (e.g., antipsychotics plus mood stabilizers or antidepressants) in an effort to enhance response, the experts gave little support to any of these strategies, with the exception of antidepressants for patients with dysphoria/depression, antidepressants or ECT for patients with suicidal behavior, and mood stabilizers for patients with aggression/violence.

When asked about indicators of remission and recovery, the experts considered acute improvement in psychotic symptoms the most important indicator of remission, whereas they considered more sustained improvement in multiple outcome domains (e.g., occupational/educational functioning, peer relationships, independent living) important in assessing recovery.

LIMITATIONS AND ADVANTAGES OF EXPERT CONSENSUS GUIDELINES

These guidelines can be viewed as an expert consultation, to be weighed in conjunction with other information and in the context of each individual patient-physician relationship. The recommendations do not replace clinical judgment, which must be tailored to the particular needs of each patient and clinical situation. We describe groups of patients and make suggestions intended to apply to the average patient in each group. However, individual patients will differ greatly in their treatment preferences and capacities, history of response to previous treatments, family history of treatment response, and tolerance for different side effects. Therefore, the experts' first line recommendations certainly will not be appropriate in all circumstances.

We remind readers of several other limitations of these guidelines:

1. The guidelines are based on a synthesis of the opinions of a large group of experts. From question to question, some of the individual experts would differ with the consensus view.
2. We have relied on expert opinion precisely because we are asking crucial questions that are not yet well answered by the literature. One thing that the history of medicine teaches us is that expert opinion at any given time can be very wrong. Accumulating research will ultimately reveal better and clearer answers. For example, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a multisite investigation sponsored by the National Institute of Mental Health, is currently underway to determine the long-term effects and usefulness of a number of antipsychotic medications.[74] The study will enroll 1600 patients with schizophrenia for whom a medication change may be indicated for reasons of limited efficacy or tolerability. It will evaluate the atypical antipsychotics clozapine, olanzapine, quetiapine, risperidone, and ziprasidone and the conventional antipsychotics perphenazine and fluphenazine decanoate for up to 18 months of treatment. It is estimated that the study will be completed in the fall of 2004. We hope to revise the guidelines periodically based on new research information and on reassessment of expert opinion to keep them up-to-date.
3. The guidelines are financially sponsored by the pharmaceutical industry, which could possibly introduce biases. Because of this, we have made every step in guideline development transparent, reported all results, and taken little or no editorial liberty.
4. These guidelines are comprehensive but not exhaustive; because of the nature of our method, we omit some interesting topics on which we did not query the expert panel.

Despite the limitations, these guidelines represent a significant advance because of their specificity, ease of use, and the credibility that comes from achieving a very high response rate from a large sample of the leading experts in the field.

FINAL WORD

Advances in public health do not always require technological breakthroughs or long periods of waiting for new data. Immediate gains can be made by increasing the speed with which best practices are implemented. Guidelines offer a rapid means for communicating a distillate of expert opinion. When reaching a clinical decision point, practitioners and patients can use guidelines to generate a menu of reasonable choices and then select the option that is judged best for each individual. This process drives the next round of expert opinion and the next round of empirical studies.

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Guideline Organization and Key Terms

Guideline Organization

I. Medication Selection, Dosing, and Dose Equivalence
II. Compliance
III. Long-Acting Injectable Antipsychotics
IV. Defining Remission and Recovery

Terminology Used in the Ratings

First line is used to designate treatment strategies that came out on top when the experts' responses to the survey were statistically aggregated. These are options that the panel feels are usually appropriate as initial treatments for a given situation. ***Treatment of choice*** indicates an especially strong first line recommendation: an option that received the highest rating of "9" (extremely appropriate) from at least 50% of the experts.

Second line is used to indicate treatments that are reasonable choices for patients who cannot tolerate or do not respond to the first line choices. "High second line" refers to options for which the confidence intervals overlap with the first line category.

Third line is used to indicate options that are usually inappropriate or used only when preferred alternatives have not been effective.

Definitions of Terms Used in the Survey

Psychotic disorders. The term "psychotic disorder" in the survey refers to one of the disorders that appears in the DSM-IV-TR section on "Schizophrenia and Other Psychotic Disorders": schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, and brief psychotic disorder.

Phases of treatment

- Acute treatment: goal is to resolve the symptoms and signs of a current psychotic episode
- Maintenance treatment: goal is to prevent development of a new psychotic episode (a recurrence).

Levels of compliance (adherence)

We asked about the following levels of treatment compliance:

- Compliant: only misses occasional doses (e.g., < 20% of prescribed medication)
- Partially compliant: misses more than occasional doses (e.g., misses 20%–80% of medication)
- Noncompliant: misses > 80% of medication

Antipsychotics

We presented antipsychotics alphabetically within questions and told respondents to opt out of answering questions about any medication with which they were unfamiliar by drawing a line through that single line item. We asked about the following specific antipsychotics in this survey.

- Conventional Antipsychotics:
  - High potency (e.g., haloperidol [Haldol], fluphenazine [Prolixin])
  - Medium potency (e.g., thiothixene [Navane], perphenazine [Trilafon], trifluoperazine [Stelazine])
  - Low potency (e.g., chlorpromazine [Thorazine], thioridazine [Mellaril])
- Atypical Antipsychotics: aripiprazole (Abilify), clozapine (Clozaril), olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel), ziprasidone (Geodon)

I. MEDICATION SELECTION, DOSING, AND DOSE EQUIVALENCE

Guideline 1: Selecting Initial Pharmacologic Treatment for a Psychotic Disorder[Questions 1–3]

1A. First-Episode Patient

For *a first-episode patient with predominantly positive symptoms*, the experts consider oral risperidone the treatment of choice. Other recommended medications for this clinical situation are aripiprazole, olanzapine, ziprasidone, and quetiapine (although the first two were rated first line and the second two high second line, these options clustered together and all were rated first line by approximately two-thirds of the experts).

For *a first-episode patient with predominantly negative symptoms*, the experts recommend one of the newer oral atypical antipsychotics. Risperidone and aripiprazole received first line ratings, and the other three were rated high second line; however, all the options clustered together with only small differences in their confidence intervals.

For *a first-episode patient with both prominent positive and negative symptoms*, the experts prefer oral risperidone. Other recommended medications for this clinical situation are aripiprazole, ziprasidone, olanzapine, and quetiapine (again these four options clustered together with only small differences in their confidence intervals).

The experts as a group varied in their ratings of using a long-acting injectable atypical antipsychotic for a first-episode patient to such an extent that there was no consensus on this item (with approximately a quarter of the experts rating it first line and approximately a third giving it third line ratings). The experts did not recommend the use of either oral or depot conventional antipsychotics for a first-episode patient (conventional antipsychotics received third line ratings in every case).

(*bold italics* = treatment of choice)

Presentation	First Line*	High Second Line	Other Second Line
Predominantly *positive* psychopathology	***Risperidone*** Aripiprazole Olanzapine	Ziprasidone Quetiapine	Long-acting injectable atypical†
Predominantly *negative* psychopathology	Risperidone Aripiprazole	Ziprasidone Olanzapine Quetiapine	Long-acting injectable atypical
Both prominent positive and negative symptomatology	Risperidone Aripiprazole Ziprasidone	Olanzapine Quetiapine	Long-acting injectable atypical

*In this survey, we asked only about oral and long-acting injectable formulations of antipsychotics. Unless otherwise specified, all medications listed in the tables refer to the oral formulation.

†At the time of this survey, a long-acting injectable atypical antipsychotic was not available in the United States, although it was available in several other countries. In the survey, we asked the experts to rate how they would use such a formulation if it were available.

1B. Multi-Episode Patient

For ***a multi-episode patient with predominantly positive symptoms***, the experts consider oral risperidone the treatment of choice. Other recommended first line medications for this clinical situation are aripiprazole, ziprasidone, olanzapine, and quetiapine and a long-acting atypical antipsychotic. Clozapine was rated high second line. Other lower rated second line options were a long-acting conventional antipsychotic (depot) and an oral high-potency conventional.

For ***a multi-episode patient with predominantly negative symptoms***, risperidone, aripiprazole, and ziprasidone were rated first line; high second line choices were olanzapine, quetiapine, a long-acting atypical antipsychotic, and clozapine. (It should be noted that all these options tended to cluster together, with only small differences in their confidence intervals.) A long-acting conventional antipsychotic was a lower rated second line option.

For ***a multi-episode patient with both prominent positive and negative symptoms***, the experts preferred risperidone followed by aripiprazole. Other first line options were ziprasidone and olanzapine. High second line choices were a long-acting atypical antipsychotic, quetiapine, and clozapine. (Ratings for most of these options tended to cluster together with only small differences in their confidence intervals.) Other lower rated second line options were a long-acting depot conventional antipsychotic and an oral high-potency conventional.

The experts are clearly more willing to consider using clozapine or a long-acting injectable antipsychotic in a patient with a history of previous psychotic episodes. The experts did not recommend the use of mid- or low-potency conventional antipsychotics and gave only very limited support to the use of oral high-potency conventionals.

(***bold italics*** = treatment of choice)

Presentation	First Line	High Second Line	Other Second Line
Predominantly ***positive*** psychopathology	***Risperidone*** Aripiprazole Ziprasidone Olanzapine Long-acting injectable atypical Quetiapine	Clozapine	Long-acting conventional (depot) Oral high-potency conventional
Predominantly ***negative*** psychopathology	Risperidone Aripiprazole Ziprasidone	Olanzapine Quetiapine Long-acting injectable atypical Clozapine	Long-acting conventional
Both prominent positive and negative symptomatology	Risperidone Aripiprazole Ziprasidone Olanzapine	Long-acting injectable atypical Quetiapine Clozapine	Long-acting conventional Oral high-potency conventional

Guideline 2: Adequate Dose of Antipsychotics

Questions 4 & 6

We asked the experts to write-in doses of conventional and atypical antipsychotics that they would recommend in different treatment situations. We used the mean and standard deviations of their responses to generate real-world doses rounded to currently available pill strengths. The experts' dosing recommendations generally agree closely with recommended doses given in the package labeling. For olanzapine and quetiapine, their recommendations for highest acute dose are somewhat higher than the highest doses for which safety data from clinical trials are available (20 mg of olanzapine and 800 mg of quetiapine). The panel would generally use higher doses for a patient who had had multiple episodes of psychosis than for a first-episode patient. The recommended dose ranges for maintenance treatment are also slightly lower than for acute treatment.

	First-episode patient		Multi-episode patient		
Medication	Acute treatment (mg/day)*	Maintenance treatment (mg/day)	Acute treatment (mg/day)*	Maintenance treatment (mg/day)	Highest final acute dose (mg/day)
Atypicals					
Aripiprazole	10–20	10–20	15–30	15–20	30
Clozapine	300–500	250–500	400–600	300–550	850
Olanzapine	10–20	10–20	15–25	12.5–22.5	40†
Quetiapine	350–700	300–600	500–800	400–750	950†
Risperidone	2.5–5.0	2.0–4.5	4.0–6.5	3.5–5.5	10.5
Ziprasidone	100–160	80–160	140–180	120–180	180
Conventionals					
Chlorpromazine	200–650	150–600	400–800	250–750	950
Fluphenazine	2.5–15.0	2.5–12.5	5.0–22.5	5.0–15.0	25.0
Haloperidol	3.0–13.5	1.5–10.5	7.0–18.5	6.0–13.5	25.0
Perphenazine	8–38	6–36	16–48	12–42	56
Thioridazine‡	225–550	150–500	350–650	250–550	650
Thiothixene	5–30	2–30	10–40	10–35	40
Trifluoperazine	5–30	2–20	10–35	10–30	40
Fluphenazine decanoate (mg/2–3 wk)	12.5–37.5	6.25–37.5	12.5–62.5	12.5–50.0	50.0
Haloperidol decanoate (mg/4 wk)	50–200	50–200	100–250	100–200	250

*In beginning treatment with an oral antipsychotic for which titration is not required or with a long-acting injectable antipsychotic, the experts recommend either starting with a low dose and increasing the dose based on level of response and side effects, or starting with a moderate dose. The experts do not recommend starting with a relatively high dose and then decreasing it if possible.

Questions 10 & 11

†Safety of doses of olanzapine > 20 mg/day and of quetiapine > 800 mg/day have not been evaluated in clinical trials.

‡The package labeling for thioridazine includes a black box warning stating that this agent "has been shown to prolong the QTc interval in a dose related manner, and drugs with this potential, including thioridazine, have been associated with torsades de pointes-type arrhythmias and sudden death. Due to its potential for significant, possibly life-threatening, proarrhythmic effects, thioridazine should be reserved for use in the treatment of schizophrenic patients who fail to show an acceptable response to adequate courses of treatment with other antipsychotic drugs."

Guideline 3: Therapeutic Drug Monitoring (Using Plasma Levels)[Question 5]

Over 50% of the experts reported that plasma level assays were available to them only for clozapine, haloperidol, and haloperidol decanoate. Clozapine was the agent for which the experts considered plasma levels most clinically useful. Over half the experts use plasma levels of clozapine and haloperidol to monitor compliance; 88% of the experts use clozapine levels to adjust dose, primarily if there has been an inadequate response or side effects are a problem. 50% of the experts use plasma levels of haloperidol (oral or decanoate) to adjust dose levels if the patient has an inadequate response or problematic side effects.

Guideline 4: Duration of an Adequate Trial[Question 13]

If a patient is having little or no response to the initial or to the second antipsychotic that is tried, the experts recommend waiting a minimum of 3 weeks and a maximum of 6 weeks before making a major change in treatment regimen. If the patient is showing a partial response to treatment, the experts would extend the duration of the trial somewhat, waiting 4–10 weeks before making a change for the initial antipsychotic and 5–11 weeks for the second antipsychotic. A major change in treatment regimen could mean either a significant dose increase or switching to a different agent. Note that the experts would wait longer if the patient is having a partial response, especially in the second trial. Although the differences were not dramatic, they are interesting, particularly given the lack of data from controlled trials addressing these issues. These results are similar to those from the 1996 *Expert Consensus Guidelines on the Treatment of Schizophrenia,** which recommended waiting 3–8 weeks if there is no response and 5–12 weeks if there is a partial response before switching to another pharmacologic strategy.

4A. Inadequate Response to Initial Antipsychotic

	Minimum number of weeks to wait	Maximum number of weeks to wait
Little or no response to treatment	3	6
Partial response to treatment	4	10

4B. Inadequate Response to Second Antipsychotic

	Minimum number of weeks to wait	Maximum number of weeks to wait
Little or no response to treatment	3	6
Partial response to treatment	5	11

* McEvoy JP, Weiden PJ, Smith TE, et al. The expert consensus guideline series: treatment of schizophrenia. J Clin Psychiatry 1996;57(suppl 12b):1–58

Guideline 5: Dose Equivalency

5A. To Haloperidol[Question 7]

We asked the experts to write-in doses of conventional and atypical antipsychotics that they would consider equivalent to a range of haloperidol doses. We used the mean and standard deviations of their responses to generate real-world doses rounded to currently available pill strengths. The goal was to obtain a better sense of the equivalency between the older conventional antipsychotics and the new generation of atypical antipsychotics. In general, the experts' responses followed a very linear pattern, indicating that it would probably be possible to use linear formulas to calculate dose equivalency. It is interesting to note that, in every case, the dose the experts consider equivalent to 30 mg of haloperidol is higher than the highest acute dose the experts indicated they would usually use (see Guideline 2).

Haloperidol	1 mg	5 mg	10 mg	20 mg	30 mg
Atypicals					
Aripiprazole	5	10	20	30	35
Clozapine	75	250	425	675	900
Olanzapine	2.5	10	20	30	45
Quetiapine	100	325	600	900	1200
Risperidone	1.0	3.0	5.5	10.5	15.0
Ziprasidone	40	100	140	180	240
Conventionals					
Chlorpromazine	60	250	500	900	1300
Fluphenazine	1	5	10	20	30
Perphenazine	4	16	32	64	88
Thioridazine	50	200	450	750	1000
Thiothixene	3	12	25	40	60
Trifluoperazine	3	12	25	40	55
Fluphenazine decanoate* (mg/2–3 wk)	6.25	12.5	25	50	75
Haloperidol decanoate* (mg/4 wk)	25	100	150	250	300

*For fluphenazine decanoate and haloperidol decanoate, the experts were asked to indicate the dosage they consider equivalent to that dose of oral haloperidol being given daily on an ongoing basis.

5B. To Risperidone[Question 8]

We asked the experts to write-in doses of conventional and atypical antipsychotics that they would consider equivalent to a range of risperidone doses. We used the mean ± the standard deviation of their responses to generate real-world doses rounded to currently available pill strengths. The goal here was to obtain a better sense of the equivalency of doses among the new generation of atypical antipsychotics. Again, the experts' responses generally followed a very linear pattern, indicating that it would probably be possible to use linear formulas to calculate dose equivalency. It is interesting to note that the doses the experts consider equivalent to 10 mg of risperidone are closest to those they consider equivalent to 20 mg of haloperidol (as would be expected since they indicated that they considered 10.5 mg of risperidone to be equivalent to 20 mg of haloperidol, see Guideline 5A).

Risperidone	1 mg	2 mg	4 mg	6 mg	10 mg
Atypicals					
Aripiprazole	5	10	15	25	30
Clozapine	75	175	350	500	700
Olanzapine	5	7.5	15	20	30
Quetiapine	100	225	450	600	825
Ziprasidone	40	60	120	160	200
Conventionals					
Chlorpromazine	80	175	350	550	800
Fluphenazine	1	5	7.5	12.5	15
Haloperidol	1.5	3.5	7.5	11.5	17
Perphenazine	6	12	24	40	54
Thioridazine	75	150	300	475	650
Thiothixene	4	8	17	25	35
Trifluoperazine	4	10	15	25	35
Fluphenazine decanoate* (mg/2–3 wk)	6.25	12.5	25	37.5	50
Haloperidol decanoate* (mg/4 wk)	25	50	100	150	225

*For fluphenazine decanoate and haloperidol decanoate, the experts were asked to indicate the dosage that they consider equivalent to that dose of oral risperidone being given daily on an ongoing basis.

Guideline 6: Dose Adjustment

6A. Factors to Consider in Dose Adjustment[Question 9]

The experts considered the use of concomitant medications, the patient's age, and the presence of hepatic disease the most important factors to consider in adjusting the acute antipsychotic dose. The priority given to the use of concomitant medications reflects our expanding knowledge of drug-drug interactions and their potential consequences. Other important factors to consider are the presence of cardiovascular or renal disease, whether or not the patient smokes, and the patient's weight. There was no consensus about the importance of the patient's sex, with 30% of the experts saying they would nearly always consider the patient's sex in dose adjustment and 23% saying they would rarely or never consider it. It is surprising that many of the experts (45%) would only sometimes consider the patient's weight in adjusting the dose. This is consistent with the observation that the determination of psychiatric drug dosage is infrequently influenced by the patient's weight, despite the fact that (given the highly lipophilic nature of these compounds) blood levels may ultimately be influenced by body mass. It may also reflect the pharmaceutical industry's desire to simplify dosage determination in the treatment of psychiatric disorders.

Always consider	Sometimes consider
Use of concomitant medications	Presence of cardiovascular disease*
Patient's age	Presence of renal disease
Presence of hepatic disease	Whether or not the patient smokes
	Patient's weight
	Patient's sex

*Very high second line

6B. Dose Selection for Special Populations[Question 12]

Dose Selection for Children and Adolescents. A majority of the experts would not generally use the following medications in children with a psychotic disorder who are 12 years of age or younger: aripiprazole, clozapine, chlorpromazine, fluphenazine, perphenazine, thioridazine, thiothixene, trifluoperazine, fluphenazine decanoate, and haloperidol decanoate. A majority of the experts would not generally use the following medications in an adolescent (13–18 years old) with a psychotic disorder: chlorpromazine, perphenazine, thioridazine, thiothixene, trifluoperazine. The doses recommended for pediatric patients are generally much lower than those given for adult patients (see Guideline 2), while the doses recommended for adolescents are only somewhat lower than those recommended for adults. These results underscore the need for more data on optimum dosing for children and adolescents.

Dose Selection for Elderly Patients. The experts generally recommend using lower doses in elderly patients than in younger adults. This probably reflects concerns about slower metabolism and greater sensitivity to adverse effects in older patients. Older patients are also more likely to have comorbid medical conditions and to be taking multiple medications, increasing the risk for adverse effects and drug-drug interactions. The experts generally recommend using much lower doses in elderly patients with dementia than in those with a psychotic disorder. The majority of the experts would not generally use the following medications in an elderly patient with a psychotic disorder or with dementia: chlorpromazine, thioridazine, thiothixene, trifluoperazine; 70% would also avoid haloperidol or fluphenazine decanoate in elderly patients with dementia.

Medication	Children with a psychotic disorder (mg/day)	Adolescents with a psychotic disorder (mg/day)	Elderly Patients with	
			Psychotic disorder (mg/day)	Dementia with behavioral disturbance and/or psychosis (mg/day)
Atypicals				
Aripiprazole	(10–15)*	10–20	10–15	10–15
Clozapine	(100–350)*	225–450	175–375	50–175
Olanzapine	5–10	10–15	5–15	5–10
Quetiapine	150–400	250–550	225–450	75–300
Risperidone	1.0–2.0	2.5–4.0	1.5–3.5	1.0–3.0
Ziprasidone	40–100	80–140	80–140	40–100
Conventionals				
Chlorpromazine	(150–200)*	(225–375)*	(150–300)*	(75–150)*
Fluphenazine	(1.5–5.0)*	2.5–10.0	2.5–7.5	1.0–5.0
Haloperidol	1.0–4.0	2.0–9.0	2.0–6.0	1.0–3.5
Perphenazine	(6–12)*	(12–22)*	6–24	2–14
Thioridazine	(100–250)*	(225–325)*	(150–300)*	(50–125)*
Thiothixene	(4–7)*	(4–20)*	(2–20)*	(1–11)*
Trifluoperazine	(2–10)*	(6–15)*	(4–15)*	(3–10)*
Fluphenazine decanoate	(6.25–12.5 mg/2–3 wk)*	12.5–25.0 mg/2–3 wk	6.25–25.0 mg/2–3 wk	(6.25–12.5 mg/2–3 wk)*
Haloperidol decanoate	(15–50 mg/4 wk)* †	50–150 mg/4 wk	25–100 mg/4 wk	(15–100 mg/4 wk)* †

*A majority of the experts would not generally use this medication in this population.

†Although with current formulations it would be difficult to administer 15 mg of haloperidol decanoate, this low mean suggests that the experts would be very cautious in dosing if it is decided to use this medication in children or elderly patients with dementia.

Guideline 7: Strategies When There Is an Inadequate Response

7A. When to Switch Antipsychotics[Question 14]

For each antipsychotic, we asked the experts whether they would increase the dose or switch to another agent if a multiepisode patient was having an inadequate response to the average target dose of the medication (see Guideline 2 for recommended target doses). Over 90% of the experts would first increase the dose of clozapine and olanzapine before switching, going as high as 850 mg/day of clozapine and 40 mg/day of olanzapine. Over 80% would increase the dose of quetiapine and risperidone before switching, going as high as 1100 mg/day of quetiapine and 10 mg/day of risperidone. Approximately 60% or more of the experts would also increase the dose of aripiprazole, ziprasidone, and the decanoate formulations of fluphenazine and haloperidol. The experts are divided fairly evenly as to whether increasing the dose or switching is the best strategy if a patient is having an inadequate response to the recommended target dose of one of the conventional oral antipsychotics, except for thioridazine, where 67% would switch to another agent. The experts may be less willing to increase the dose of the conventional oral medications because of concern about side effects, especially EPS and TD, at higher doses.

Inadequate response to adequate dose of	**Strategy**		
Atypicals	**Increase dose (% of experts)**	**Target dose (mg/day)**	**Switch medications (% of experts)**
Aripiprazole	68%	30–35	32%
Clozapine	93%	600–850	7%
Olanzapine	93%	25–40	7%
Quetiapine	84%	650–1100	16%
Risperidone	84%	6–10	16%
Ziprasidone	57%	160–220	43%
Conventionals			
Chlorpromazine	56%	550–1300	44%
Fluphenazine	55%	10–30	45%
Haloperidol	52%	10–30	48%
Perphenazine	51%	24–64	49%
Thioridazine	33%	500–800	67%
Thiothixene	49%	25–50	51%
Trifluoperazine	53%	20–55	47%
Fluphenazine decanoate	64%	37.5–62.5 mg/2–3 wk	36%
Haloperidol decanoate	64%	125–325 mg/4 wk	36%

7B. Switching Antipsychotics: Selecting the Next Agent[Question 15]

We asked the experts to indicate the first and second antipsychotics they would try after an inadequate response to the initial medication. The table lists those agents written in by 10% or more of the experts in Question 15. Note that, after trials of two atypical antipsychotics, 30% or more of the experts would switch to clozapine; this was recommended as a first line strategy in this situation by 70% of the experts in Question 18. The discrepancy between the responses in Questions 15 and 18 probably reflects differences in the way the question was posed as well as lack of certainty in the field as to the most appropriate place for clozapine in the treatment algorithm. The editors would endorse the response given in question 18, where approximately three quarters of the experts recommend switching to clozapine after inadequate response to two atypical antipsychotics (see Guideline 7G). For patients who had started with a conventional antipsychotic, the experts are more likely to try two other atypical antipsychotics before moving on to clozapine.

Inadequate response to:	First medication you would switch to* (%)	Second medication you would switch to (%)
Aripiprazole	Risperidone (54%) Olanzapine (19%) Ziprasidone (16%)	Clozapine (39%) Olanzapine (25%) Risperidone (19%)
Clozapine	Risperidone (34%) Aripiprazole (25%)	Olanzapine (23%) Quetiapine (17%) Aripiprazole (13%) Risperidone (13%) Ziprasidone (10%)
Olanzapine	Risperidone (60%) Aripiprazole (12%) Ziprasidone (12%)	Clozapine (43%) Aripiprazole (21%) Quetiapine (12%) Risperidone (10%)
Quetiapine	Risperidone (64%) Olanzapine (14%) Aripiprazole (12%)	Olanzapine (38%) Clozapine (31%) Aripiprazole (14%)
Risperidone	Olanzapine (50%) Aripiprazole (19%) Clozapine (12%) Quetiapine (10%) Ziprasidone (10%)	Clozapine (35%) Aripiprazole (25%) Quetiapine (13%)
Ziprasidone	Risperidone (44%) Aripiprazole (21%) Olanzapine (21%) Quetiapine (10%)	Clozapine (34%) Olanzapine (29%) Aripiprazole (16%) Risperidone (13%)
Chlorpromazine	Risperidone (64%) Olanzapine (18%)	Olanzapine (35%) Clozapine (19%) Quetiapine (14%) Aripiprazole (11%) Risperidone (11%) Ziprasidone (11%)
Fluphenazine	Risperidone (62%) Olanzapine (16%) Aripiprazole (11%)	Olanzapine (29%) Clozapine (18%) Quetiapine (15%) Risperidone (15%) Aripiprazole (12%) Ziprasidone (12%)

7B. *continued*

Inadequate response to:	First medication you would switch to* (%)	Second medication you would switch to (%)
Haloperidol	Risperidone (59%) Olanzapine (18%) Aripiprazole (13%)	Olanzapine (28%) Clozapine (19%) Quetiapine (14%) Risperidone (14%) Ziprasidone (14%) Aripiprazole (11%)
Perphenazine	Risperidone (62%) Olanzapine (14%) Aripiprazole (11%) Ziprasidone (11%)	Olanzapine (29%) Clozapine (18%) Quetiapine (15%) Risperidone (15%) Aripiprazole (12%) Ziprasidone (12%)
Thioridazine	Risperidone (68%) Olanzapine (14%)	Olanzapine (29%) Clozapine (18%) Aripiprazole (15%) Risperidone (15%) Quetiapine (12%) Ziprasidone (12%)
Thiothixene	Risperidone (64%) Olanzapine (14%) Aripiprazole (11%)	Olanzapine (30%) Clozapine (18%) Risperidone (15%) Aripiprazole (12%) Quetiapine (12%) Ziprasidone (12%)
Trifluoperazine	Risperidone (61%) Olanzapine (17%) Aripiprazole (11%)	Olanzapine (27%) Clozapine (18%) Risperidone (15%) Ziprasidone (15%) Aripiprazole (12%) Quetiapine (12%)
Long-acting injectable atypical	Clozapine (27%) Risperidone (24%) Haloperidol decanoate (15%)	Clozapine (40%) Olanzapine (17%) Aripiprazole (10%) Ziprasidone (10%)
Injectable fluphenazine decanoate	Long-acting injectable atypical (38%) Risperidone (24%)	Clozapine (41%) Olanzapine (21%)
Injectable haloperidol decanoate	Long-acting injectable atypical (39%) Risperidone (22%)	Clozapine (45%) Olanzapine (15%)

*If the patient did not respond to the initial antipsychotic you tried and you have switched to another antipsychotic, the experts recommend waiting 3–6 weeks before making a major change in treatment regimen (e.g., switching to yet another antipsychotic) if the patient is having little or no response to treatment, and waiting 5–11 weeks if the patient is having a partial response to treatment.[Quoted in 13]

7C. Switching Antipsychotics: Target Doses[Question 15]

The recommended target doses for the second and third antipsychotics the experts would try are, for the most part, consistent with the acute target doses shown in Guideline 2, although there is a tendency to consider using doses at the higher end of the range, especially for the third medication tried.

	Dosing of first switch (mg/day)	Dosing of second switch (mg/day)
Atypicals		
Aripiprazole	20–30	15–30
Clozapine	350–450	350–500
Olanzapine	15–30	15–25
Quetiapine	550–750	500–800
Risperidone	3.5–7	4.5–8
Ziprasidone	120–160	120–180
Long-acting injectable atypical (risperidone)	37.5–50 mg/2 wk	50 mg/2 wk*
Conventionals		
Fluphenazine	—	50*
Haloperidol	10*	10–20
Fluphenazine decanoate	6.25–62.5 mg/2–3 wk	75 mg/2–3 wk*
Haloperidol decanoate	100–250 mg/4 wk	100–450 mg/4 wk

*Only one write in.

7D. Preferred Switching Strategies for Oral Antipsychotics[Question 16]

We asked the experts what strategy they would use in switching to each of the oral atypical antipsychotics, assuming that the first antipsychotic does not require tapering before discontinuation. In switching to any of the oral atypicals except clozapine, the experts recommend using cross-titration (gradually tapering the dose of the first antipsychotic while gradually increasing the dose of the second) or overlap and taper (continuing the same dose of the first antipsychotic while gradually increasing the second to a therapeutic level and then tapering the first). For each drug, a larger percentage of the experts considered cross-titration first line. In switching to clozapine, the experts recommend using cross-titration, probably reflecting the need to institute clozapine treatment gradually and not to withdraw the previous medication abruptly or prematurely. They would also consider using overlap and taper in switching to clozapine (rated high second line). The experts do not recommend strategies that involve stopping the first antipsychotic before beginning the second.

When switching to:	First Line	High Second Line
Oral atypical antipsychotic other than clozapine		Cross-titration Overlap and taper
Clozapine	Cross-titration	Overlap and taper

7E. Preferred Switching Strategies for Injectable Antipsychotics[Question 17]

In switching to a depot conventional antipsychotic, the experts recommend either continuing the oral antipsychotic at the same dose until therapeutic drug levels of the injectable antipsychotic are achieved and then gradually tapering the oral antipsychotic or else beginning to taper the oral antipsychotic gradually after giving the first injection, with a larger percentage of the experts favoring the first strategy. Some experts would consider discontinuing the oral antipsychotic immediately once therapeutic levels of the injectable antipsychotic are achieved.

The experts' recommendations for switching to a long-acting atypical antipsychotic are similar, except that there is stronger support for continuing the oral antipsychotic at the same dose until therapeutic drug levels of the injectable antipsychotic are achieved and then gradually tapering the oral antipsychotic compared with the other options.

It should be noted that the experts definitely do not recommend stopping the oral antipsychotic when the first long-acting injection is given, since this would leave the patient without adequate antipsychotic coverage during the switchover and potentially increase the risk of relapse.

When switching to:	First Line	High Second Line	Other Second Line
Depot conventional		Continue oral antipsychotic at same dose until patient achieves therapeutic blood levels of the injectable antipsychotic and then gradually taper the oral antipsychotic Taper the oral antipsychotic gradually after giving the first long-acting injection	Continue oral antipsychotic at same dose until patient achieves therapeutic blood levels of the injectable antipsychotic and then immediately discontinue the oral antipsychotic
Long-acting injectable atypical		Continue oral antipsychotic at same dose until patient achieves therapeutic blood levels of the injectable antipsychotic and then gradually taper the oral antipsychotic	Taper the oral antipsychotic gradually after giving the first long-acting injection Continue oral antipsychotic at same dose until patient achieves therapeutic blood levels of the injectable antipsychotic and then immediately discontinue the oral antipsychotic

7F. Strategies When There Is a Partial Response[Question 19]

We asked the experts about the appropriateness of a number of strategies to try to improve response in a patient who is having a partial but still inadequate response (e.g., a patient with some persisting positive symptoms). The experts gave only limited support to any of the options and rated many of them third line, probably reflecting the lack of empirical data concerning these strategies.

If partial response to:	First Line	High Second Line	Other Second Line
Oral conventional			Add a long-acting injectable atypical antipsychotic Add an oral atypical antipsychotic Add valproate Add a benzodiazepine
Oral atypical			Add a long-acting injectable atypical antipsychotic Add valproate Add an oral atypical antipsychotic Add a benzodiazepine Add lithium Add ECT
Depot conventional			Add an oral atypical antipsychotic Add valproate

7G. When to Switch to Clozapine[Question 18]

Clozapine is indicated for treatment-refractory schizophrenia. However, clinicians vary in how they define treatment-refractory illness and there are no universally accepted criteria for treatment-refractoriness in schizophrenia. We therefore asked the experts in what clinical situations they would be most likely to consider a switch to clozapine. The experts consider a trial of clozapine a strategy of choice for a patient who has failed to respond to adequate trials of one or more conventional antipsychotics and two atypical antipsychotics. They would also consider it a strategy of choice for a patient who had failed to respond to trials of one or more conventionals and all the atypicals. However, 13% of the experts rated this option third line, probably because there would be no advantage in trying all the other five atypical antipsychotics before going to clozapine. The experts also consider a trial of clozapine a first line option for patients who have failed to respond to trials of two or three atypicals or trials of one or more conventionals and one atypical. Although some experts would consider clozapine for patients who have not responded to two conventionals or one atypical, there was much less support for these options. When it is most appropriate to switch to clozapine remains an area of controversy with few data to inform clinical practice. We may in fact be doing our patients a disservice by trying multiple drugs before going to clozapine.

(***bold italics*** = indications receiving the highest rating from at least 50% of the experts)

First Line	High Second Line	Other Second Line
Trials of one or more conventional antipsychotics and two atypical antipsychotics		Trials of two conventional antipsychotics Trial of one atypical antipsychotic
Trials of one or more conventional antipsychotics and all of the other atypical antipsychotics		
Trials of three atypical antipsychotics		
Trials of two atypical antipsychotics		
Trials of one or more conventional antipsychotics and one atypical antipsychotic		

Guideline 8: Pharmacologic Strategies for Managing Relapse

8A. Relapse When Taking an Oral Antipsychotic[Questions 20–22]

If a patient relapses whom the clinician believes is compliant with medication based on all available evidence (e.g., family report, plasma levels), the experts recommend (high second line ratings) either switching to a different oral antipsychotic or increasing the dose of the current medication. Another second line option the experts would consider is switching to a long-acting injectable antipsychotic. This probably reflects concerns that the patient may not actually be compliant, since studies have found that clinicians are often incorrect in their assessment of patients' compliance. It may also reflect concerns about absorption problems with the oral formulations.

When the clinician is unsure of the level of compliance or there is clear evidence of noncompliance, the experts' first line recommendation is to switch to a long-acting injectable atypical. They would also consider a long-acting conventional depot antipsychotic (high second line). If the clinician is unsure of the level of compliance, the experts would also consider adding a long-acting atypical to the oral antipsychotic.

Relapse	First Line	High Second Line	Other Second Line
Despite compliance		Switch to a different oral antipsychotic Increase the dose of the current antipsychotic	Switch to long-acting injectable atypical antipsychotic Add an adjunctive agent Add a long-acting injectable atypical antipsychotic Add another oral antipsychotic Switch to long-acting conventional depot
When unsure of level of compliance	Switch to long-acting injectable atypical antipsychotic*	Switch to long-acting conventional depot Add a long-acting injectable atypical antipsychotic	Switch to a different oral antipsychotic Add a long-acting conventional depot Add an adjunctive agent
When noncompliant	Switch to long-acting injectable atypical antipsychotic	Switch to long-acting conventional depot	Switch to a different oral antipsychotic

*At the time of this survey, a long-acting injectable atypical antipsychotic was not available in the United States, although it was available in several other countries. In the survey we asked the experts to rate how they would use such a formulation if it were available.

8B. Relapse on a Long-Acting Injectable Antipsychotic[Questions 23, 54]

If a patient relapses when receiving a long-acting conventional antipsychotic (depot), the experts' first line recommendation is to switch to a long-acting injectable atypical antipsychotic. They would also consider increasing the dose or the frequency of injections of the long-acting conventional (high second line options).

If a patient relapses when receiving a long-acting injectable atypical antipsychotic, the experts' first line recommendation is to increase the dose of the injectable antipsychotic. They would also strongly consider adding the oral form of the injectable antipsychotic to try to boost response (very high second line). The experts do not recommend switching to a conventional depot antipsychotic (third line rating).

Current Treatment	First Line	High Second Line	Other Second Line
Long-acting depot conventional antipsychotic	Switch to long-acting injectable atypical antipsychotic*	Increase the dose of the long-acting conventional antipsychotic Increase the frequency of injections of the long-acting conventional antipsychotic	Add an oral antipsychotic Obtain plasma levels Add an adjunctive agent Switch to a different oral antipsychotic Switch to a different conventional depot agent if not previously tried
Long-acting injectable atypical antipsychotic	Increase the dose of the long-acting injectable atypical	Add the oral form of the long-acting injectable atypical	Add an adjunctive agent Obtain plasma levels Add a different oral antipsychotic Switch to a different oral antipsychotic

*At the time of this survey, a long-acting injectable atypical antipsychotic was not available in the United States, although it was available in several other countries. In the survey we asked the experts to rate how they would use such a formulation if it were available.

Guideline 9: Dose Adjustment in Stable Patients[Question 24]

If the patient is being treated with an atypical antipsychotics or with fluphenazine or haloperidol decanoate, the majority of the experts would continue maintenance treatment with the same dose that was effective acutely, although over 40% would lower the dose of olanzapine or risperidone. A majority of the experts said they would lower the dose of an oral conventional antipsychotic for maintenance treatment; however, the percentages are very close, with 40% or more of the experts recommending continuing the acute dose of the conventional antipsychotic. The uncertainties shown in this area are consistent with a lack of information concerning optimum doses for maintenance treatment with both conventional and atypical antipsychotics.

Medications to continue at acute dose during maintenance treatment	
	% of experts endorsing this strategy
Aripiprazole	78%
Clozapine	66%
Olanzapine	59%
Quetiapine	71%
Risperidone	51%
Ziprasidone	72%
Fluphenazine decanoate	59%
Haloperidol decanoate	58%

Medications	Target maintenance dose if it is decided to lower dose* (mg/day)
Atypicals	
Aripiprazole	(10–15)†
Clozapine	(225–375)†
Olanzapine	(7.5–15.0)†
Quetiapine	(250–500)†
Risperidone	(2.5–4.0)†
Ziprasidone	(60–120)†
Conventionals	
Chlorpromazine	175–425
Fluphenazine	3.5–10
Haloperidol	3–8
Perphenazine	8–24
Thioridazine	150–350
Thiothixene	7–20
Trifluoperazine	5–20
Fluphenazine decanoate (mg/2–3 wk)	(6.25–25)†
Haloperidol decanoate (mg/4 wk)	(50–125)†

*The experts recommend waiting at least 6 months and preferably a year after a patient has become stable before lowering the dose of the antipsychotic.[Question 25]

†The majority of the experts would not lower the dose of this medication during maintenance treatment.

Guideline 10: Managing Complicating Problems

10A. Selecting Antipsychotics for Patients With Complicating Problems[Question 26]

The experts consider clozapine the treatment of choice for patients who present with suicidal behavior. This is consistent with a new indication for clozapine for "reducing the risk of recurrent suicidal behavior." Clozapine is also the top choice for aggression and violence. Other highly rated options for aggression and violence are risperidone (rated first line), olanzapine, and a long-acting injectable atypical (both rated high second line). There were no first line recommendations for the other problems we asked about—dysphoria/depression, cognitive problems, and substance abuse—for which all of the oral atypical antipsychotics as well as a long-acting injectable atypical received second line ratings. The experts would also consider a long-acting depot conventional for a patient with substance abuse. The lack of first line consensus on these items probably reflects the fact that, although an increasing number of studies have looked at the effects of atypical antipsychotics on mood, cognition, and substance use, the data are not yet sufficiently consistent or dramatic to influence clinical practice. It is interesting that the experts would not recommend oral conventional antipsychotics for patients with any of the problems that we asked about, except aggression/violence, for which conventional orals were second line options. It is possible that these complicating problems may be caused or exacerbated by noncompliance. Therefore, it is not surprising that a long-acting atypical antipsychotic was a prominent alternative, especially for aggression/violence and substance-abuse problems.

(***bold italics*** = treatments of choice)

Complicating problem	First Line*	High Second Line	Other Second Line
Aggression/violence	Clozapine Risperidone	Olanzapine Long-acting injectable atypical	Quetiapine Ziprasidone Aripiprazole Long-acting depot conventional Conventional
Suicidal behavior	***Clozapine***	Risperidone Olanzapine Ziprasidone	Aripiprazole Quetiapine Long-acting injectable atypical Long-acting depot conventional
Dysphoria/depression		Olanzapine Clozapine Aripiprazole Risperidone Ziprasidone	Quetiapine Long-acting injectable atypical
Cognitive problems		Risperidone Aripiprazole Olanzapine Ziprasidone Clozapine	Quetiapine Long-acting injectable atypical
Substance abuse		Clozapine Risperidone Long-acting injectable atypical Aripiprazole Olanzapine	Quetiapine Ziprasidone Long-acting depot conventional

*In this survey, we asked only about oral and long-acting injectable formulations of antipsychotics. Unless otherwise specified, all medications listed in the tables refer to the oral formulation.

10B. Selecting Adjunctive Treatments for Patients With Complicating Problems[Questions 27–30]

When we asked about a number of adjunctive medications that are commonly used in clinical practice to treat a variety of complicating problems in patients with schizophrenia, the experts as a group had few strong recommendations, probably reflecting the lack of decisive empirical data in this area. The only first line recommendation was a selective serotonin reuptake inhibitor (SSRI) for dysphoria/depression, reflecting studies showing that antidepressants can be helpful for patients with comorbid depression. Venlafaxine was a very high second line for dysphoria/depression. For aggression and violence, valproate and lithium received high second line ratings. For suicidal behavior, the same two antidepressants recommended for dysphoria/depression received high second line ratings, with ECT another high second line option. The question of how to treat persisting negative symptoms has long been a difficult issue in the field. Although there was no consensus on any of the adjunctive treatments which were rated second line for negative symptoms, it should be noted that approximately a quarter of the experts or more rated the following options first line: a glutaminergic agent, an SSRI, another antipsychotic, or venlafaxine.

Complicating problem	First Line	High Second Line	Other Second Line
Aggression/violence		Valproate Lithium	Carbamazepine Beta-blocker Benzodiazepine Gabapentin ECT Lamotrigine Topiramate
Suicidal behavior		Selective serotonin reuptake inhibitor (SSRI) Electroconvulsive therapy (ECT) Venlafaxine	Mirtazapine Lithium Valproate Bupropion Nefazodone Lamotrigine
Dysphoria/depression	SSRI	Venlafaxine	ECT Mirtazapine Bupropion Nefazodone Lithium Tricyclic antidepressant Valproate Lamotrigine Trazodone
Persisting negative symptoms			A glutamatergic agent (e.g., glycine, cyclo-serine) SSRI Another antipsychotic Venlafaxine A stimulant

10C. Strategies for a Patient With Clinically Significant Obesity[Questions 31, 32]

There is increasing concern about long-term medical problems in patients with schizophrenia, especially obesity and its complications. Many antipsychotics can contribute to weight gain and clinicians face difficult clinical dilemmas when a patient with clinically significant obesity (BMI ≥ 30) responds well to a medication that is likely to be contributing to the patient's weight problem. If a patient with clinically significant obesity has responded to an antipsychotic other than clozapine, the experts recommend a trial of a different antipsychotic with less weight gain liability combined with nutritional and exercise counseling if possible. They would also consider (high second line) continuing the same antipsychotic and providing nutritional and exercise counseling to try to help the patient lose weight. However, reflecting the fact that most patients receiving clozapine have already failed to respond to other agents, the experts would continue clozapine in this situation and try to address the weight problem with nutritional and exercise counseling. Although the experts gave a high second line rating to lowering the dose of clozapine in this situation, clinical studies have found that weight gain does not appear to be a dose-related effect. It is interesting that the experts gave second line ratings to the addition of topiramate. Although there have been case reports of weight loss with this agent in schizophrenia, there are no controlled studies supporting this practice. The experts did not recommend the use of weight loss medications (orlistat, sibutramine) or surgical treatment of obesity in this population.

Clinical presentation	First Line	High Second Line	Other Second Line
Patient who has responded well to an antipsychotic other than clozapine	Switch to a different antipsychotic with less weight gain liability and provide nutritional and exercise counseling	Switch to a different antipsychotic with less weight gain liability Continue treatment with the same antipsychotic at the same dose and provide nutritional and exercise counseling	Lower the dose of the current antipsychotic and provide nutritional and exercise counseling Add topiramate and provide nutritional and exercise counseling
Patient with treatment resistant illness who has responded well to clozapine	Continue treatment with clozapine at the same dose and provide nutritional and exercise counseling	Lower the clozapine dose and provide nutritional and exercise counseling	Switch to a different antipsychotic with less weight gain liability and provide nutritional and exercise counseling Add topiramate and provide nutritional and exercise counseling

10D. Monitoring for Comorbid Conditions and Risk Factors[Question 33]

Many patients with schizophrenia rely on their psychiatric care provider for general medical care. With the improving outcomes being achieved with the newer atypical antipsychotics, more attention is being focused on short- and long-term health and wellness in this population. We asked the experts which conditions and risk factors they felt it was *most important* to monitor. We also asked which ones it was feasible to monitor in a psychiatric treatment setting. The experts felt that it was important to monitor for all the conditions we asked about, with obesity and diabetes considered the most important (rated 9 by 60% and 56% of the experts, respectively). The experts' ratings of feasibility reflect the relative difficulty of the assessments involved (e.g., it is relatively simple to monitor weight and blood pressure, but much harder to evaluate osteoporosis). Although we did not ask about obtaining lipid profiles, the editors note that clinicians should also obtain lipid levels on a regular basis, because some antipsychotics are associated with hyperlipidemia. A recent expert conference concluded that, as part of routine care, a lipid panel should be obtained if one is not available. Given that individuals with schizophrenia, as a group, are considered to be at high risk for coronary heart disease, lipid screening should be carried out at least once every 5 years and more often when there is evidence of lipid levels that approach those that would lead to treatment.* The same conference also recommended that clinicians should be aware of, and monitor regularly for, symptoms of increased prolactin. If clinically indicated, prolactin should be measured, and, if elevated, a work-up for the cause of the elevation should be initiated. Consideration should also be given to switching to a prolactin-sparing medication—if the symptoms disappear and prolactin levels fall to normal, an endocrine work-up can then be avoided. Recommendations on other complicating conditions, such as cardiac problems (QTc prolongation and myocarditis), cataracts, and EPS will also be included in the Mount Sinai guideline when it is published.

(***bold italics*** = conditions receiving the highest rating from at least 50% of the experts)

Conditions and risk factors to monitor for	First Line	Second Line
Most important	***Obesity***	Galactorrhea
	Diabetes	Osteoporosis
	Cardiovascular problems	
	HIV risk behavior	
	Medical complications of substance abuse	
	Heavy smoking	
	Hypertension	
	Amenorrhea	
Most feasible for psychiatric treatment team to monitor	***Obesity***	HIV risk behavior
	Hypertension	Medical complications of substance abuse
	Amenorrhea	Osteoporosis
	Diabetes	
	Heavy smoking	
	Galactorrhea	
	Cardiovascular problems	

*Marder SR, Essock SM, Miller AL, et al. The Mount Sinai Conference on the Health Monitoring of Patients with Schizophrenia. Am J Psychiatry (submitted)

II. COMPLIANCE (ADHERENCE)

Guideline 11: Levels of Compliance

11A. Defining Levels of Compliance[Question 36]

We provided the experts with the definitions of compliance given below to use as benchmarks in answering a series of questions about the assessment and management of compliance problems. We also asked them to tell us how they would define levels of compliance. On average, the expert panel would set a higher threshold for compliance, as shown below, and would consider a patient who missed more than 65% of his or her medication noncompliant.

Level of compliance	Definitions provided in the survey	Average of experts' preferred definitions
Compliant	Misses < 20% of medication	Misses < 25% of medication
Partially compliant	Misses 20%–80% of medication	Misses 25%–65% of medication
Noncompliant	Misses > 80% of medication	Misses > 65% of medication

11B. Reported Extent of Compliance[Questions 34 & 35]

Not surprisingly, the experts report that their patients show higher levels of compliance than are generally reported in the literature.

Level of compliance	Levels reported in the literature	Experts' estimate of compliance levels in their patients
Compliant (misses < 20% of medication)	28%	43%
Partially compliant (misses 20%–80% of medication)	46%	38%
Noncompliant (misses > 80% of medication)	26%	19%

Guideline 12: Assessing Compliance[Question 37]

The experts consider asking the caregiver or patient first line strategies for assessing compliance; they would also consider pill counts, obtaining blood levels, and using self-rating scales. They did not consider routine use of urine tests appropriate.

Preferred strategies	Also consider
Asking relative or caregiver	Pill counts
Asking patient	Blood levels
	Self-rating scale for compliance

Guideline 13: When to Intervene for Compliance Problems[Question 38]

The experts were unanimous about the need to intervene if a patient is missing more than 80% of medication. They would usually intervene if a patient is missing approximately 50% of prescribed medication (91% would usually intervene). The majority of the experts (52%) would also usually intervene when a patient is missing approximately 20% of medication. There was less agreement about whether to intervene if a patient is only missing occasional doses (13% would usually intervene, 39% would sometimes intervene, and 48% would generally not intervene).

(***bold italics*** = over 50% of the experts gave the highest rating to intervention)

Usually intervene	Sometimes intervene
Patient missing more than 80% of medication doses or has stopped medication completely	Patient missing occasional doses
Patient missing approximately 50% of medication	
Patient missing approximately 20% of medication*	

*High second line

Guideline 14: Strategies for Addressing Compliance Problems

14A. Selecting Initial Strategies[Questions 39 & 40]

We asked the experts about the appropriateness of three different types of strategies that have been used to address compliance problems:

- Pharmacologic interventions (e.g., switching to a long-acting medication)
- Psychosocial interventions (e.g., patient education, compliance therapy [focused cognitive-behavioral therapy targeting compliance issues])
- Programmatic interventions (e.g., intensive case management, assertive community treatment)

The experts gave first line ratings to all three types of interventions. The editors note that clinicians should generally employ a combination of strategies tailored to the specific needs of the patient. The experts gave the highest ratings to psychosocial interventions for patients who are partially compliant, probably reflecting findings that such interventions can improve compliance levels. Psychopharmacologic interventions received the highest ratings for noncompliant patients, probably reflecting the fact that patients who are not taking their medication are at the highest risk for relapse and it is especially important to try to get the patient back on medication as quickly as possible.

(***bold italics*** = intervention of choice)

Clinical presentation	Preferred interventions to improve compliance
Partially compliant	***Psychosocial interventions***
	Pharmacologic interventions
	Programmatic interventions
Noncompliant	***Pharmacologic interventions***
	Programmatic interventions
	Psychosocial interventions

14B. Psychosocial and Programmatic Interventions to Improve Compliance[Questions 41 & 42]

Among psychosocial interventions for improving compliance, the experts gave the highest ratings to patient/family education, medication monitoring, and compliance therapy. Their ratings agree with research findings concerning the efficacy of these strategies in improving compliance. Findings concerning the efficacy of group and individual psychotherapy in improving compliance are equivocal, as shown by the lower ratings given to these options.

Among programmatic interventions the experts recommend assertive community treatment (ACT), ensuring continuity of treatment provider across treatment settings, and intensive case management services. These recommendations reflect findings in the literature that intensive case management, in particular the kind of assistance provided by ACT programs, can significantly improve compliance levels. Lack of continuity in care providers can lead to serious compliance problems, since patients may be continued on an ineffective or difficult-to-tolerate treatment regimen or may not receive continuing medication coverage after discharge. The experts also considered supervised residential services, partial hospitalization, rehabilitation services, and involuntary outpatient commitment useful options for improving compliance.

Psychosocial interventions		Programmatic interventions	
Preferred	**Also consider**	**Preferred**	**Also consider**
Patient education	Symptom and side effect monitoring	Assertive community treatment (ACT)	Supervised residential services
Family education and support	Individual or group psychotherapy	Continuity of primary clinician across treatment modalities (e.g., inpatient, outpatient, and residential programs)	Partial hospitalization services
Medication monitoring		Intensive services (e.g., contact 1–5 times weekly or more frequently as needed)	Rehabilitation services
Compliance therapy (focused cognitive-behavioral therapy targeting compliance issues)			Involuntary outpatient commitment

14C. Pharmacologic Strategies for Addressing Compliance Problems[Questions 43 & 44]

There was strong agreement among the experts that the first line pharmacologic strategy for addressing compliance problems is to switch the patient to a long-acting injectable atypical antipsychotic once this option is available (rated first line for partially compliant patients and treatment of choice for noncompliant patients). High second line options are to switch to a long-acting depot conventional or add a long-acting injectable atypical. Another high second line option for a patient who is partially compliant is to continue the same pharmacotherapy and intensify psychosocial interventions to improve compliance. However, the experts do not recommend this strategy for a patient who is noncompliant.

(***bold italics*** = treatment of choice)

Clinical presentation	First Line	High Second Line	Other Second Line
Partially compliant	Switch to a long-acting atypical antipsychotic*	Switch to a long-acting conventional depot antipsychotic Add a long-acting injectable atypical antipsychotic No change in pharmacotherapy; intensify psychosocial treatment	Switch to a different oral antipsychotic that has not previously been used Regular monitoring of plasma levels Add a long-acting conventional depot antipsychotic
Noncompliant	***Switch to a long-acting atypical antipsychotic***	Switch to a long-acting conventional depot antipsychotic Add a long-acting injectable atypical antipsychotic	Add a long-acting conventional depot antipsychotic Regular monitoring of plasma levels Switch to a different oral antipsychotic that has not previously been used

*At the time of this survey, a long-acting injectable atypical antipsychotic was not available in the United States, although it was available in several other countries. In the survey we asked the experts to rate how they would use such a formulation if it were available.

III. Long-Acting Injectable Antipsychotics

Guideline 15: Benefits of Long-Acting Injectable Antipsychotics[Question 45]

The experts consider the greatest benefit of a long-acting injectable antipsychotic to be assured medication delivery. Other important advantages are the ability to know immediately when a patient misses medication and the fact that the patient continues to have some medication in his or her system even after a missed dose. Additional advantages are the reduced risk of relapse associated with continuous medication, and the ability to know that relapse, if it occurs, is not the result of compliance problems.

(***bold italics*** = benefits receiving the highest rating from at least 50% of the experts)

Most important	Somewhat important
Assured medication delivery	Regular contact with patient
Knowing immediately when medication is missed	Convenience for patient
Reduced risk of relapse	Ability to use lower effective dose
Some continuing medication coverage after a missed dose	
Knowing that relapse has occurred despite adequate pharmacotherapy	

Guideline 16: Potential Disadvantages of Long-Acting Injectable Antipsychotics[Question 46]

The experts consider lack of patient acceptance the most important potential disadvantage of long-acting injectable antipsychotics. To some extent, this response probably reflects an assumption that patients will not accept the idea of continuing injections. However, once they try a long-acting medication, many patients are surprised to find how easy it is to tolerate receiving medication in this way. Although lack of patient autonomy is another potential concern that is sometimes mentioned, patient surveys do not support this as being a major factor. Although the experts said that they considered inability to stop medication immediately should side effects become a problem somewhat important as a potential disadvantage, the editors were hard pressed to find examples of situations in which immediate discontinuation of an antipsychotic in a long-acting formulation was a medical necessity. Even in neuroleptic malignant syndrome, there is no evidence that mortality rates are higher among patients receiving a long-acting injectable antipsychotic than in those receiving an oral medication (assuming that the condition is identified and appropriately treated).

Most important	Somewhat important	Not too important
Lack of patient acceptance	Logistical issues	Reimbursement issues
	Inability to stop medication immediately should side effects become a problem	Inadequately established benefit
	Negative physician perceptions	
	Stigma associated with injections or depot clinics	
	Inadequately appreciated benefit	
	Local effects of repeated injections	

Guideline 17: Factors Favoring Use of Long-Acting Injectable Antipsychotics[Question 47]

In deciding whether to use a long-acting injectable antipsychotic, 96% of the experts consider the availability of an atypical antipsychotic in such a formulation very important. This probably reflects concerns about side effects associated with the conventional depot antipsychotics. Other factors that the experts consider very important in deciding to use a long-acting injectable are good patient acceptance of the injection, evidence that the rate of relapses and side effects will be lower than with oral equivalents, better quality of life for their patients, and ease of administration.

(***bold italics*** = factors receiving the highest rating from at least 50% of the experts)

Most important	Somewhat important
Availability of an atypical antipsychotic in a long-acting injectable formulation	Longer interval between injections
Good patient acceptance of injection	Demonstrated superior efficacy to oral equivalent
Demonstrated fewer relapses/hospital admissions than oral equivalent	Easy preparation of injection
Fewer side effects than oral medications	Little dose titration required with long-acting injectable formulation
Better quality of life/patients say they feel better	Easy dose conversion from oral equivalent
Easy administration of injection	Easy dose conversion from other oral antipsychotic agent

Guideline 18: Indications for Switching From an Oral Antipsychotic to a Long-Acting Injectable Atypical[Questions 48 & 49]

We asked the experts about the appropriateness of using a long-acting injectable atypical antipsychotic in a variety of clinical situations. The experts consider a long-acting atypical antipsychotic the treatment of choice for a patient who is taking an oral atypical and requests the long-acting formulation, for a patient who relapses because of noncompliance with an oral atypical antipsychotic, and for a patient who is experiencing EPS on a depot conventional antipsychotic. The experts consider a long-acting injectable atypical first line for a patient in involuntary outpatient commitment, for a patient who is chronically relapsing on an oral conventional, for a patient with lack of insight or denial of illness, for a patient taking an oral atypical antipsychotic who is relapsing for reasons that are unclear, and for a patient with a history of aggressive or violent behavior. It is interesting that the experts perceive a role for the use of long-acting injectable atypicals that goes well beyond treatment of patients with compliance problems (see the many other second line indications listed below). Of all the situations that we asked about, the only ones in which the experts would not generally consider a long-acting injectable atypical are a patient taking an oral atypical or conventional who is stable and not experiencing EPS or a patient who has been newly diagnosed with schizophrenia and has had no previous antipsychotic treatment.

Further recommendations: We asked the experts how concern about the potential for TD would affect their decision to switch to an injectable atypical antipsychotic. The majority of the experts would definitely switch if there is concern about TD in a patient who is experiencing EPS on a depot or oral conventional antipsychotic (96% and 73% first line, respectively). Even if the patient is not experiencing EPS, many of the experts would consider switching from a depot or oral conventional if there is concern about TD (49% and 38% first line, respectively). The editors were unsure on what basis a clinician would decide that there was in fact no or minimal risk of TD.[Question 50]

We asked the experts about the appropriateness of beginning treatment with a long-acting injectable atypical while the patient is hospitalized, given shorter lengths of hospital stays. This strategy was rated high second line by the expert panel, in order to ensure continuing medication coverage when the patient is discharged and to facilitate acceptance of an injectable medication in outpatient treatment. The experts also noted that this strategy may be helpful because patients are most vulnerable to relapse soon after discharge.[Questions 52 & 53]

(***bold italics*** = indications receiving the highest rating from at least 50% of the experts)

First Line	High Second Line	Other Second Line
Patient taking an* oral atypical antipsychotic *who requests a long-acting antipsychotic	History of or potential for suicidal behavior	Other severe psychosocial stressor
Patient taking an* oral atypical antipsychotic *who is experiencing relapse because he or she stopped taking medication	Homelessness	Early episode schizophrenia
Patient taking a* depot conventional antipsychotic *who is stable but experiencing EPS	Comorbid substance abuse problems	Patient taking a depot conventional antipsychotic who is stable and is not experiencing serous EPS
Involuntary outpatient commitment	Lack of social supports	Bipolar mania with psychosis
Patient taking an oral conventional antipsychotic who is chronically relapsing	Elderly patient taking an oral conventional antipsychotic who forgets to take medication	Dementia with psychosis
Persistent lack of insight/denial of illness	Patient taking an oral conventional antipsychotic who is stable but experiencing EPS	Elderly patient taking an oral conventional antipsychotic who is having troublesome side effects
Patient taking an oral atypical antipsychotic who is experiencing relapse for reasons that are unclear		A patient with treatment-refractory illness who is taking clozapine and having troublesome side effects
History of or potential for aggressive or violent behavior		

Guideline 19: Factors Motivating Patients to Return for Repeat Injections[Question 51]

The experts consider the influence of family/caregivers and physician/treatment team to be most important in motivating patients to return for repeat injections.

Most important	Somewhat important
Urging/insistence of family or caregivers	Involuntary outpatient commitment
Urging of physician/treatment team	Contact with treatment team
	Decreased risk of relapse
	Not having to remember to take oral medication
	Convenience
	Better efficacy

IV. Defining Remission and Recovery

Guideline 20: Indicators of Remission and Recovery[Question 55]

With improving outcomes, research studies are now trying to evaluate the effectiveness of different antipsychotics not only in producing remission of symptoms but in promoting long-term recovery in patients with schizophrenia. However, as yet there is no general consensus on how best to define these terms. We therefore asked the experts to rate the appropriateness of a number of factors as indicators of remission and recovery. There was strong agreement that the level of positive symptoms is the single most important indicator of remission. High second line indicators are levels of cognitive/disorganized, negative, and depressive symptoms, reflecting studies that show that these associated symptoms contribute in a substantial way to the functional disability associated with schizophrenia. In defining recovery, however, the experts gave almost equal weight to all of the indicators that we asked about, indicating that recovery is a concept involving improvement in multiple domains.

Rank ordering of symptomatic indicators: When the experts were asked to rank order four key indicators of remission and recovery, their responses agreed very closely with those presented in the table below: 89% considered level of positive symptoms the most important indicator of remission, followed by cognitive/disorganized symptoms, negative symptoms, and depressive symptoms, all three of which were ranked similarly. However, there was less agreement on the most important indicator of recovery, with 41% considering level of positive symptoms most important, 33% giving the highest ranking to level of cognitive/disorganized symptoms, and 28% ranking level of negative symptoms as most important.[Question 56]

Rank ordering of functional outcomes. When asked to rank order three functional outcomes as indicators of remission, the experts were divided, with 45% considering independent living, 32% occupational/education functioning, and 20% peer relationships the most important functional indicator of remission. This division among the panel may reflect the fact that one is unlikely to see major changes in any of these areas in the shorter time frame that is usually used to measure remission (see Guideline 21). However, when asked about the same functional outcomes as indicators of recovery, the majority (64%) felt that occupational/educational functioning was the most important functional outcome in recovery, followed by peer relationships (considered most important by 20%) and independent living (considered most important by 18%). When asked about the most appropriate way of defining functional improvement in their patients, 86% of the experts considered relative rather than absolute change in the patient the most appropriate indicator.[Questions 57 & 58]

(***bold italics*** = indicators receiving the highest rating from at least 50% of the experts)

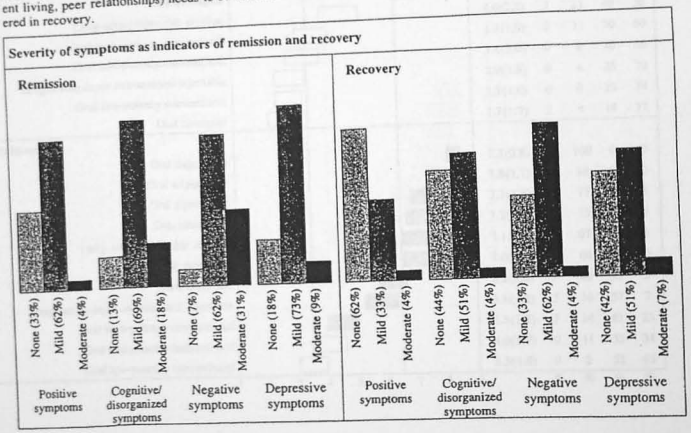
Remission			Recovery
First Line	**High second line**	**Other second line**	**First line**
Level of positive symptoms	Level of cognitive/ disorganized symptoms	Meaningful peer relationships	Occupational/educational functioning
	Level of negative symptoms	Ability to live independently	Meaningful peer relationships
	Level of depressive symptoms	Occupational/educational functioning	Level of negative symptoms
			Ability to live independently
			Level of positive symptoms
			Level of cognitive/disorganized symptoms
			Level of depressive symptoms

Guideline 21: Severity and Duration of Symptoms as Indicators of Remission and Recovery[Questions 59 & 60]

We asked the experts what levels of symptom severity were most appropriate to use in defining remission and recovery. Their ratings are presented in the bar charts below. The majority of the experts would consider a patient in remission who had mild levels of positive, cognitive/disorganized, negative, and depressive symptoms (62%, 69%, 62%, and 73% of the experts, respectively). However, a third of the experts felt that no positive symptoms should be present for a patient to be considered in remission.

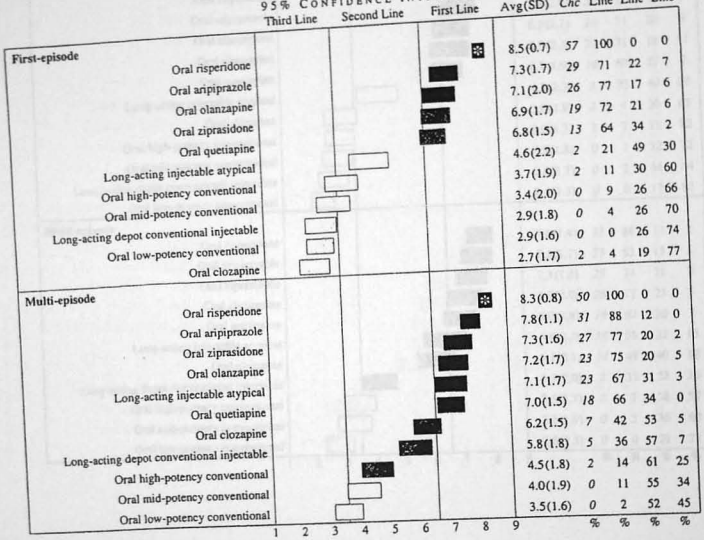
The experts' ratings shifted to the left when asked about indicators for recovery, with a majority (62%) saying that there should be no positive symptoms for a patient to be considered in recovery. In terms of negative symptoms, 62% of the panel would consider a patient in recovery who had mild negative symptoms while 33% would look for no negative symptoms. The panel was more evenly split as to whether a patient could have mild cognitive or depressive symptoms and still be considered in recovery.

Duration of symptoms. The expert panel said that the improvement in symptomatic indicators should be maintained for at least 3 months for a patient to be considered in remission and for a year or more for a patient to be considered in recovery. The experts believe that improvement in functional indicators (occupational/vocational functioning, independent living, peer relationships) needs to be maintained for somewhat longer, 15–17 months, for the patient to be considered in recovery.



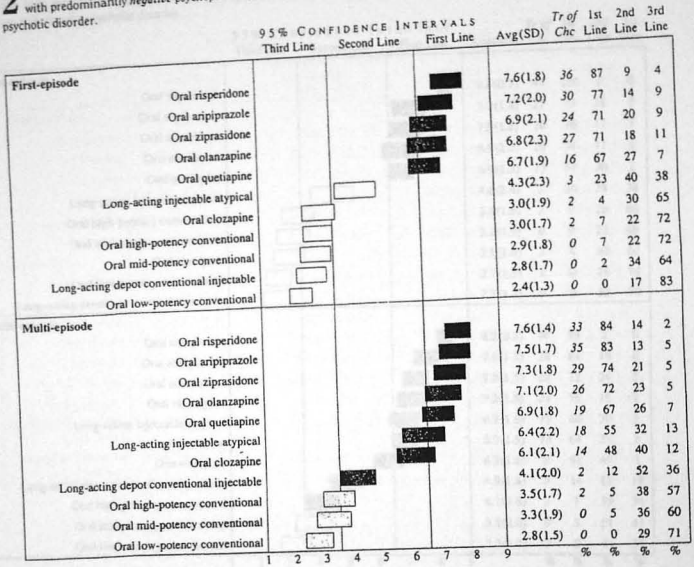
Expert Survey Results and Guideline References

1 Medication selection. Please rate the appropriateness of each of the following as initial pharmacologic treatment for a patient with predominantly ***positive*** psychopathology who is 1) having a first episode of psychosis or 2) has had previous episodes of a psychotic disorder.

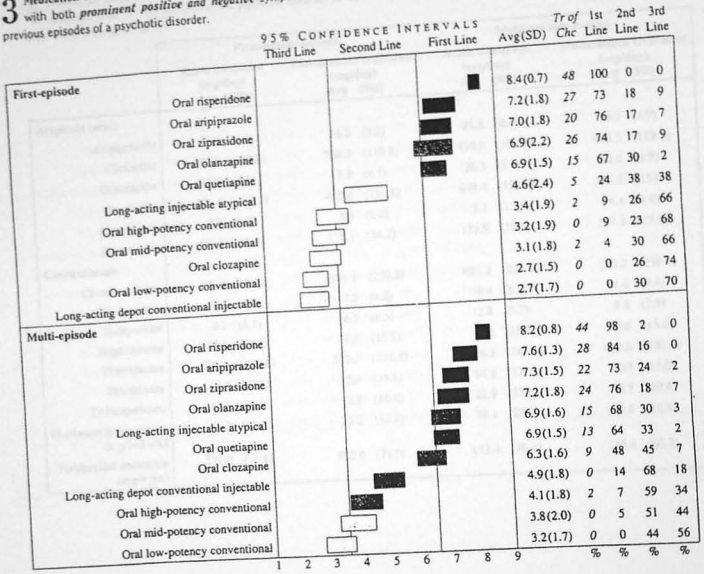


	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
First-episode					
Oral risperidone	8.5(0.7)	*57*	100	0	0
Oral aripiprazole	7.3(1.7)	29	71	22	7
Oral olanzapine	7.1(2.0)	26	77	17	6
Oral ziprasidone	6.9(1.7)	*19*	72	21	6
Oral quetiapine	6.8(1.5)	*13*	64	34	2
Long-acting injectable atypical	4.6(2.2)	*2*	21	49	30
Oral high-potency conventional	3.7(1.9)	2	11	30	60
Oral mid-potency conventional	3.4(2.0)	*0*	9	26	66
Long-acting depot conventional injectable	2.9(1.8)	*0*	4	26	70
Oral low-potency conventional	2.9(1.6)	*0*	0	26	74
Oral clozapine	2.7(1.7)	2	4	19	77
Multi-episode					
Oral risperidone	8.3(0.8)	*50*	100	0	0
Oral aripiprazole	7.8(1.1)	*31*	88	12	0
Oral ziprasidone	7.3(1.6)	27	77	20	2
Oral olanzapine	7.2(1.7)	*23*	75	20	5
Long-acting injectable atypical	7.1(1.7)	*23*	67	31	3
Oral quetiapine	7.0(1.5)	*18*	66	34	0
Oral clozapine	6.2(1.5)	7	42	53	5
Long-acting depot conventional injectable	5.8(1.8)	5	36	57	7
Oral high-potency conventional	4.5(1.8)	2	14	61	25
Oral mid-potency conventional	4.0(1.9)	*0*	11	55	34
Oral low-potency conventional	3.5(1.6)	*0*	2	52	45
			%	%	%

2 Medication selection. Please rate the appropriateness of each of the following as initial pharmacologic treatment for a patient with predominantly *negative* psychopathology who is 1) having a first episode of psychosis or 2) has had previous episodes of a psychotic disorder.



3 **Medication selection.** Please rate the appropriateness of each of the following as initial pharmacologic treatment for a patient with both ***prominent positive and negative*** symptomatology who is 1) having a first episode of psychosis or 2) has had previous episodes of a psychotic disorder.



4 **Dosing of antipsychotics.** Please write in the ***average daily target*** dose you would use for each antipsychotic to ensure an adequate trial for the treatment of a psychotic disorder in each clinical situation. If you are not familiar with a medication, draw a line through that row.

	First-episode patient		Multi-episode patient	
	Acute treatment (mg/day) Avg (SD)	Maintenance treatment (mg/day) Avg (SD)	Acute treatment (mg/day) Avg (SD)	Maintenance treatment (mg/day) Avg (SD)
Atypicals (oral)				
Aripiprazole	17.0 (4.4)	16.2 (3.5)	21.8 (6.1)	19.3 (4.9)
Clozapine	393.8 (107.6)	364.3 (110.2)	490.0 (106.9)	443.3 (119.5)
Olanzapine	15.8 (4.3)	13.8 (4.1)	20.3 (5.1)	18.0 (4.9)
Quetiapine	524.4 (168.8)	465.6 (151.8)	644.4 (152.3)	582.2 (153.4)
Risperidone	3.9 (1.2)	3.5 (1.2)	5.1 (1.2)	4.4 (1.0)
Ziprasidone	131.4 (30.3)	118.1 (34.2)	155.9 (18.6)	144.5 (27.9)
Conventionals				
Chlorpromazine	438.4 (225.2)	379.1 (229.2)	601.2 (215.9)	501.2 (238.2)
Fluphenazine	9.3 (6.0)	7.3 (4.8)	14.4 (8.4)	11.0 (4.4)
Haloperidol	8.2 (5.3)	6.2 (4.5)	12.8 (5.7)	9.8 (3.9)
Perphenazine	23.9 (15.1)	20.8 (15.5)	32.6 (15.7)	27.6 (15.6)
Thioridazine	397.1 (163.6)	317.1 (174.4)	486.2 (147.1)	419.6 (158.7)
Thiothixene	18.4 (13.7)	15.4 (13.6)	24.8 (13.1)	20.7 (13.0)
Trifluoperazine	16.2 (11.6)	12.8 (10.4)	22.9 (12.0)	18.7 (10.4)
Fluphenazine decanoate (mg/2–3 wk)	24.3 (13.5)	21.2 (12.7)	38.1 (27.1)	29.8 (12.8)
Haloperidol decanoate (mg/4 wk)	127.0 (72.8)	107.9 (71.0)	172.4 (70.4)	145.8 (63.7)

5 Use of therapeutic drug monitoring of antipsychotics. Please indicate 1) whether plasma level assays are available to you for each of the following agents and 2) if so, whether and how you use plasma levels to adjust the dose. If you are not familiar with a medication, draw a line through that row.

	Are plasma level assays of this agent available to you?		If yes, do you use these levels to monitor compliance?		If yes, do you use these levels to adjust dose?		If you use plasma levels to adjust dose, how do you use them?		
	Yes	No	Yes	No	Yes	No	Routinely	If response inadequate	If side effects a problem
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n*	*n*	*n*
Clozapine	43 (96%)	2 (4%)	26 (59%)	18 (41%)	38 (88%)	5 (12%)	12	33	30
Haloperidol	33 (77%)	10 (23%)	20 (57%)	15 (43%)	15 (50%)	15 (50%)	0	17	12
Haloperidol decanoate	27 (64%)	15 (36%)	7 (27%)	19 (73%)	12 (50%)	12 (50%)	0	14	9
Fluphenazine	16 (39%)	25 (61%)	6 (27%)	16 (73%)	3 (18%)	14 (82%)	1	4	2
Risperidone	16 (37%)	27 (63%)	7 (29%)	17 (71%)	3 (14%)	18 (86%)	0	4	4
Fluphenazine decanoate	15 (37%)	26 (63%)	4 (19%)	17 (81%)	4 (27%)	11 (73%)	0	5	2
Olanzapine	15 (35%)	28 (65%)	6 (25%)	18 (75%)	4 (21%)	15 (79%)	0	6	4
Chlorpromazine	11 (26%)	31 (74%)	4 (21%)	15 (79%)	2 (14%)	12 (86%)	0	2	3
Quetiapine	7 (16%)	36 (84%)	2 (12%)	15 (88%)	1 (8%)	11 (92%)	0	2	1
Perphenazine	5 (13%)	35 (88%)	1 (7%)	13 (93%)	0 (0%)	9 (100%)	0	0	0
Ziprasidone	5 (12%)	37 (88%)	2 (13%)	14 (88%)	0 (0%)	12 (100%)	0	1	1
Thioridazine	4 (10%)	36 (90%)	2 (14%)	12 (86%)	1 (11%)	8 (89%)	0	1	0
Thiothixene	4 (10%)	36 (90%)	2 (14%)	12 (86%)	2 (20%)	8 (80%)	0	2	0
Trifluoperazine	3 (7%)	38 (93%)	1 (8%)	12 (92%)	1 (11%)	8 (89%)	0	1	0
Aripiprazole	1 (2%)	40 (98%)	2 (13%)	14 (88%)	0 (0%)	11 (100%)	0	1	1

6 **Highest final acute dose.** What is the highest final acute dose of each of the following agents you would use in an average healthy young adult? If you are not familiar with a medication, draw a line through that row.

		Highest final acute dose (mg/day) Avg (SD)
Atypicals (oral)		
	Aripiprazole	30.9 (5.4)
	Clozapine	853.3 (147.1)
	Olanzapine	43.2 (34.9)
	Quetiapine	968.5 (261.5)
	Risperidone	10.6 (4.1)
	Ziprasidone	182.3 (43.0)
Conventionals		
	Chlorpromazine	972.7 (303.7)
	Fluphenazine	27.7 (15.0)
	Haloperidol	26.6 (11.7)
	Perphenazine	57.2 (21.1)
	Thioridazine	650.0 (149.1)
	Thiothixene	42.2 (17.6)
	Trifluoperazine	41.3 (17.2)
	Fluphenazine decanoate (mg/2–3 wk)	54.3 (18.9)
	Haloperidol decanoate (mg/4 wk)	243.9 (81.5)

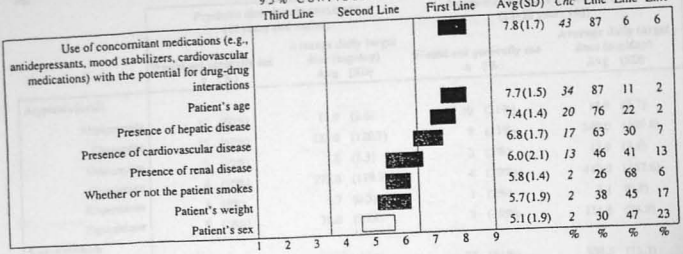
7 **Dose equivalency of antipsychotics.** Please write in the doses (mg) of each of the following antipsychotics that you would consider equivalent to each of the doses of haloperidol listed below. In this question, we are trying to get a feeling for the equivalency of doses between the older conventional antipsychotics and the new generation of atypical antipsychotics. If you are not familiar with a medication, draw a line through that row.

	Haloperidol 1 mg Avg (SD)	Haloperidol 5 mg Avg (SD)	Haloperidol 10 mg Avg (SD)	Haloperidol 20 mg Avg (SD)	Haloperidol 30 mg Avg (SD)
Atypicals (oral)					
Aripiprazole	4.8 (2.7)	11.9 (3.8)	20.7 (7.9)	31.1 (14.5)	33.5 (11.6)
Clozapine	68.8 (37.9)	235.2 (80.0)	427.3 (134.9)	670.7 (153.7)	897.3 (196.5)
Olanzapine	3.4 (1.6)	10.2 (3.6)	18.1 (5.1)	31.0 (11.7)	43.3 (19.4)
Quetiapine	97.6 (66.6)	325.0 (118.7)	582.6 (185.1)	902.5 (336.6)	1234.8 (520.4)
Risperidone	0.9 (0.4)	3.2 (1.0)	5.7 (1.8)	10.4 (4.1)	14.8 (5.2)
Ziprasidone	35.3 (24.6)	90.4 (35.2)	142.1 (41.4)	183.0 (51.7)	236.9 (91.8)
Conventionals					
Chlorpromazine	61.0 (29.6)	248.3 (64.9)	491.9 (123.4)	886.3 (213.3)	1310.5 (369.5)
Fluphenazine	1.1 (0.2)	4.9 (0.3)	10.0 (0.8)	19.5 (1.7)	30.5 (2.7)
Perphenazine	4.5 (1.9)	17.5 (6.5)	33.3 (13.0)	61.8 (20.8)	86.5 (29.9)
Thioridazine	52.4 (26.7)	218.4 (55.7)	435.5 (135.0)	742.6 (207.5)	980.4 (365.2)
Thiothixene	3.2 (1.5)	12.5 (5.4)	24.1 (10.7)	43.0 (17.4)	59.1 (24.5)
Trifluoperazine	3.0 (1.4)	11.8 (5.3)	22.9 (10.3)	42.4 (21.4)	54.3 (19.9)
Fluphenazine decanoate (mg/2–3 wk)	5.5 (3.0)	15.7 (7.3)	29.1 (13.2)	52.7 (25.8)	75.8 (39.5)
Haloperidol decanoate (mg/4 wk)	28.6 (22.7)	83.3 (43.0)	144.0 (62.4)	245.0 (77.5)	328.4 (109.9)

8 **Dose equivalency of antipsychotics.** Please write in the doses (mg) of each of the following antipsychotics that you would consider equivalent to each of the doses of risperidone listed below. In this question, we are trying to get a feeling for the equivalency of doses among the new generation of antipsychotics. If you are not familiar with a medication, draw a line through that row.

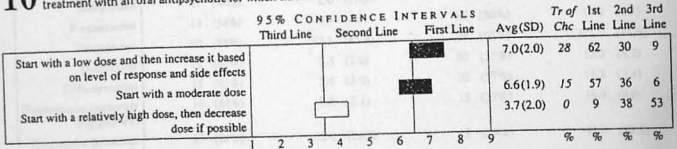
	Risperidone 1 mg Avg (SD)	Risperidone 2 mg Avg (SD)	Risperidone 4 mg Avg (SD)	Risperidone 6 mg Avg (SD)	Risperidone 8 mg Avg (SD)
Atypicals (oral)					
Aripiprazole	4.9 (1.8)	9.7 (2.6)	17.2 (5.4)	25.1 (5.5)	31.4 (7.6)
Clozapine	82.2 (35.4)	168.7 (60.3)	340.2 (90.1)	499.0 (109.5)	690.0 (148.6)
Olanzapine	4.1 (1.8)	8.0 (2.7)	14.4 (3.4)	20.4 (4.8)	28.4 (6.6)
Quetiapine	100.5 (39.8)	221.3 (73.3)	439.0 (144.7)	604.4 (148.1)	819.1 (187.2)
Ziprasidone	37.1 (18.2)	69.9 (25.9)	115.3 (34.2)	158.2 (42.7)	197.3 (55.4)
Conventionals					
Chlorpromazine	81.4 (25.5)	174.4 (53.6)	361.3 (136.6)	553.8 (169.9)	789.5 (249.1)
Fluphenazine	1.8 (1.2)	4.2 (2.3)	8.1 (4.2)	11.5 (4.8)	16.7 (7.3)
Haloperidol	1.6 (0.5)	3.7 (1.2)	7.3 (2.6)	11.5 (4.3)	16.8 (6.7)
Perphenazine	6.0 (2.0)	13.0 (6.3)	25.2 (12.5)	39.2 (16.8)	54.0 (19.2)
Thioridazine	65.0 (32.1)	142.5 (64.2)	308.3 (131.2)	468.6 (154.9)	655.9 (186.2)
Thiothixene	3.8 (1.4)	8.4 (4.1)	16.8 (8.1)	25.7 (11.5)	33.7 (12.4)
Trifluoperazine	4.2 (2.1)	8.6 (4.1)	17.1 (6.8)	24.5 (9.5)	34.7 (14.2)
Fluphenazine decanoate (mg/2–3 wk)	6.8 (3.4)	12.4 (5.9)	23.9 (11.1)	38.6 (20.7)	58.7 (40.9)
Haloperidol decanoate (mg/4 wk)	29.4 (14.5)	58.9 (27.0)	112.6 (50.2)	169.9 (73.5)	226.2 (89.8)

9 **Acute dose adjustment.** Please rate the appropriateness of adjusting ***acute*** antipsychotic dose based on the following factors. Please give a rating of 7, 8, or 9 to those factors that you would nearly always consider in selecting antipsychotic dose; a rating of 4, 5, or 6 to those factors you would sometimes consider; and a rating of 1, 2, or 3 to those factors you would rarely or never consider.



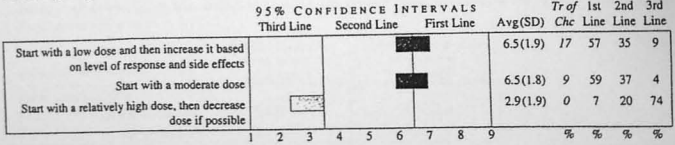
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Use of concomitant medications (e.g., antidepressants, mood stabilizers, cardiovascular medications) with the potential for drug-drug interactions	7.8(1.7)	*43*	87	6	6
Patient's age	7.7(1.5)	*34*	87	11	2
Presence of hepatic disease	7.4(1.4)	*20*	76	22	2
Presence of cardiovascular disease	6.8(1.7)	*17*	63	30	7
Presence of renal disease	6.0(2.1)	*13*	46	41	13
Whether or not the patient smokes	5.8(1.4)	*2*	26	68	6
Patient's weight	5.7(1.9)	*2*	38	45	17
Patient's sex	5.1(1.9)	*2*	30	47	23
			%	%	%	%

10 **Titrating the first oral antipsychotic used.** Please rate the appropriateness of the following strategies for beginning treatment with an oral antipsychotic for which titration is not required.



	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Start with a low dose and then increase it based on level of response and side effects	7.0(2.0)	*28*	62	30	9
Start with a moderate dose	6.6(1.9)	*15*	57	36	6
Start with a relatively high dose, then decrease dose if possible	3.7(2.0)	*0*	9	38	53
			%	%	%	%

11 **Titrating the first long-acting injectable antipsychotic used.** Please rate the appropriateness of the following strategies for beginning treatment with a long-acting injectable antipsychotic.



	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Start with a low dose and then increase it based on level of response and side effects	6.5(1.9)	*17*	57	35	9
Start with a moderate dose	6.5(1.8)	*9*	59	37	4
Start with a relatively high dose, then decrease dose if possible	2.9(1.9)	*0*	7	20	74
			%	%	%	%

12 **Dose selection for special populations.** Please write in the ***average daily target*** dose you would use for each antipsychotic for the ***acute treatment*** of each of the following types of patients. If you would not generally use this medication to treat this type of patient, please place an X in the appropriate boxes. If you are not familiar with a medication, draw a line through that row.

	Psychotic disorders in CHILDREN (12 years and under)		Psychotic disorders in ADOLESCENTS (13–18 years old)	
	Would not generally use *n* (%)	Average daily target dose (mg/day) Avg (SD)	Would not generally use *n* (%)	Average daily target dose (mg/day) Avg (SD)
Atypicals (oral)				
Aripiprazole	12 (60%)	11.9 (2.6)	10 (31%)	14.9 (2.7)
Clozapine	15 (58%)	223.9 (120.7)	9 (23%)	340.0 (109.4)
Olanzapine	5 (19%)	7.6 (2.3)	2 (5%)	12.9 (3.6)
Quetiapine	4 (16%)	272.6 (119.9)	4 (10%)	410.0 (157.6)
Risperidone	1 (4%)	1.7 (0.5)	1 (2%)	3.1 (0.8)
Ziprasidone	9 (38%)	76.0 (30.4)	7 (18%)	111.6 (28.9)
Conventionals				
Chlorpromazine	17 (71%)	180.4 (24.9)	22 (61%)	304.5 (71.3)
Fluphenazine	14 (58%)	3.1 (1.6)	17 (49%)	6.2 (3.7)
Haloperidol	11 (44%)	2.6 (1.5)	15 (42%)	5.6 (3.7)
Perphenazine	13 (54%)	9.4 (3.9)	18 (50%)	17.2 (5.3)
Thioridazine	20 (83%)	178.1 (85.6)	24 (67%)	271.9 (44.6)
Thiothixene	15 (63%)	5.5 (2.0)	20 (57%)	12.2 (8.2)
Trifluoperazine	15 (63%)	5.6 (3.0)	20 (57%)	11.3 (5.1)
Fluphenazine decanoate (mg/2–3 wk)	16 (64%)	7.6 (3.1)	13 (37%)	18.9 (9.0)
Haloperidol decanoate (mg/4 wk)	15 (60%)	33.3 (18.6)	13 (36%)	95.9 (59.5)

12 Dose selection for special populations, *continued*

	Elderly patients (65 years and older) with psychotic disorders (e.g., schizophrenia, schizoaffective disorder)		Elderly patients (65 years and older) with dementia who have a behavioral disturbance and/or psychosis	
	Would not generally use *n* (%)	Average daily target dose (mg/day) Avg (SD)	Would not generally use *n* (%)	Average daily target dose (mg/day) Avg (SD)
Atypicals (oral)				
Aripiprazole	6 (15%)	13.2 (4.1)	9 (33%)	11.5 (4.1)
Clozapine	6 (13%)	268.4 (96.7)	22 (41%)	113.9 (63.1)
Olanzapine	1 (3%)	10.8 (4.5)	7 (18%)	7.5 (3.4)
Quetiapine	3 (7%)	343.2 (116.2)	7 (15%)	194.4 (111.6)
Risperidone	0 (0%)	2.6 (1.0)	0 (0%)	1.8 (1.0)
Ziprasidone	11 (28%)	103.4 (31.7)	13 (37%)	75.0 (29.2)
Conventionals				
Chlorpromazine	21 (60%)	225.9 (75.1)	24 (73%)	101.4 (35.6)
Fluphenazine	11 (31%)	5.0 (2.8)	13 (39%)	3.4 (2.6)
Haloperidol	9 (24%)	4.0 (2.2)	8 (23%)	2.3 (1.3)
Perphenazine	14 (38%)	14.3 (9.3)	15 (43%)	8.4 (6.1)
Thioridazine	24 (69%)	223.9 (81.5)	24 (73%)	90.3 (42.3)
Thiothixene	18 (53%)	10.9 (8.7)	18 (56%)	6.3 (5.0)
Trifluoperazine	18 (53%)	9.7 (5.4)	18 (56%)	5.9 (3.1)
Fluphenazine decanoate (mg/2–3 wk)	12 (35%)	15.0 (7.1)	23 (72%)	9.0 (3.6)
Haloperidol decanoate (mg/4 wk)	12 (33%)	68.8 (43.2)	23 (70%)	53.1 (35.3)

13 **Duration of adequate trial.** Please indicate the average minimum and maximum number of weeks you would wait before making a major change in treatment regimen in a patient with a psychotic disorder 1) who is having an inadequate response to the ***initial antipsychotic tried*** and 2) who is having an inadequate response to the ***second antipsychotic tried***, depending on whether the patient is having ***little or no response*** or ***a partial response***. Assume that the patient is receiving a dose level that you consider optimal.

Inadequate response to:	Minimum number of weeks to wait Avg (SD)	Maximum number of weeks to wait Avg (SD)
INITIAL ANTIPSYCHOTIC		
Little or no response	2.6 (1.3)	5.5 (2.6)
Partial response	4.4 (1.7)	9.9 (5.1)
SECOND ANTIPSYCHOTIC		
Little or no response	2.8 (1.3)	5.8 (2.6)
Partial response	4.7 (2.2)	11.2 (8.0)

14 Treatment strategy if there is an inadequate response. Assume that a multi-episode patient has had an inadequate response to the average target dose of the medication you indicated you would use for acute treatment in Question 4. For each medication, please indicate whether you would increase the dose or switch to another antipsychotic. If you would increase the dose, please indicate to what average daily target dose you would go. If you are not familiar with a medication, draw a line through that row.

	If inadequate response to this medication, would you increase dose or switch to a different antipsychotic? (check one)		If you would INCREASE dose, what dose would you go to
	Increase dose *n* (%)	Switch medications *n* (%)	Average daily target dose (mg/day) Avg (SD)
Atypicals (oral)			
Aripiprazole	26 (68%)	12 (32%)	30.8 (2.7)
Clozapine	39 (93%)	3 (7%)	723.1 (136.6)
Olanzapine	42 (93%)	3 (7%)	31.0 (7.6)
Quetiapine	37 (84%)	7 (16%)	873.0 (208.4)
Risperidone	38 (84%)	7 (16%)	8.1 (2.1)
Ziprasidone	24 (57%)	18 (43%)	195.0 (34.0)
Conventionals			
Chlorpromazine	23 (56%)	18 (44%)	943.5 (389.4)
Fluphenazine	22 (55%)	18 (45%)	21.9 (11.6)
Haloperidol	22 (52%)	20 (48%)	20.8 (7.6)
Perphenazine	19 (51%)	18 (49%)	46.1 (16.3)
Thioridazine	13 (33%)	26 (67%)	673.1 (156.3)
Thiothixene	18 (49%)	19 (51%)	38.9 (13.6)
Trifluoperazine	20 (53%)	18 (47%)	38.3 (17.3)
Fluphenazine decanoate (mg/2–3 wk)	25 (64%)	14 (36%)	50.7 (16.8)
Haloperidol decanoate (mg/4 wk)	27 (64%)	15 (36%)	233.3 (103.5)

15 **Switching antipsychotics if there is an inadequate response.** Assume that the patient has had an inadequate response to the current antipsychotic and you have raised the dose as high as you feel is safe or the patient can tolerate and you have decided to switch to a different antipsychotic. For each medication, please indicate to which drug you would first switch and what medication you would try next if there was an inadequate response to the first one you switched to. Please also write in the average daily target dose you would initially use for each medication. If you are not familiar with a medication, draw a line through that row.

Inadequate response to:	First medication you would switch to	*n*	(%)	Second medication you would switch to	*n*	(%)
Oral aripiprazole	risperidone	20	(54%)	clozapine	14	(39%)
	olanzapine	7	(19%)	olanzapine	9	(25%)
	ziprasidone	6	(16%)	risperidone	7	(19%)
	quetiapine	3	(8%)	quetiapine	3	(8%)
	haloperidol	1	(3%)	ziprasidone	2	(6%)
				aripiprazole	1	(3%)
Oral clozapine	risperidone	11	(34%)	olanzapine	7	(23%)
	aripiprazole	8	(25%)	quetiapine	5	(17%)
	olanzapine	3	(9%)	aripiprazole	4	(13%)
	ziprasidone	2	(6%)	risperidone	4	(13%)
	add risperidone	2	(6%)	ziprasidone	3	(10%)
	add lamotrigine/other adjunctive	1	(3%)	ECT	2	(7%)
	add valproate	1	(3%)	add ECT	1	(3%)
	haloperidal	1	(3%)	add lamotrigine/other adjunctive	1	(3%)
	long-acting injectable atypical	1	(3%)	clozapine	1	(3%)
	NEVER	1	(3%)	combinations	1	(3%)
	quetiapine	1	(3%)	long-acting injectable atypical	1	(3%)
Oral olanzapine	risperidone	25	(60%)	clozapine	18	(43%)
	aripiprazole	5	(12%)	aripiprazole	9	(21%)
	ziprasidone	5	(12%)	quetiapine	5	(12%)
	clozapine	3	(7%)	risperidone	4	(10%)
	quetiapine	3	(7%)	olanzapine	2	(5%)
	haloperidal	1	(2%)	ziprasidone	2	(5%)
				add lamotrigine/other adjunctive	1	(2%)
				long-acting injectable atypical	1	(2%)
Oral quetiapine	risperidone	27	(64%)	olanzapine	16	(38%)
	olanzapine	6	(14%)	clozapine	13	(31%)
	aripiprazole	5	(12%)	aripiprazole	6	(14%)
	ziprasidone	3	(7%)	ziprasidone	3	(7%)
	clozapine	1	(2%)	risperidone	2	(5%)
				haloperidal	1	(2%)
				long-acting injectable atypical	1	(2%)
Oral risperidone	olanzapine	21	(50%)	clozapine	14	(35%)
	aripiprazole	8	(19%)	aripiprazole	10	(25%)
	clozapine	5	(12%)	quetiapine	5	(13%)
	quetiapine	4	(10%)	olanzapine	3	(8%)
	ziprasidone	4	(10%)	ziprasidone	3	(8%)
				add lamotrigine/other adjunctive	1	(3%)
				add valproate	1	(3%)
				haloperidal	1	(3%)
				long-acting injectable atypical	1	(3%)
				NEVER	1	(3%)

15 Switching antipsychotics if there is an inadequate response, *continued*

Inadequate response to:	First medication you would switch to	*n*	(%)	Second medication you would switch to	*n*	(%)
Oral ziprasidone	risperidone	17	(44%)	clozapine	13	(34%)
	aripiprazole	8	(21%)	olanzapine	11	(29%)
	olanzapine	8	(21%)	aripiprazole	6	(16%)
	quetiapine	4	(10%)	risperidone	5	(13%)
	clozapine	1	(3%)	quetiapine	2	(5%)
	haloperidal	1	(3%)	long-acting injectable atypical	1	(3%)
Oral chlorpromazine	risperidone	25	(64%)	olanzapine	13	(35%)
	olanzapine	7	(18%)	clozapine	7	(19%)
	aripiprazole	3	(8%)	quetiapine	5	(14%)
	ziprasidone	3	(8%)	aripiprazole	4	(11%)
	quetiapine	1	(3%)	risperidone	4	(11%)
				ziprasidone	4	(11%)
Oral fluphenazine	risperidone	23	(62%)	olanzapine	10	(29%)
	olanzapine	6	(16%)	clozapine	6	(18%)
	aripiprazole	4	(11%)	quetiapine	5	(15%)
	ziprasidone	3	(8%)	risperidone	5	(15%)
	quetiapine	1	(3%)	aripiprazole	4	(12%)
				ziprasidone	4	(12%)
Oral haloperidol	risperidone	23	(59%)	olanzapine	10	(28%)
	olanzapine	7	(18%)	clozapine	7	(19%)
	aripiprazole	5	(13%)	quetiapine	5	(14%)
	ziprasidone	3	(8%)	risperidone	5	(14%)
	quetiapine	1	(3%)	ziprasidone	5	(14%)
				aripiprazole	4	(11%)
Oral perphenazine	risperidone	23	(62%)	olanzapine	10	(29%)
	olanzapine	5	(14%)	clozapine	6	(18%)
	aripiprazole	4	(11%)	quetiapine	5	(15%)
	ziprasidone	4	(11%)	risperidone	5	(15%)
	quetiapine	1	(3%)	aripiprazole	4	(12%)
				ziprasidone	4	(12%)
Oral thioridazine	risperidone	25	(68%)	olanzapine	10	(29%)
	olanzapine	5	(14%)	clozapine	6	(18%)
	aripiprazole	3	(8%)	aripiprazole	5	(15%)
	quetiapine	2	(5%)	risperidone	5	(15%)
	ziprasidone	2	(5%)	quetiapine	4	(12%)
				ziprasidone	4	(12%)
Oral thiothixene	risperidone	23	(64%)	olanzapine	10	(30%)
	olanzapine	5	(14%)	clozapine	6	(18%)
	aripiprazole	4	(11%)	risperidone	5	(15%)
	ziprasidone	3	(8%)	aripiprazole	4	(12%)
	quetiapine	1	(3%)	quetiapine	4	(12%)
				ziprasidone	4	(12%)
Oral trifluoperazine	risperidone	22	(61%)	olanzapine	9	(27%)
	olanzapine	6	(17%)	clozapine	6	(18%)
	aripiprazole	4	(11%)	risperidone	5	(15%)
	ziprasidone	3	(8%)	ziprasidone	5	(15%)
	quetiapine	1	(3%)	aripiprazole	4	(12%)
				quetiapine	4	(12%)

15 Switching antipsychotics if there is an inadequate response, *continued*

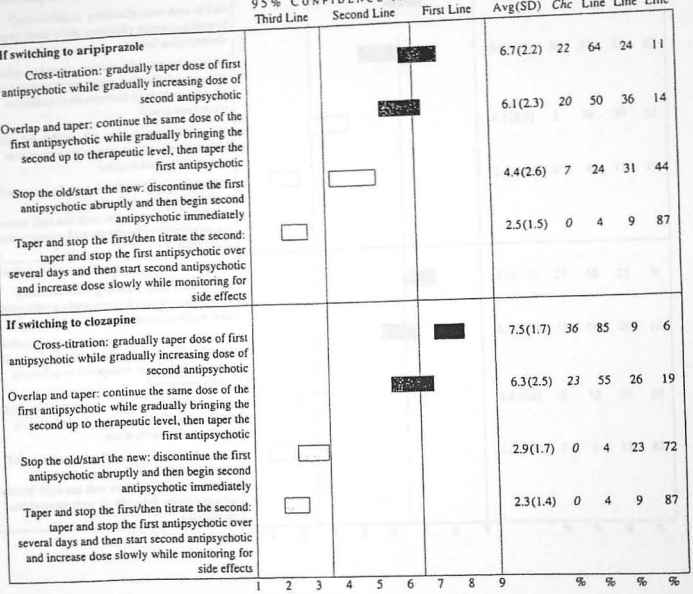
Inadequate response to:	First medication you would switch to	*n*	(%)	Second medication you would switch to	*n*	(%)
Long-acting injectable atypical	clozapine	9	(27%)	clozapine	12	(40%)
	risperidone	8	(24%)	olanzapine	5	(17%)
	haloperidol decanoate	5	(15%)	aripiprazole	3	(10%)
	aripiprazole	3	(9%)	ziprasidone	3	(10%)
	ziprasidone	3	(9%)	add valproate	1	(3%)
	haloperidol	2	(6%)	fluphenazine decanoate	1	(3%)
	quetiapine	2	(6%)	NEVER	1	(3%)
	olanzapine	1	(3%)	quetiapine	1	(3%)
				risperidone	1	(3%)
Injectable fluphenazine decanoate	long-acting injectable atypical	14	(38%)	clozapine	14	(41%)
	risperidone	9	(24%)	olanzapine	7	(21%)
	aripiprazole	3	(8%)	risperidone	3	(9%)
	olanzapine	3	(8%)	ziprasidone	3	(9%)
	ziprasidone	3	(8%)	aripiprazole	2	(6%)
	haloperidol decanoate	2	(5%)	quetiapine	2	(6%)
	quetiapine	2	(5%)	haloperidol	1	(3%)
	clozapine	1	(3%)	haloperidol decanoate	1	(3%)
				long-acting injectable atypical	1	(3%)
Injectable haloperidol decanoate	long-acting injectable atypical	14	(39%)	clozapine	15	(45%)
	risperidone	8	(22%)	olanzapine	5	(15%)
	aripiprazole	3	(8%)	risperidone	3	(9%)
	olanzapine	3	(8%)	ziprasidone	3	(9%)
	ziprasidone	3	(8%)	aripiprazole	2	(6%)
	fluphenazine decanoate	2	(6%)	quetiapine	2	(6%)
	quetiapine	2	(6%)	fluphenazine	1	(3%)
	clozapine	1	(3%)	fluphenazine decanoate	1	(3%)
				long-acting injectable atypical	1	(3%)

Target doses when switching antipsychotics

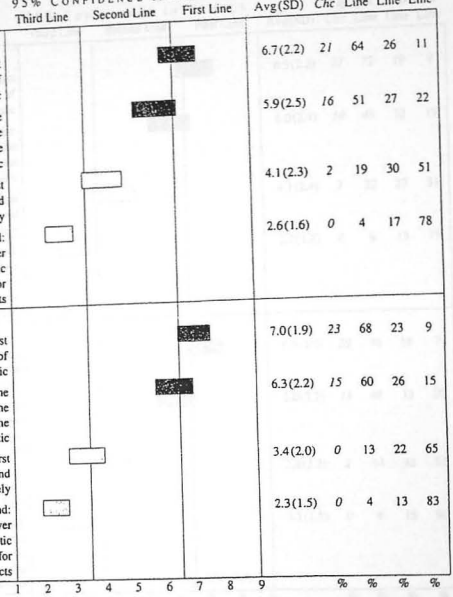
	Dosing of first switch (mg/day)	Dosing of second switch (mg/day)
	Avg (SD)	Avg (SD)
Atypicals		
Aripiprazole	27.8 (5.3)	24.1 (7.6)
Clozapine	400.0 (62.4)	419.3 (65.9)
Olanzapine	21.0 (7.5)	20.1 (6.0)
Quetiapine	663.8 (104.3)	670.0 (135.9)
Risperidone	5.5 (1.7)	6.4 (1.8)
Ziprasidone	144.0 (22.9)	151.2 (30.0)
Long-acting injectable atypical	36.4 (11.8)	50.0 *
Conventionals		
Fluphenazine	— —	50.0 *
Haloperidol	10.0 *	15.0 (7.1)
Fluphenazine decanoate (mg/2–3 wk)	31.3 (26.5)	75.0 *
Haloperidol decanoate (mg/4 wk)	166.7 (66.1)	275.0 (176.8)

*Only one write-in.

16 **Switching strategies.** Suppose the initial antipsychotic (after adequate dose and duration of treatment) has produced an inadequate response and you have decided to switch to a different antipsychotic. Assume that the first antipsychotic does not require tapering before discontinuation. Please rate the appropriateness of the following strategies for switching to each of the following antipsychotics. Give your highest rating to the strategy you consider most appropriate.



16 Switching strategies, *continued*



16 **Switching strategies**, *continued*

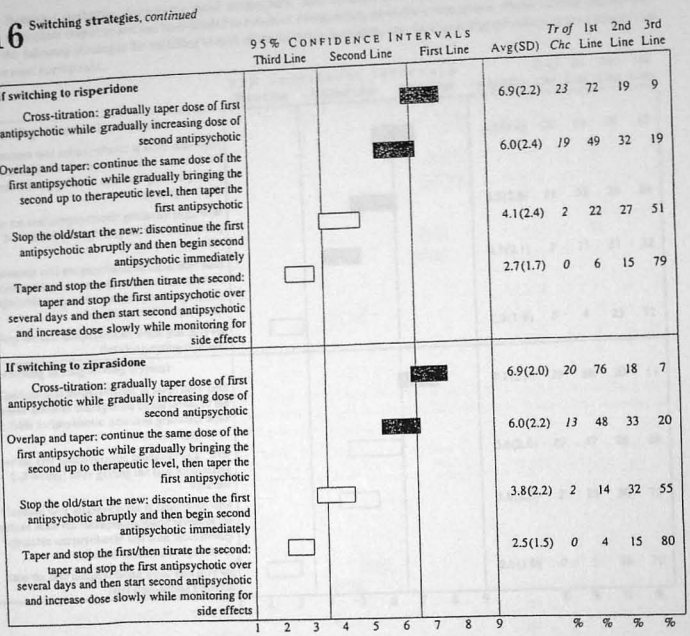


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Exhibit A
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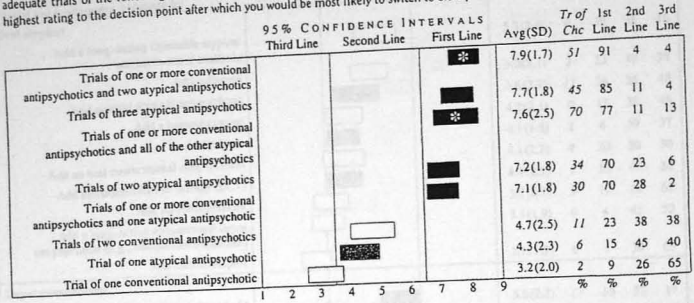
B C D

17 **Switching strategies.** Suppose the initial antipsychotic (after adequate dose and duration of treatment) has produced an inadequate response and you have decided to switch to a long-acting injectable antipsychotic. Please rate the appropriateness of the following strategies for switching to each of the following antipsychotics. Give your highest rating to the strategy you consider most appropriate.

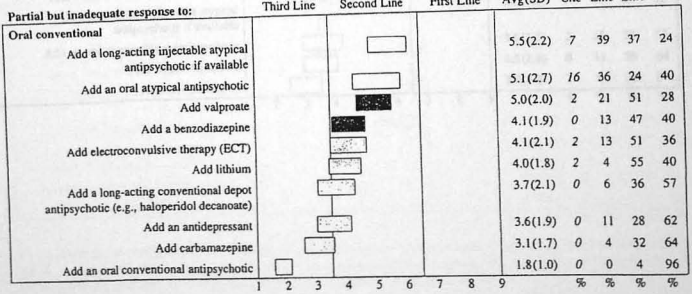
	95% Confidence Intervals: Third Line / Second Line / First Line	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
If switching to conventional depot						
Continue oral antipsychotic at same dose until patient achieves therapeutic blood levels of the injectable antipsychotic and then gradually taper oral antipsychotic		6.5(2.4)	*20*	61	24	15
Taper the oral antipsychotic gradually (e.g., over 2–4 weeks) after giving the first long-acting injection		5.8(2.6)	*15*	52	24	24
Continue oral antipsychotic at same dose until patient achieves therapeutic blood levels of the injectable antipsychotic and then immediately discontinue oral antipsychotic		4.7(2.1)	*2*	17	51	32
Stop the oral antipsychotic when you give the first long-acting injection		2.9(1.9)	*0*	4	23	72
If switching to long-acting atypical						
Continue oral antipsychotic at same dose until patient achieves therapeutic blood levels of the injectable antipsychotic and then gradually taper oral antipsychotic		7.1(2.3)	*30*	68	20	11
Taper the oral antipsychotic gradually (e.g., over 2–4 weeks) after giving the first long-acting injection		5.6(2.8)	*23*	47	26	28
Continue oral antipsychotic at same dose until patient achieves therapeutic blood levels of the injectable antipsychotic and then immediately discontinue oral antipsychotic		5.0(2.2)	*2*	25	50	25
Stop the oral antipsychotic when you give the first long-acting injection		2.5(1.9)	*0*	5	16	79
	1 2 3 4 5 6 7 8 9			%	%	%	%

18 **Use of clozapine.** Although clozapine is usually not used as a first line medication, it can sometimes help patients when other medications have failed. Please rate the appropriateness of switching to clozapine if the patient has not responded to adequate trials of the following treatments. Assume the patient is medication adherent and is not abusing substances. Give the highest rating to the decision point after which you would be most likely to switch to clozapine.



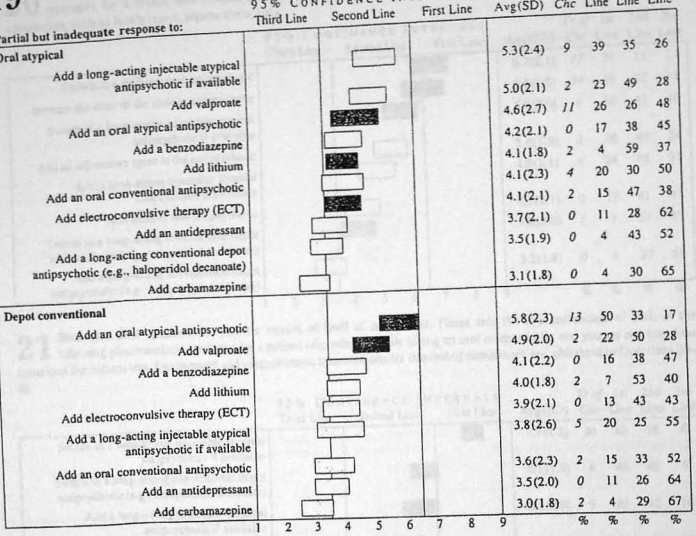
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Trials of one or more conventional antipsychotics and two atypical antipsychotics	7.9(1.7)	*51*	91	4	4
Trials of three atypical antipsychotics	7.7(1.8)	*45*	85	11	4
Trials of one or more conventional antipsychotics and all of the other atypical antipsychotics	7.6(2.5)	*70*	77	11	13
Trials of two atypical antipsychotics	7.2(1.8)	*34*	70	23	6
Trials of one or more conventional antipsychotics and one atypical antipsychotic	7.1(1.8)	*30*	70	28	2
Trials of two conventional antipsychotics	4.7(2.5)	*11*	23	38	38
Trial of one atypical antipsychotic	4.3(2.3)	*6*	15	45	40
Trial of one conventional antipsychotic	3.2(2.0)	*2*	9	26	65
			%	%	%	%

19 **Strategies when there is partial response.** Please rate the appropriateness of each of the following strategies for a patient who is having a ***partial but still inadequate response*** (some persisting positive symptoms) to each of the following types of antipsychotics (we are not asking about cross-titration while switching here).



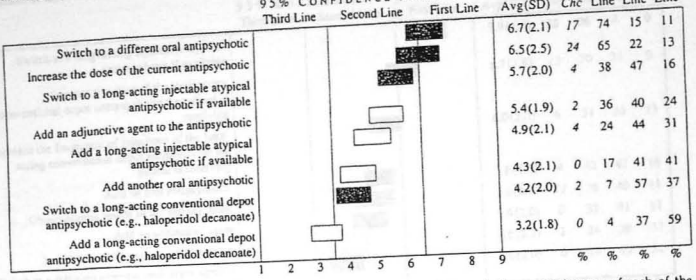
Partial but inadequate response to:	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Oral conventional					
Add a long-acting injectable atypical antipsychotic if available	5.5(2.2)	7	39	37	24
Add an oral atypical antipsychotic	5.1(2.7)	*16*	36	24	40
Add valproate	5.0(2.0)	2	21	51	28
Add a benzodiazepine	4.1(1.9)	*0*	13	47	40
Add electroconvulsive therapy (ECT)	4.1(2.1)	2	13	51	36
Add lithium	4.0(1.8)	2	4	55	40
Add a long-acting conventional depot antipsychotic (e.g., haloperidol decanoate)	3.7(2.1)	*0*	6	36	57
Add an antidepressant	3.6(1.9)	*0*	11	28	62
Add carbamazepine	3.1(1.7)	*0*	4	32	64
Add an oral conventional antipsychotic	1.8(1.0)	*0*	0	4	96
			%	%	%	%

19 Strategies when there is partial response, *continued*



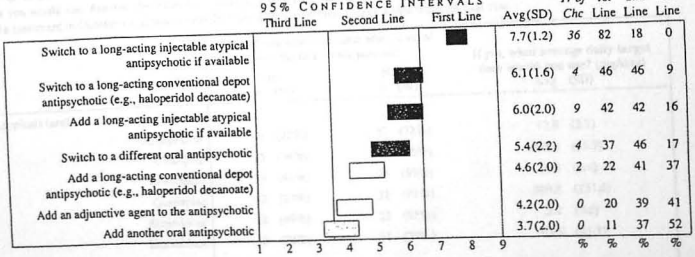
Partial but inadequate response to:	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Oral atypical					
Add a long-acting injectable atypical antipsychotic if available	5.3(2.4)	9	39	35	26
Add valproate	5.0(2.1)	2	23	49	28
Add an oral atypical antipsychotic	4.6(2.7)	*11*	26	26	48
Add a benzodiazepine	4.2(2.1)	*0*	17	38	45
Add lithium	4.1(1.8)	2	4	59	37
Add an oral conventional antipsychotic	4.1(2.3)	*4*	20	30	50
Add electroconvulsive therapy (ECT)	4.1(2.1)	2	15	47	38
Add an antidepressant	3.7(2.1)	*0*	11	28	62
Add a long-acting conventional depot antipsychotic (e.g., haloperidol decanoate)	3.5(1.9)	*0*	4	43	52
Add carbamazepine	3.1(1.8)	*0*	4	30	65
Depot conventional					
Add an oral atypical antipsychotic	5.8(2.3)	*13*	50	33	17
Add valproate	4.9(2.0)	2	22	50	28
Add a benzodiazepine	4.1(2.2)	*0*	16	38	47
Add lithium	4.0(1.8)	2	7	53	40
Add electroconvulsive therapy (ECT)	3.9(2.1)	*0*	13	43	43
Add a long-acting injectable atypical antipsychotic if available	3.8(2.6)	*5*	20	25	55
Add an oral conventional antipsychotic	3.6(2.3)	2	15	33	52
Add an antidepressant	3.5(2.0)	*0*	11	26	64
Add carbamazepine	3.0(1.8)	2	4	29	67
			%	%	%	%

20 **Strategies after relapse despite compliance.** Please rate the appropriateness of each of the following pharmacologic strategies for a patient who relapses despite compliance with an oral antipsychotic regimen (based on all available information, such as family report, plasma levels, etc.).



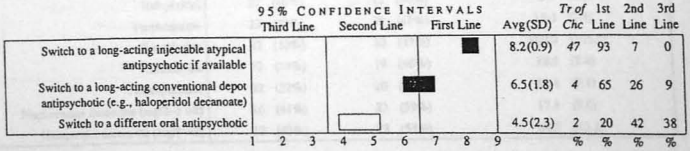
	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
Switch to a different oral antipsychotic	6.7(2.1)	17	74	15	11
Increase the dose of the current antipsychotic	6.5(2.5)	24	65	22	13
Switch to a long-acting injectable atypical antipsychotic if available	5.7(2.0)	4	38	47	16
Add an adjunctive agent to the antipsychotic	5.4(1.9)	2	36	40	24
Add a long-acting injectable atypical antipsychotic if available	4.9(2.1)	4	24	44	31
Add another oral antipsychotic	4.3(2.1)	0	17	41	41
Switch to a long-acting conventional depot antipsychotic (e.g., haloperidol decanoate)	4.2(2.0)	2	7	57	37
Add a long-acting conventional depot antipsychotic (e.g., haloperidol decanoate)	3.2(1.8)	0	4	37	59
		%	%	%	%

21 **Strategies after relapse when you are unsure of level of compliance.** Please rate the appropriateness of each of the following pharmacologic strategies for a patient who relapses while taking an oral antipsychotic and you are not sure how compliant the patient was. Psychosocial and programmatic interventions for improving compliance are addressed in Questions 39–42.



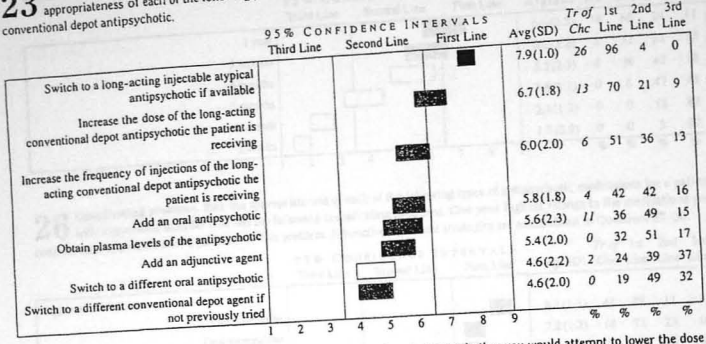
	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
Switch to a long-acting injectable atypical antipsychotic if available	7.7(1.2)	36	82	18	0
Switch to a long-acting conventional depot antipsychotic (e.g., haloperidol decanoate)	6.1(1.6)	4	46	46	9
Add a long-acting injectable atypical antipsychotic if available	6.0(2.0)	9	42	42	16
Switch to a different oral antipsychotic	5.4(2.2)	4	37	46	17
Add a long-acting conventional depot antipsychotic (e.g., haloperidol decanoate)	4.6(2.0)	2	22	41	37
Add an adjunctive agent to the antipsychotic	4.2(2.0)	0	20	39	41
Add another oral antipsychotic	3.7(2.0)	0	11	37	52
		%	%	%	%

22 **Strategies after relapse in a noncompliant patient.** Please rate the appropriateness of each of the following pharmacologic strategies for a patient who relapses and there is clear evidence of noncompliance with an oral antipsychotic. Psychosocial and programmatic interventions for improving compliance are addressed in Questions 39–42.



	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
Switch to a long-acting injectable atypical antipsychotic if available	8.2(0.9)	47	93	7	0
Switch to a long-acting conventional depot antipsychotic (e.g., haloperidol decanoate)	6.5(1.8)	4	65	26	9
Switch to a different oral antipsychotic	4.5(2.3)	2	20	42	38
		%	%	%	%

23 **Strategies after relapse in a patient receiving a long-acting CONVENTIONAL DEPOT antipsychotic.** Please rate the appropriateness of each of the following pharmacologic strategies for a patient who relapses while receiving a long-acting conventional depot antipsychotic.

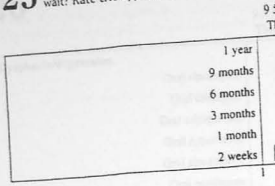


	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
			%	%	%
Switch to a long-acting injectable atypical antipsychotic if available	7.9(1.0)	26	96	4	0
Increase the dose of the long-acting conventional depot antipsychotic the patient is receiving	6.7(1.8)	13	70	21	9
Increase the frequency of injections of the long-acting conventional depot antipsychotic the patient is receiving	6.0(2.0)	6	51	36	13
Add an oral antipsychotic	5.8(1.8)	4	42	42	16
Obtain plasma levels of the antipsychotic	5.6(2.3)	11	36	49	15
Add an adjunctive agent	5.4(2.0)	0	32	51	17
Switch to a different oral antipsychotic	4.6(2.2)	2	24	39	37
Switch to a different conventional depot agent if not previously tried	4.6(2.0)	0	19	49	32

24 **Lowering the dose in a stable patient.** For each medication, please indicate whether you would attempt to lower the dose of the medication after several months if the patient is stable. If you would do so, please write in the average daily target dose you would use. Assume the patient is receiving the average target dose of the medication you indicated you would use for acute treatment in Question 4. If you are not familiar with a medication, draw a line through that row.

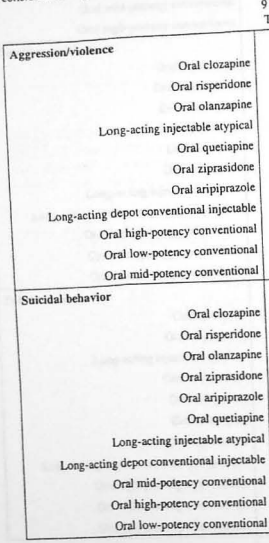
	Would you lower the dose after several months in a stable patient? Yes *n* (%)	No) *n* (%)	If yes, what average daily target dose would you use? (mg/day) Avg (SD)
Atypicals (oral)			
Aripiprazole	9 (22%)	32 (78%)	12.9 (2.7)
Clozapine	15 (34%)	29 (66%)	303.3 (66.7)
Olanzapine	19 (41%)	27 (59%)	11.5 (3.4)
Quetiapine	13 (29%)	32 (71%)	380.8 (131.6)
Risperidone	22 (49%)	23 (51%)	3.1 (0.8)
Ziprasidone	12 (28%)	31 (72%)	85.5 (31.1)
Conventionals			
Chlorpromazine	26 (59%)	18 (41%)	307.4 (122.2)
Fluphenazine	24 (57%)	18 (43%)	5.9 (2.7)
Haloperidol	27 (60%)	18 (40%)	5.5 (2.3)
Perphenazine	22 (52%)	20 (48%)	16.4 (7.4)
Thioridazine	23 (53%)	20 (47%)	260.9 (105.5)
Thiothixene	22 (54%)	19 (46%)	12.5 (5.4)
Trifluoperazine	22 (52%)	20 (48%)	12.4 (7.1)
Fluphenazine decanoate (mg/2–3 wk)	16 (41%)	23 (59%)	17.1 (9.6)
Haloperidol decanoate (mg/4 wk)	17 (43%)	23 (58%)	84.5 (43.2)

25 **Dose lowering strategies.** If have decided to lower the dose of the antipsychotic in a stable patient, how long would you wait? Rate the appropriateness of lowering the dose after the patient has been stable for the following time periods.



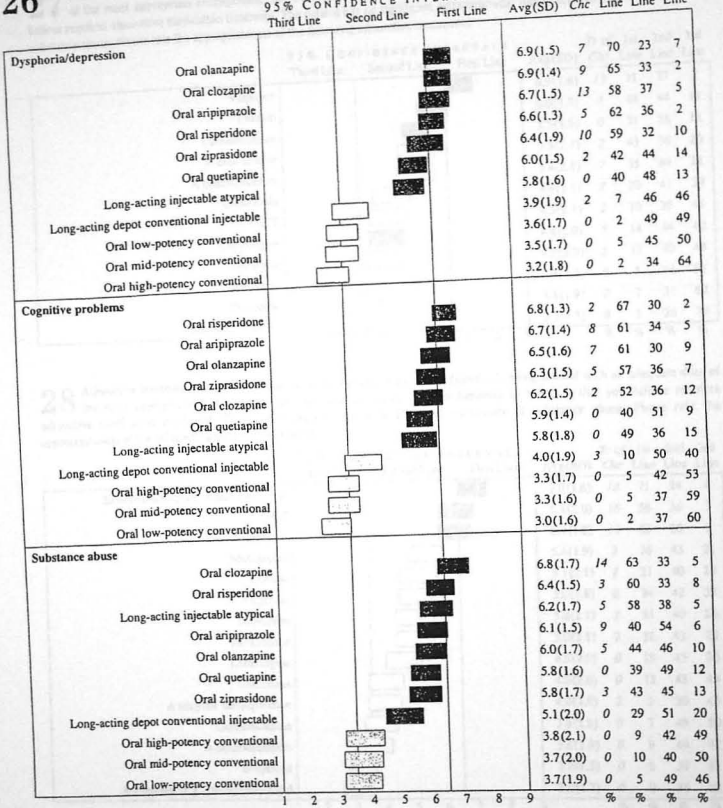
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
1 year	6.6(2.3)	*16*	66	24	11
9 months	6.0(2.2)	*5*	55	32	13
6 months	5.5(2.3)	*8*	39	42	18
3 months	3.8(2.1)	*0*	8	47	45
1 month	2.4(1.2)	*0*	0	18	82
2 weeks	1.7(0.9)	*0*	0	3	97
			%	%	%	%

26 **Complicating problems.** Rate the appropriateness of each of the following types of antipsychotic medications for a patient with a psychotic disorder who has the following complicating problems. Give your highest ratings to the medications you consider most appropriate for a patient with this problem. Adjunctive treatment strategies are asked about in Questions 27–30.



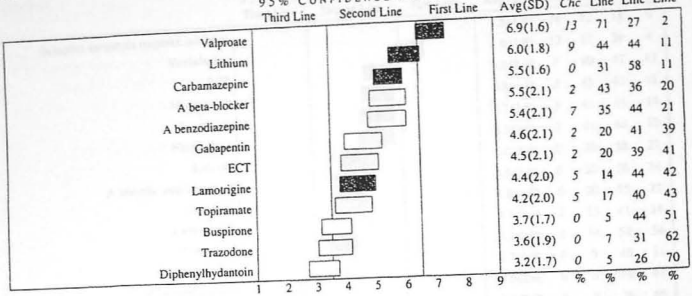
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Aggression/violence					
Oral clozapine	8.1(1.1)	*43*	89	11	0
Oral risperidone	7.2(1.2)	*14*	77	23	0
Oral olanzapine	6.9(1.4)	7	72	26	2
Long-acting injectable atypical	6.4(1.8)	*5*	60	33	8
Oral quetiapine	5.9(1.6)	*0*	42	47	12
Oral ziprasidone	5.8(1.6)	*5*	33	58	10
Oral aripiprazole	5.7(1.7)	*5*	32	57	11
Long-acting depot conventional injectable	5.5(1.8)	*0*	34	49	17
Oral high-potency conventional	5.2(2.0)	*2*	32	43	25
Oral low-potency conventional	5.1(1.9)	*0*	28	51	21
Oral mid-potency conventional	4.8(2.0)	*0*	19	52	29
Suicidal behavior					
Oral clozapine	8.3(1.1)	*59*	95	5	0
Oral risperidone	6.8(0.9)	*2*	64	36	0
Oral olanzapine	6.7(1.2)	*2*	62	33	4
Oral ziprasidone	6.2(1.6)	*3*	51	41	8
Oral aripiprazole	6.1(1.2)	*0*	35	62	3
Oral quetiapine	6.0(1.4)	*0*	41	51	7
Long-acting injectable atypical	5.8(1.8)	*3*	41	46	13
Long-acting depot conventional injectable	4.6(1.8)	*0*	13	56	31
Oral mid-potency conventional	4.0(1.8)	*0*	7	49	44
Oral high-potency conventional	3.9(1.9)	*0*	7	42	51
Oral low-potency conventional	3.8(1.8)	*0*	5	50	45
			%	%	%	%

26 Complicating problems, *continued*



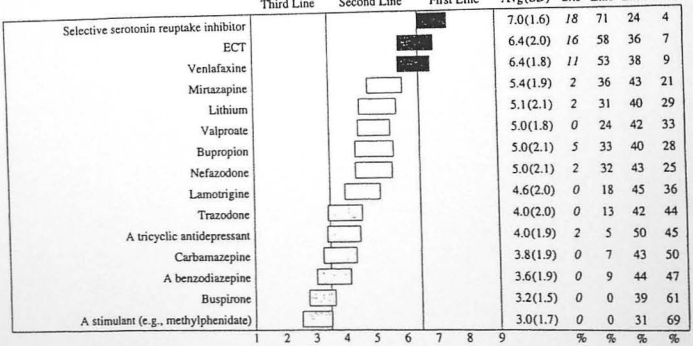
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Dysphoria/depression					
Oral olanzapine	6.9(1.5)	7	70	23	7
Oral clozapine	6.9(1.4)	9	65	33	2
Oral aripiprazole	6.7(1.5)	13	58	37	5
Oral risperidone	6.6(1.3)	5	62	36	2
Oral ziprasidone	6.4(1.9)	10	59	32	10
Oral quetiapine	6.0(1.5)	2	42	44	14
Long-acting injectable atypical	5.8(1.6)	0	40	48	13
Long-acting depot conventional injectable	3.9(1.9)	2	7	46	46
Oral low-potency conventional	3.6(1.7)	0	2	49	49
Oral mid-potency conventional	3.5(1.7)	0	5	45	50
Oral high-potency conventional	3.2(1.8)	0	2	34	64
Cognitive problems					
Oral risperidone	6.8(1.3)	2	67	30	2
Oral aripiprazole	6.7(1.4)	8	61	34	5
Oral olanzapine	6.5(1.6)	7	61	30	9
Oral ziprasidone	6.3(1.5)	5	57	36	7
Oral clozapine	6.2(1.5)	2	52	36	12
Oral quetiapine	5.9(1.4)	0	40	51	9
Long-acting injectable atypical	5.8(1.8)	0	49	36	15
Long-acting depot conventional injectable	4.0(1.9)	3	10	50	40
Oral high-potency conventional	3.3(1.7)	0	5	42	53
Oral mid-potency conventional	3.3(1.6)	0	5	37	59
Oral low-potency conventional	3.0(1.6)	0	2	37	60
Substance abuse					
Oral clozapine	6.8(1.7)	14	63	33	5
Oral risperidone	6.4(1.5)	3	60	33	8
Long-acting injectable atypical	6.2(1.7)	5	58	38	5
Oral aripiprazole	6.1(1.5)	9	40	54	6
Oral olanzapine	6.0(1.7)	5	44	46	10
Oral quetiapine	5.8(1.6)	0	39	49	12
Oral ziprasidone	5.8(1.7)	3	43	45	13
Long-acting depot conventional injectable	5.1(2.0)	0	29	51	20
Oral high-potency conventional	3.8(2.1)	0	9	42	49
Oral mid-potency conventional	3.7(2.0)	0	10	40	50
Oral low-potency conventional	3.7(1.9)	0	5	49	46
			%	%	%	%

27 **Adjunctive treatment for aggression/violence.** A patient with a psychotic disorder is being treated with an adequate dose of the most appropriate antipsychotic, but continues to display problems with ***aggression/violence*** to a degree that you believe requires adjunctive medication treatment. The patient has no significant extrapyramidal side effects (EPS) and no history of substance abuse. Please rate the appropriateness of the following adjunctive treatments



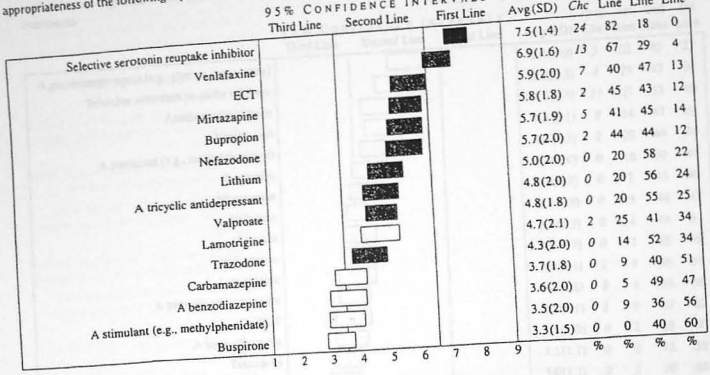
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Valproate	6.9(1.6)	*13*	71	27	2
Lithium	6.0(1.8)	9	44	44	11
Carbamazepine	5.5(1.6)	*0*	31	58	11
A beta-blocker	5.5(2.1)	2	43	36	20
A benzodiazepine	5.4(2.1)	7	35	44	21
Gabapentin	4.6(2.1)	2	20	41	39
ECT	4.5(2.1)	2	20	39	41
Lamotrigine	4.4(2.0)	5	14	44	42
Topiramate	4.2(2.0)	5	17	40	43
Buspirone	3.7(1.7)	*0*	5	44	51
Trazodone	3.6(1.9)	*0*	7	31	62
Diphenylhydantoin	3.2(1.7)	*0*	5	26	70
			%	%	%	%

28 **Adjunctive treatment for suicidal behavior.** A patient with a psychotic disorder is being treated with an adequate dose of the most appropriate antipsychotic, but continues to display ***suicidal behavior*** to a degree that you believe requires adjunctive medication treatment. The patient has no significant EPS and no history of substance abuse. Please rate the appropriateness of the following adjunctive treatments.



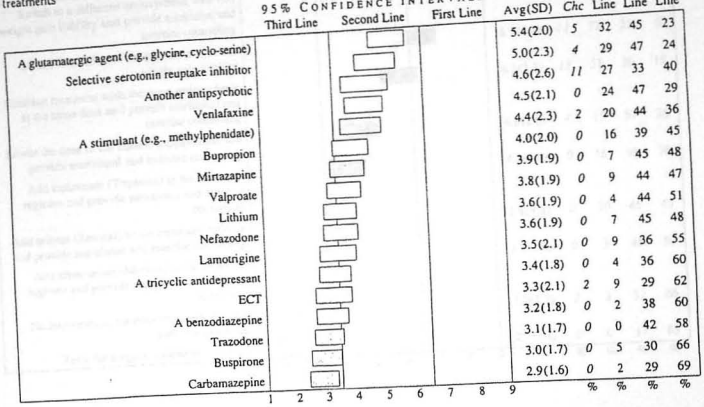
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Selective serotonin reuptake inhibitor	7.0(1.6)	*18*	71	24	4
ECT	6.4(2.0)	*16*	58	36	7
Venlafaxine	6.4(1.8)	*11*	53	38	9
Mirtazapine	5.4(1.9)	2	36	43	21
Lithium	5.1(2.1)	2	31	40	29
Valproate	5.0(1.8)	*0*	24	42	33
Bupropion	5.0(2.1)	5	33	40	28
Nefazodone	5.0(2.1)	2	32	43	25
Lamotrigine	4.6(2.0)	*0*	18	45	36
Trazodone	4.0(2.0)	*0*	13	42	44
A tricyclic antidepressant	4.0(1.9)	2	5	50	45
Carbamazepine	3.8(1.9)	*0*	7	43	50
A benzodiazepine	3.6(1.9)	*0*	9	44	47
Buspirone	3.2(1.5)	*0*	0	39	61
A stimulant (e.g., methylphenidate)	3.0(1.7)	*0*	0	31	69
			%	%	%	%

29 **Adjunctive treatment for dysphoria/depression.** A patient with a psychotic disorder is being treated with an adequate dose of the most appropriate antipsychotic, but continues to display ***dysphoria/depression*** to a degree that you believe requires adjunctive medication treatment. The patient has no significant EPS and no history of substance abuse. Please rate the appropriateness of the following adjunctive treatments



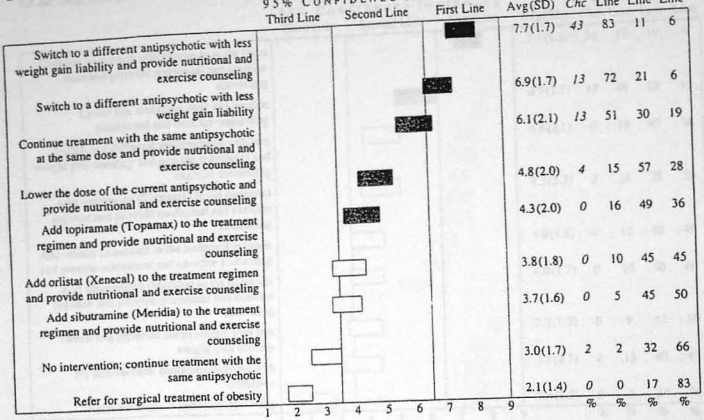
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Selective serotonin reuptake inhibitor	7.5(1.4)	*24*	82	18	0
Venlafaxine	6.9(1.6)	*13*	67	29	4
ECT	5.9(2.0)	7	40	47	13
Mirtazapine	5.8(1.8)	2	45	43	12
Bupropion	5.7(1.9)	5	41	45	14
Nefazodone	5.7(2.0)	2	44	44	12
Lithium	5.0(2.0)	*0*	20	58	22
A tricyclic antidepressant	4.8(2.0)	*0*	20	56	24
Valproate	4.8(1.8)	*0*	20	55	25
Lamotrigine	4.7(2.1)	2	25	41	34
Trazodone	4.3(2.0)	*0*	14	52	34
Carbamazepine	3.7(1.8)	*0*	9	40	51
A benzodiazepine	3.6(2.0)	*0*	5	49	47
A stimulant (e.g., methylphenidate)	3.5(2.0)	*0*	9	36	56
Buspirone	3.3(1.5)	*0*	0	40	60
			%	%	%

30 Adjunctive treatment for persisting negative symptoms. A patient with a psychotic disorder is being treated with an adequate dose of the most appropriate antipsychotic. The positive symptoms are well controlled, but the patient continues to display significant ***persisting negative symptoms*** to a degree that you believe requires adjunctive medication treatment. The patient has no significant EPS and no history of substance abuse. Please rate the appropriateness of the following adjunctive treatments



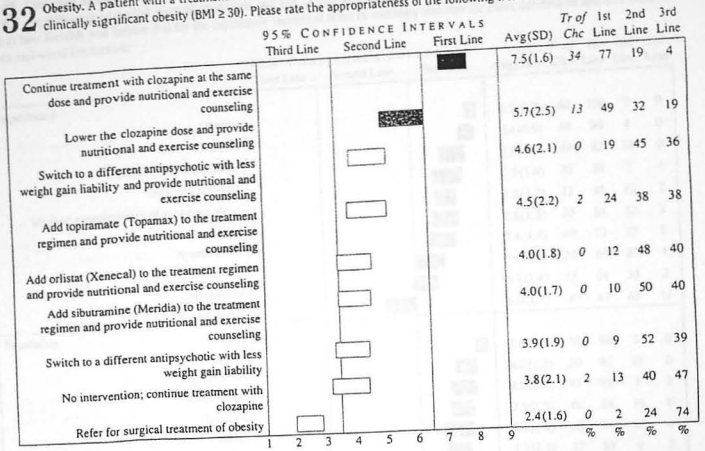
	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
			%	%	%
A glutamatergic agent (e.g., glycine, cyclo-serine)	5.4(2.0)	5	32	45	23
Selective serotonin reuptake inhibitor	5.0(2.3)	4	29	47	24
Another antipsychotic	4.6(2.6)	11	27	33	40
Venlafaxine	4.5(2.1)	0	24	47	29
A stimulant (e.g., methylphenidate)	4.4(2.3)	2	20	44	36
Bupropion	4.0(2.0)	0	16	39	45
Mirtazapine	3.9(1.9)	0	7	45	48
Valproate	3.8(1.9)	0	9	44	47
Lithium	3.6(1.9)	0	4	44	51
Nefazodone	3.6(1.9)	0	7	45	48
Lamotrigine	3.5(2.1)	0	9	36	55
A tricyclic antidepressant	3.4(1.8)	0	4	36	60
ECT	3.3(2.1)	2	9	29	62
A benzodiazepine	3.2(1.8)	0	2	38	60
Trazodone	3.1(1.7)	0	0	42	58
Buspirone	3.0(1.7)	0	5	30	66
Carbamazepine	2.9(1.6)	0	2	29	69

31 **Obesity.** A patient with a psychotic disorder has responded well to treatment with ***an antipsychotic other than clozapine*** but has clinically significant obesity (BMI ≥ 30). Please rate the appropriateness of the following treatment strategies.

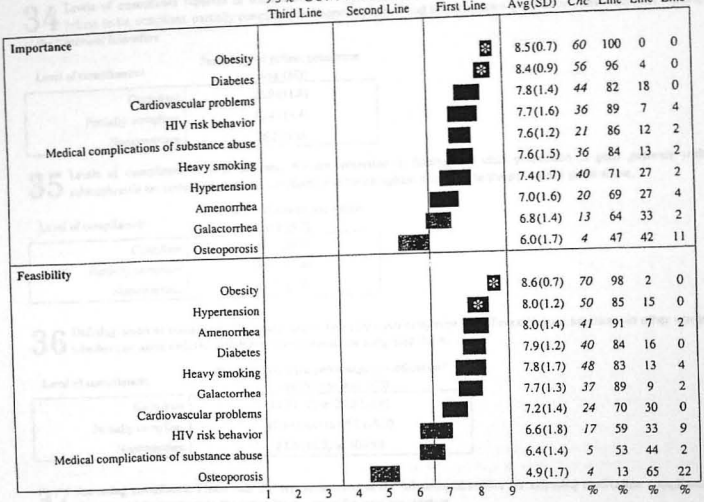


	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
Switch to a different antipsychotic with less weight gain liability and provide nutritional and exercise counseling	7.7(1.7)	43	83	11	6
Switch to a different antipsychotic with less weight gain liability	6.9(1.7)	13	72	21	6
Continue treatment with the same antipsychotic at the same dose and provide nutritional and exercise counseling	6.1(2.1)	13	51	30	19
Lower the dose of the current antipsychotic and provide nutritional and exercise counseling	4.8(2.0)	4	15	57	28
Add topiramate (Topamax) to the treatment regimen and provide nutritional and exercise counseling	4.3(2.0)	0	16	49	36
Add orlistat (Xenecal) to the treatment regimen and provide nutritional and exercise counseling	3.8(1.8)	0	10	45	45
Add sibutramine (Meridia) to the treatment regimen and provide nutritional and exercise counseling	3.7(1.6)	0	5	45	50
No intervention; continue treatment with the same antipsychotic	3.0(1.7)	2	2	32	66
Refer for surgical treatment of obesity	2.1(1.4)	0	0	17	83
			%	%	%	%

32 **Obesity.** A patient with a treatment-resistant psychotic disorder has responded well to treatment with ***clozapine*** but has clinically significant obesity (BMI ≥ 30). Please rate the appropriateness of the following treatment strategies.



33 Comorbid medical conditions. We are interested in knowing 1) how ***important*** you believe it is to routinely monitor for the following comorbid medical conditions and risk factors in a patient being treated with an antipsychotic medication and 2) how ***feasible*** you believe it is for the psychiatric treatment team to routinely monitor for these conditions and risk factors, given real-world limitations.



	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Importance					
Obesity	8.5(0.7)	*60*	100	0	0
Diabetes	8.4(0.9)	*56*	96	4	0
Cardiovascular problems	7.8(1.4)	*44*	82	18	0
HIV risk behavior	7.7(1.6)	*36*	89	7	4
Medical complications of substance abuse	7.6(1.2)	*21*	86	12	2
Heavy smoking	7.6(1.5)	*36*	84	13	2
Hypertension	7.4(1.7)	*40*	71	27	2
Amenorrhea	7.0(1.6)	*20*	69	27	4
Galactorrhea	6.8(1.4)	*13*	64	33	2
Osteoporosis	6.0(1.7)	*4*	47	42	11
Feasibility					
Obesity	8.6(0.7)	*70*	98	2	0
Hypertension	8.0(1.2)	*50*	85	15	0
Amenorrhea	8.0(1.4)	*41*	91	7	2
Diabetes	7.9(1.2)	*40*	84	16	0
Heavy smoking	7.8(1.7)	*48*	83	13	4
Galactorrhea	7.7(1.3)	*37*	89	9	2
Cardiovascular problems	7.2(1.4)	*24*	70	30	0
HIV risk behavior	6.6(1.8)	*17*	59	33	9
Medical complications of substance abuse	6.4(1.4)	*5*	53	44	2
Osteoporosis	4.9(1.7)	*4*	13	65	22
			%	%	%	%

We are using the following definitions of compliance levels in this survey:

- *Compliant:* only misses occasional doses (e.g., < 20% of prescribed medication)
- *Partially compliant:* misses more than occasional doses (e.g., 20%–80% of medication)
- *Noncompliant:* misses > 80% of medication

34 **Levels of compliance reported in the literature.** Please indicate what proportion of patients with schizophrenia you believe to be compliant, partially compliant, and noncompliant, using the definitions given above, based on your reading of the ***treatment literature***.

Level of compliance:	Percentage of patient population Avg (SD)
Compliant	28.0 (11.8)
Partially compliant	46.4 (14.4)
Noncompliant	26.2 (9.8)

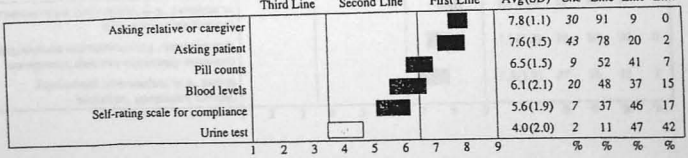
35 **Levels of compliance in your patients.** We are interested in finding out what proportion of ***your patients*** with schizophrenia are compliant, partially compliant, and noncompliant according to the definitions given above.

Level of compliance:	Percentage of patient population Avg (SD)
Compliant	43.1 (20.6)
Partially compliant	38.7 (17.4)
Noncompliant	19.2 (11.7)

36 **Defining levels of compliance.** We would like to know how you categorize compliance in your practice—in other words, whether you agree with the definitions of compliance we suggested above.

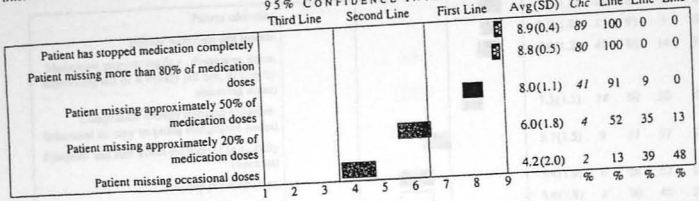
Level of compliance:	Patient misses what percentage of medication? Avg (SD) to Avg (SD)
Compliant	10.9 (7.2) to 25.5 (14.6)
Partially compliant	27.4 (16.4) to 64.7 (19.9)
Noncompliant	67.6 (19.3) to 100 (0)

37 **Assessing compliance.** Please rate the appropriateness of the following strategies for assessing medication compliance. Give your highest ratings to the strategies you consider most appropriate.



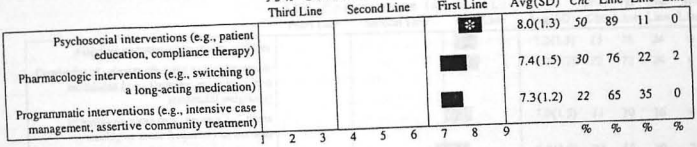
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Asking relative or caregiver	7.8(1.1)	*30*	91	9	0
Asking patient	7.6(1.5)	*43*	78	20	2
Pill counts	6.5(1.5)	*9*	52	41	7
Blood levels	6.1(2.1)	*20*	48	37	15
Self-rating scale for compliance	5.6(1.9)	*7*	37	46	17
Urine test	4.0(2.0)	*2*	11	47	42
		%	%	%	%

38 **When to intervene for compliance problems.** Please rate the appropriateness of intervening in the following clinical situations. Give a rating of 7, 8, or 9 to those situations in which you would usually intervene; a rating of 4, 5, or 6 to those situations in which you would sometimes intervene; and a rating of 1, 2, or 3 to those situations in which you would generally not intervene.



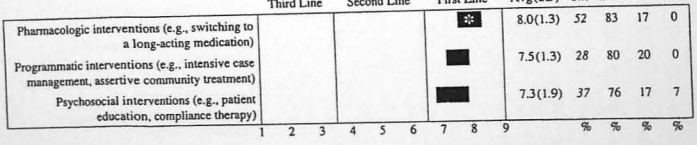
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Patient has stopped medication completely	8.9(0.4)	*89*	100	0	0
Patient missing more than 80% of medication doses	8.8(0.5)	*80*	100	0	0
Patient missing approximately 50% of medication doses	8.0(1.1)	*41*	91	9	0
Patient missing approximately 20% of medication doses	6.0(1.8)	*4*	52	35	13
Patient missing occasional doses	4.2(2.0)	*2*	13	39	48
			%	%	%	%

39 **Addressing partial compliance.** Please rate the appropriateness of the following strategies for addressing compliance problems in a patient who is ***partially compliant***. Give your highest ratings to the strategy or strategies you would try first (ties permitted).



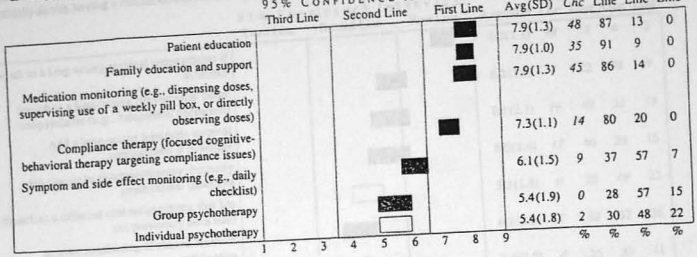
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Psychosocial interventions (e.g., patient education, compliance therapy)	8.0(1.3)	*50*	89	11	0
Pharmacologic interventions (e.g., switching to a long-acting medication)	7.4(1.5)	*30*	76	22	2
Programmatic interventions (e.g., intensive case management, assertive community treatment)	7.3(1.2)	22	65	35	0
			%	%	%	%

40 **Addressing noncompliance.** Please rate the appropriateness of the following strategies for addressing compliance problems in a patient who is ***noncompliant***. Give your highest ratings to the strategy or strategies you would try first (ties permitted).



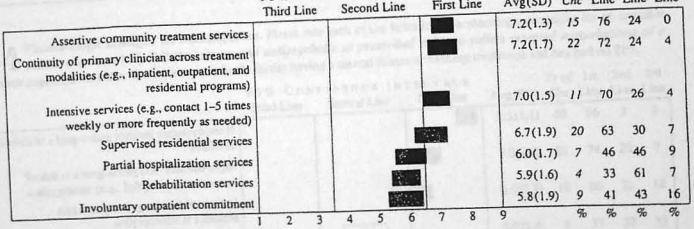
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Pharmacologic interventions (e.g., switching to a long-acting medication)	8.0(1.3)	*52*	83	17	0
Programmatic interventions (e.g., intensive case management, assertive community treatment)	7.5(1.3)	*28*	80	20	0
Psychosocial interventions (e.g., patient education, compliance therapy)	7.3(1.9)	*37*	76	17	7
			%	%	%	%

41 **Psychosocial services to improve compliance.** Please rate the importance of the following psychosocial services for a patient with compliance problems.



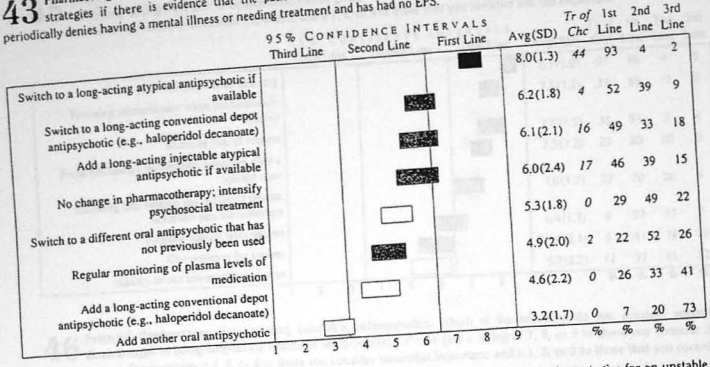
	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
Patient education	7.9(1.3)	48	87	13	0
Family education and support	7.9(1.0)	35	91	9	0
Medication monitoring (e.g., dispensing doses, supervising use of a weekly pill box, or directly observing doses)	7.9(1.3)	45	86	14	0
Compliance therapy (focused cognitive-behavioral therapy targeting compliance issues)	7.3(1.1)	14	80	20	0
Symptom and side effect monitoring (e.g., daily checklist)	6.1(1.5)	9	37	57	7
Group psychotherapy	5.4(1.9)	0	28	57	15
Individual psychotherapy	5.4(1.8)	2	30	48	22
		%	%	%	%

42 **Programmatic interventions to improve compliance.** Please rate the importance of the following programmatic interventions for a patient with compliance problems.



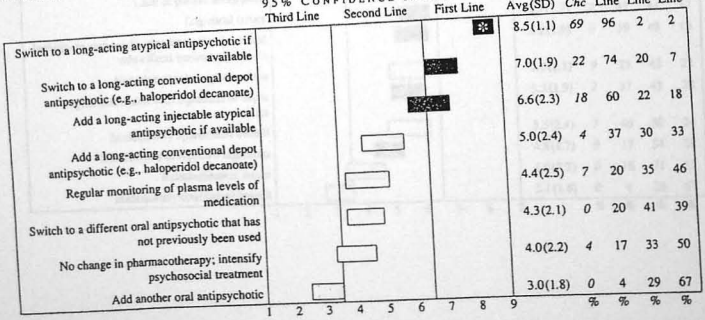
	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
Assertive community treatment services	7.2(1.3)	15	76	24	0
Continuity of primary clinician across treatment modalities (e.g., inpatient, outpatient, and residential programs)	7.2(1.7)	22	72	24	4
Intensive services (e.g., contact 1–5 times weekly or more frequently as needed)	7.0(1.5)	11	70	26	4
Supervised residential services	6.7(1.9)	20	63	30	7
Partial hospitalization services	6.0(1.7)	7	46	46	9
Rehabilitation services	5.9(1.6)	4	33	61	7
Involuntary outpatient commitment	5.8(1.9)	9	41	43	16
		%	%	%	%

43 **Pharmacologic strategies for partial compliance.** Please rate the appropriateness of each of the following pharmacologic strategies if there is evidence that the patient is only partially compliant with an oral antipsychotic. The patient periodically denies having a mental illness or needing treatment and has had no EPS.



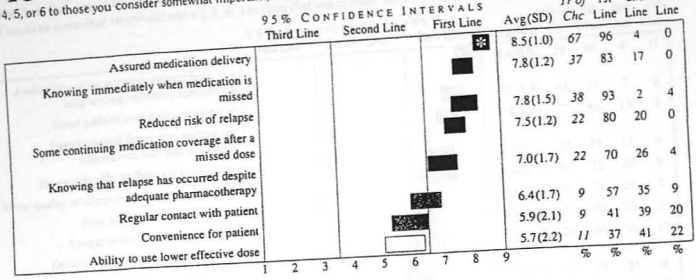
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Switch to a long-acting atypical antipsychotic if available	8.0(1.3)	*44*	93	4	2
Switch to a long-acting conventional depot antipsychotic (e.g., haloperidol decanoate)	6.2(1.8)	*4*	52	39	9
Add a long-acting injectable atypical antipsychotic if available	6.1(2.1)	*16*	49	33	18
No change in pharmacotherapy; intensify psychosocial treatment	6.0(2.4)	*17*	46	39	15
Switch to a different oral antipsychotic that has not previously been used	5.3(1.8)	*0*	29	49	22
Regular monitoring of plasma levels of medication	4.9(2.0)	*2*	22	52	26
Add a long-acting conventional depot antipsychotic (e.g., haloperidol decanoate)	4.6(2.2)	*0*	26	33	41
Add another oral antipsychotic	3.2(1.7)	*0*	7	20	73
			%	%	%	%

44 **Pharmacologic strategies for noncompliance.** Please rate each of the following pharmacologic strategies for an unstable patient who ***repeatedly fails to take an oral antipsychotic as prescribed*** and who suffers ***repeated exacerbations of a chronic psychotic disorder.*** The patient periodically denies having a mental illness or needing treatment and has had no EPS.



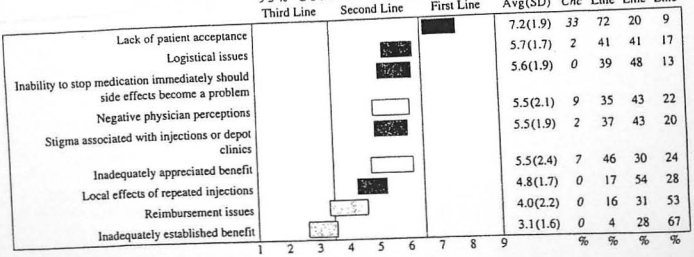
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Switch to a long-acting atypical antipsychotic if available	8.5(1.1)	*69*	96	2	2
Switch to a long-acting conventional depot antipsychotic (e.g., haloperidol decanoate)	7.0(1.9)	*22*	74	20	7
Add a long-acting injectable atypical antipsychotic if available	6.6(2.3)	*18*	60	22	18
Add a long-acting conventional depot antipsychotic (e.g., haloperidol decanoate)	5.0(2.4)	*4*	37	30	33
Regular monitoring of plasma levels of medication	4.4(2.5)	*7*	20	35	46
Switch to a different oral antipsychotic that has not previously been used	4.3(2.1)	*0*	20	41	39
No change in pharmacotherapy; intensify psychosocial treatment	4.0(2.2)	*4*	17	33	50
Add another oral antipsychotic	3.0(1.8)	*0*	4	29	67
			%	%	%	%

45 **Benefits of long-acting injectable antipsychotics.** Which of the following do you consider to be the greatest benefits of using long-acting injectable antipsychotics? Please give a rating of 7, 8, or 9 to those you consider the greatest benefits; a 4, 5, or 6 to those you consider somewhat important; and a 1, 2, or 3 to those that you consider not too important.



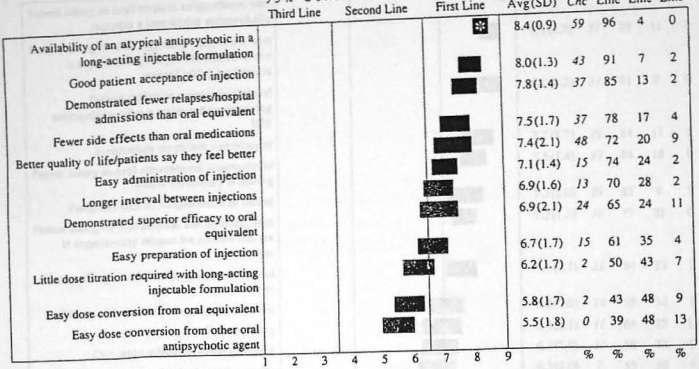
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Assured medication delivery	8.5(1.0)	*67*	96	4	0
Knowing immediately when medication is missed	7.8(1.2)	*37*	83	17	0
Reduced risk of relapse	7.8(1.5)	*38*	93	2	4
Some continuing medication coverage after a missed dose	7.5(1.2)	*22*	80	20	0
Knowing that relapse has occurred despite adequate pharmacotherapy	7.0(1.7)	*22*	70	26	4
Regular contact with patient	6.4(1.7)	*9*	57	35	9
Convenience for patient	5.9(2.1)	*9*	41	39	20
Ability to use lower effective dose	5.7(2.2)	*11*	37	41	22
			%	%	%	%

46 **Potential disadvantages of long-acting injectable antipsychotics.** Which of the following do you consider potential disadvantages to using long-acting injectable antipsychotics? Please give a rating of 7, 8, or 9 to those you consider the most important disadvantages; a 4, 5, or 6 to those you consider somewhat important; and a 1, 2, or 3 to those that you consider not too important.



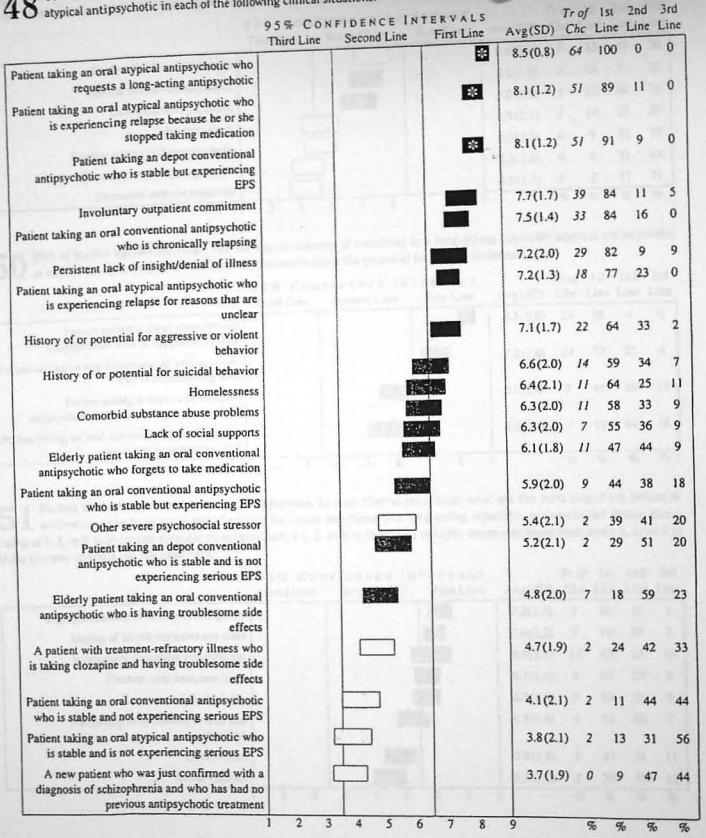
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Lack of patient acceptance	7.2(1.9)	*33*	72	20	9
Logistical issues	5.7(1.7)	*2*	41	41	17
Inability to stop medication immediately should side effects become a problem	5.6(1.9)	*0*	39	48	13
Negative physician perceptions	5.5(2.1)	*9*	35	43	22
Stigma associated with injections or depot clinics	5.5(1.9)	*2*	37	43	20
Inadequately appreciated benefit	5.5(2.4)	*7*	46	30	24
Local effects of repeated injections	4.8(1.7)	*0*	17	54	28
Reimbursement issues	4.0(2.2)	*0*	16	31	53
Inadequately established benefit	3.1(1.6)	*0*	4	28	67
			%	%	%	%

47 Factors favoring use of long-acting injectable antipsychotics. To which of the following characteristics would you attach the most importance in deciding whether or not to use a long-acting injectable antipsychotic? Please give a rating of 7, 8, or 9 to those that would be most important to you in deciding to use a long-acting injectable; a 4, 5, or 6 to those characteristics that would be somewhat important; and a 1, 2, or 3 to those that you consider not very important.

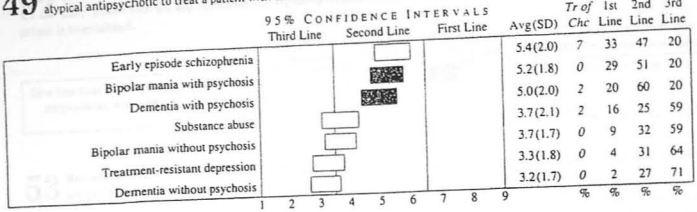


	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
			%	%	%
Availability of an atypical antipsychotic in a long-acting injectable formulation	8.4(0.9)	59	96	4	0
Good patient acceptance of injection	8.0(1.3)	43	91	7	2
Demonstrated fewer relapses/hospital admissions than oral equivalent	7.8(1.4)	37	85	13	2
Fewer side effects than oral medications	7.5(1.7)	37	78	17	4
Better quality of life/patients say they feel better	7.4(2.1)	48	72	20	9
Easy administration of injection	7.1(1.4)	15	74	24	2
Longer interval between injections	6.9(1.6)	13	70	28	2
Demonstrated superior efficacy to oral equivalent	6.9(2.1)	24	65	24	11
Easy preparation of injection	6.7(1.7)	15	61	35	4
Little dose titration required with long-acting injectable formulation	6.2(1.7)	2	50	43	7
Easy dose conversion from oral equivalent	5.8(1.7)	2	43	48	9
Easy dose conversion from other oral antipsychotic agent	5.5(1.8)	0	39	48	13

48 Use of a long-acting injectable atypical antipsychotic. Please rate the appropriate … long-acting injectable atypical antipsychotic in each of the following clinical situations.

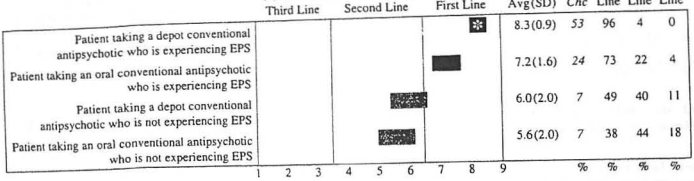


49 **Use of a long-acting injectable atypical antipsychotic.** Please rate the appropriateness of using a long-acting injectable atypical antipsychotic to treat a patient with each of the following conditions.



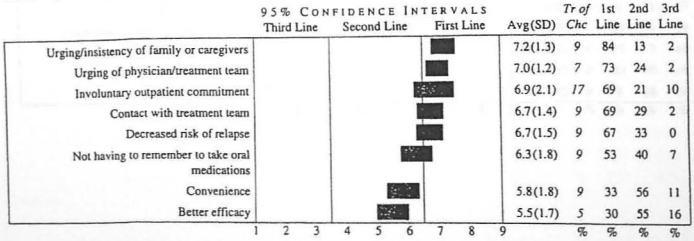
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Early episode schizophrenia	5.4(2.0)	7	33	47	20
Bipolar mania with psychosis	5.2(1.8)	0	29	51	20
Dementia with psychosis	5.0(2.0)	2	20	60	20
Substance abuse	3.7(2.1)	2	16	25	59
Bipolar mania without psychosis	3.7(1.7)	0	9	32	59
Treatment-resistant depression	3.3(1.8)	0	4	31	64
Dementia without psychosis	3.2(1.7)	0	2	27	71
		%	%	%	%

50 **Risk of tardive dyskinesia.** Please rate the appropriateness of switching to a long-acting injectable atypical antipsychotic in each of the following situations because of concern about the potential for tardive dyskinesia.



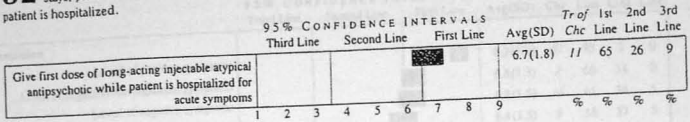
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Patient taking a depot conventional antipsychotic who is experiencing EPS	8.3(0.9)	53	96	4	0
Patient taking an oral conventional antipsychotic who is experiencing EPS	7.2(1.6)	24	73	22	4
Patient taking a depot conventional antipsychotic who is not experiencing EPS	6.0(2.0)	7	49	40	11
Patient taking an oral conventional antipsychotic who is not experiencing EPS	5.6(2.0)	7	38	44	18
		%	%	%	%

51 **Factors motivating patients to return for injections.** In your clinical experience, what are the most important factors in motivating patients to come into the clinic for repeat injections of a long-acting injectable antipsychotic? Please give a rating of 7, 8, or 9 to those you consider most important; a 4, 5, or 6 to those you consider somewhat important; and a 1, 2, or 3 to those that you consider not too important.



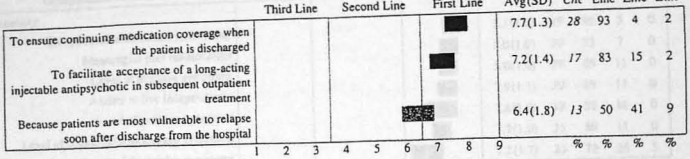
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Urging/insistency of family or caregivers	7.2(1.3)	9	84	13	2
Urging of physician/treatment team	7.0(1.2)	7	73	24	2
Involuntary outpatient commitment	6.9(2.1)	17	69	21	10
Contact with treatment team	6.7(1.4)	9	69	29	2
Decreased risk of relapse	6.7(1.5)	9	67	33	0
Not having to remember to take oral medications	6.3(1.8)	9	53	40	7
Convenience	5.8(1.8)	9	33	56	11
Better efficacy	5.5(1.7)	5	30	55	16
		%	%	%	%

52 **Use of a long-acting injectable atypical antipsychotic in the acute treatment setting.** Given shorter lengths of hospital stays, please rate the appropriateness of beginning treatment with a long-acting injectable atypical antipsychotic while a patient is hospitalized.



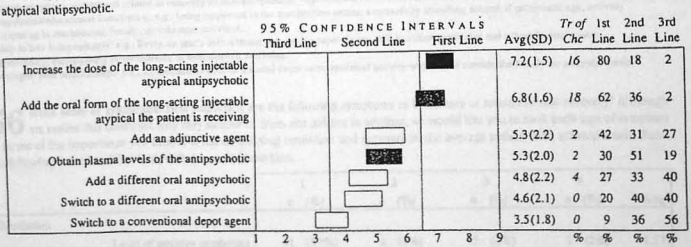
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Give first dose of long-acting injectable atypical antipsychotic while patient is hospitalized for acute symptoms	6.7(1.8)	*11*	65 %	26 %	9 %

53 **Reasons to begin injections during hospitalization.** If you would begin treatment with a long-acting injectable atypical antipsychotic while a patient is hospitalized, rate the relative importance of the following reasons for doing so.



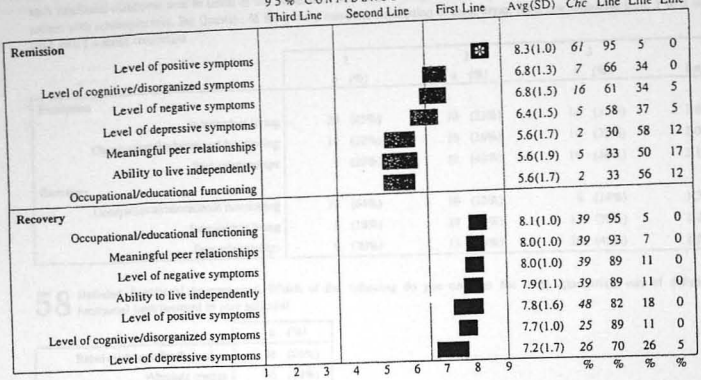
	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
To ensure continuing medication coverage when the patient is discharged	7.7(1.3)	*28*	93 %	4 %	2 %
To facilitate acceptance of a long-acting injectable antipsychotic in subsequent outpatient treatment	7.2(1.4)	*17*	83 %	15 %	2 %
Because patients are most vulnerable to relapse soon after discharge from the hospital	6.4(1.8)	*13*	50 %	41 %	9 %

54 **Strategies for relapse in a patient receiving a long-acting injectable atypical antipsychotic.** Please rate the appropriateness of each of the following strategies for a patient who relapses while receiving a long-acting injectable atypical antipsychotic.



	Avg(SD)	*Tr of Chc*	1st Line	2nd Line	3rd Line
Increase the dose of the long-acting injectable atypical antipsychotic	7.2(1.5)	*16*	80 %	18 %	2 %
Add the oral form of the long-acting injectable atypical the patient is receiving	6.8(1.6)	*18*	62 %	36 %	2 %
Add an adjunctive agent	5.3(2.2)	*2*	42 %	31 %	27 %
Obtain plasma levels of the antipsychotic	5.3(2.0)	*2*	30 %	51 %	19 %
Add a different oral antipsychotic	4.8(2.2)	*4*	27 %	33 %	40 %
Switch to a different oral antipsychotic	4.6(2.1)	*0*	20 %	40 %	40 %
Switch to a conventional depot agent	3.5(1.8)	*0*	9 %	36 %	56 %

55 **Defining remission and recovery.** We are interested in how you would define remission and recovery in your patients with schizophrenia. Please rate the appropriateness of each of the following as an indicator 1) of remission and 2) of recovery.*



	Avg(SD)	Tr of Chc	1st Line	2nd Line	3rd Line
Remission					
Level of positive symptoms	8.3(1.0)	61	95	5	0
Level of cognitive/disorganized symptoms	6.8(1.3)	7	66	34	0
Level of negative symptoms	6.8(1.5)	16	61	34	5
Level of depressive symptoms	6.4(1.5)	5	58	37	5
Meaningful peer relationships	5.6(1.7)	2	30	58	12
Ability to live independently	5.6(1.9)	5	33	50	17
Occupational/educational functioning	5.6(1.7)	2	33	56	12
Recovery					
Occupational/educational functioning	8.1(1.0)	39	95	5	0
Meaningful peer relationships	8.0(1.0)	39	93	7	0
Level of negative symptoms	8.0(1.0)	39	89	11	0
Ability to live independently	7.9(1.1)	39	89	11	0
Level of positive symptoms	7.8(1.6)	48	82	18	0
Level of cognitive/disorganized symptoms	7.7(1.0)	25	89	11	0
Level of depressive symptoms	7.2(1.7)	26	70	26	5
			%	%	%	%

*Some items in the list are adapted from the operational definition of recovery presented in Liberman RP, Kopelowicz A, Ventura J, Gutkind D. Operational criteria and factors related to recovery from schizophrenia. International Review of Psychiatry 2002;14:256–272.
Occupational/educational functioning: e.g., being employed in the competitive sector; successfully attending school; if retirement age, actively participating in recreational, family, or volunteer activities.
Ability to live independently: e.g., living on one's own without day-to-day supervision; able to initiate activities and schedule one's time independently; participating constructively in instrumental activities.
Meaningful peer relationships: e.g., an interaction such as a social event or recreational activity with a peer outside the family on a regular basis.

56 **Rank order of symptoms.** How important are the following symptoms as indicators of remission and recovery? Although we realize this construct may vary somewhat from one patient to another, we would like you to rank each type of symptom in terms of the importance you believe it has in defining remission and recovery in the average patient with schizophrenia. Rank the following from 1 to 4 (no ties), with 1 = most important.

	1		2		3		4		
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	Avg
Remission									
Level of positive symptoms	41	(89%)	2	(4%)	2	(4%)	1	(2%)	1.17
Level of cognitive/disorganized symptoms	4	(9%)	18	(39%)	11	(24%)	13	(28%)	2.68
Level of negative symptoms	1	(2%)	16	(35%)	14	(30%)	15	(33%)	2.89
Level of depressive symptoms	0	(0%)	11	(24%)	19	(41%)	16	(35%)	3.07
Recovery									
Level of positive symptoms	19	(41%)	10	(22%)	12	(26%)	5	(11%)	2.03
Level of cognitive/disorganized symptoms	15	(33%)	16	(35%)	9	(20%)	6	(13%)	2.09
Level of negative symptoms	13	(28%)	15	(33%)	11	(24%)	7	(15%)	2.22
Level of depressive symptoms	0	(0%)	8	(17%)	12	(26%)	26	(57%)	3.36

57 **Rank order of functional indicators.** How important are the following functional outcomes as indicators of remission and recovery? Although we realize this construct may vary somewhat from one patient to another, we would like you to rank each functional outcome area in terms of the importance you believe it has in defining remission and recovery in the average patient with schizophrenia. See Question 55 for a more complete description of these areas. Rank the following from 1 to 3 (no ties), with 1 = most important.

	1	2	3	
	n (%)	*n* (%)	*n* (%)	Avg
Remission				
Independent living	20 (45%)	10 (23%)	14 (32%)	1.86
Occupational/educational functioning	14 (32%)	16 (36%)	14 (32%)	2.00
Peer relationships	9 (20%)	19 (43%)	16 (36%)	2.16
Recovery				
Occupational/educational functioning	28 (64%)	10 (23%)	6 (14%)	1.50
Independent living	8 (18%)	19 (43%)	17 (39%)	2.20
Peer relationships	9 (20%)	15 (34%)	20 (45%)	2.25

58 **Defining functional improvement.** Which of the following do you consider the most appropriate way of defining functional improvement in your patients?

	n (%)
Relative change for the patient	38 (86%)
Absolute change	6 (14%)

59 **Symptom severity and duration.** We are interested in what level of symptom severity you use to define remission and recovery. Please check the level you consider most appropriate in each category and indicate how long this level of symptoms needs to be present before you would consider the patient in remission and in recovery.

No symptoms = score of 1 on the relevant items on the Brief Psychiatric Rating Scale (1–7 scale)
Mild symptoms = score of 2 or 3
Moderate = score of 4

	No symptoms	Mild symptoms	Moderate symptoms	How long must the symptoms be at this level? (Avg months)
	n (%)	*n* (%)	*n* (%)	
Remission				
Positive	15 (33%)	28 (62%)	2 (4%)	3.2
Cognitive/disorganized	6 (13%)	31 (69%)	8 (18%)	3.2
Negative	3 (7%)	28 (62%)	14 (31%)	3.5
Depressive	8 (18%)	33 (73%)	4 (9%)	3.1
Recovery				
Positive	28 (62%)	15 (33%)	2 (4%)	13.0
Cognitive/disorganized	20 (44%)	23 (51%)	2 (4%)	13.2
Negative	15 (33%)	28 (62%)	2 (4%)	12.8
Depressive	19 (42%)	23 (51%)	3 (7%)	12.0

60 **Duration of improvement in functional areas.** How long must significant improvement in the following functional areas be maintained for a patient to be considered in recovery? Please write in the minimum period (months or years) you would want to see the improvement maintained before you would consider the patient in recovery.

	Duration of improvement to be considered in recovery (months)
Employment	15.4
Independent living	14.7
Peer relationships	16.7

Commentary

Expert Consensus Guidelines for Optimizing Pharmacologic Treatment of Psychotic Disorders

John M. Kane, M.D.; Stefan Leucht, M.D.; and Daniel Carpenter, Ph.D.

The clinical trials literature provides guidance concerning a relatively small portion of the decision-making process clinicians face in practice. The *Expert Consensus Guidelines* employ a quantified methodology for measuring expert opinion as a means of filling the gap in areas where the clinical trial literature is scant, conflicting, or unclear. A key goal of the *Expert Consensus Guidelines for Optimizing Pharmacologic Treatment of Psychotic Disorders* was to address issues that have become increasingly complicated in the face of a growing class of antipsychotics, such as dosage, titration, sequencing of medications, and integration of new treatments into the existing armamentarium. The *Guidelines* were developed based on responses to a written questionnaire that was completed by leading American experts on the treatment of psychotic disorders. This commentary reviews key points discussed in the *Guidelines* and highlights interesting responses to the survey.

TREATMENT SELECTION AND DOSAGE

The experts overwhelmingly endorsed the atypical antipsychotics for the treatment of psychotic disorders. Risperidone was the top choice for first-episode and multi-episode patients, with the other newer atypicals rated first-line or high second-line depending on the clinical situation. Clozapine and a long-acting injectable atypical antipsychotic (when available) were other high second-line options for multi-episode patients (Guidelines 1A and 1B). The experts' dosing recommendations were relatively consistent with the package labeling for the drugs, although the experts indicated that, for olanzapine and quetiapine, they would use somewhat higher doses than those recommended by the manufacturer for acute usage (Guideline 2).

The responses concerning maintenance treatment and dose adjustments were especially interesting. In some cases, the experts recommended a lower dose for maintenance treatment than for acute treatment, but in other cases, they did not necessarily feel that the dose had to be lowered. The experts were more inclined to use lower doses during maintenance treatment with conventional antipsychotics, probably because of concern about the risk of tardive dyskinesia, while with the newer generation drugs, they were less concerned about tardive dyskinesia and may have felt less compelled to reduce dosage (Guideline 2). The experts' estimates of dose equivalency among the different antipsychotics were also relatively consistent with the labeling for the drugs and followed a linear pattern (Guidelines 5A and 5B).

With regard to dose adjustments when there is an inadequate response, many experts recommended increasing the dose, despite the fact that few data suggest that a dose increase is likely to enhance response. If there is an inadequate response, over 90% of the experts would increase the dose of clozapine and olanzapine, over 80% would increase the dose of quetiapine and risperidone, and approximately 60% would increase the dose of aripiprazole, ziprasidone, and the decanoate formulations of fluphenazine and haloperidol before switching to a different agent (Guideline 7).

TRIAL LENGTH

Drug trial duration is an important issue: we still have few valid data concerning the length of an adequate trial of antipsychotics. The experts indicated that an adequate trial duration in patients who are showing little or no response to initial antipsychotic treatment would be 3 to 6 weeks. If a patient had a partial response, the experts would be likely to wait somewhat longer—4 to 10 weeks—before considering another antipsychotic treatment (Guideline 4).

From the Department of Psychiatry, The Zucker Hillside Hospital, Glen Oaks, N.Y. (Drs. Kane and Leucht); Psychiatrische Klinik, Technische Universität München, Munich, Germany (Dr. Leucht); and Comprehensive NeuroScience, Inc., White Plains, N.Y. (Dr. Carpenter).

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Corresponding author and reprints: Daniel Carpenter, Ph.D., Comprehensive Neuroscience, 21 Bloomingdale Road, White Plains, NY 10605 (e-mail: dcarpenter@cnsmail.com).

SWITCHING STRATEGIES

Most experts recommended increasing the dose of a medication before switching to another treatment. If it is decided to switch to a different antipsychotic, the experts were consistent in recommending cross-titration when switching between the oral antipsychotics.

Cross-titration was a first-line recommendation when switching to clozapine and a high second-line option, along with overlap and taper, when switching to another oral atypical antipsychotic (Guideline 7D). Whenever possible, cross-titration is preferable to rapid discontinuation or rapid initiation. Some patients may have withdrawal effects that could be subtle or could be misdiagnosed, and clinicians should try to be cautious and discontinue any psychotropic drug slowly. In switching to a long-acting injectable antipsychotic, the experts recommended continuing treatment with the oral antipsychotic, either at the same dose or at a gradually tapered dose, until therapeutic levels of the injectable agent are reached, to ensure continuous medication coverage.

USE OF THERAPEUTIC DRUG MONITORING

Monitoring of plasma levels is used fairly common with clozapine and haloperidol, but not with the other antipsychotics. When asked for which antipsychotics plasma levels were available to the respondents and how they used such levels to adjust dosing, over 50% of respondents said that plasma levels for clozapine, haloperidol, and haloperidol decanoate were available to them, and over 50% used these levels to monitor compliance; 88% of the experts used plasma levels of clozapine and over 50% used levels of haloperidol to adjust dose levels in patients with inadequate response or problematic side effects (Guideline 3).

RELAPSE

Unfortunately, drug research often stops after determining whether an antipsychotic is efficacious in reducing acute positive symptoms. Few data are available concerning sequential treatment steps, including management of relapse. Given the lack of available data concerning managing relapse, the opinions of experts are highly relevant. However, clinicians often seem uncertain when deciding how to treat someone who relapses despite taking medication.

Concern remains as to how adequately clinicians can determine the level of a patient's compliance prior to relapse. Although the experts' responses clearly indicate that they believe long-acting injectable antipsychotics have an important role in the management of relapse, the editors note that such agents may come to play an even more prominent role in long-term management. Long-acting injectable atypical antipsychotics were recommended as a low second-line option when treating a compliant patient who relapses. However, for patients about whose compliance clinicians are unsure of or who are noncompliant, the experts consider switching to a long-acting atypical antipsychotic as a first-line treatment recommendation (Guideline 8).

SWITCHING ANTIPSYCHOTICS

Few data address alternatives when switching antipsychotics. Although the experts certainly confirm the value of clozapine, there was some disparity in how many different medications from which classes they would try before switching a patient to clozapine. There still may be too much hesitancy to use clozapine. The most appropriate point at which to switch to clozapine remains controversial, and clinicians may want to consider fewer trials of other agents before switching patients to clozapine.

Risperidone was overwhelmingly listed as the top drug that clinicians would switch to after an inadequate response (Guideline 7B). Clozapine and olanzapine were listed as top choices when trying a second medication.

MONITORING FOR COMORBID CONDITIONS AND RISK FACTORS

Obesity is commonly associated with schizophrenia,[1] and patients with schizophrenia also appear to have an increased risk of diabetes. Given the fact that many antipsychotics can contribute to weight gain[2] and considering the lipophilic nature of many antipsychotics, clinicians should pay close attention to weight gain and lipid levels in patients with schizophrenia being treated with antipsychotics. Obesity and diabetes were considered the most important conditions to monitor for, followed by cardiovascular problems, HIV risk behavior, substance abuse, smoking, hypertension, and amenorrhea.

NONCOMPLIANCE

Clinicians rated the compliance levels of their own patients as substantially higher (43%) than that of patients reported in the literature (28%) (Guideline 11B). It is typical for us as clinicians to assume that our patients are more compliant than other patients, but these results show how easily clinicians can overestimate compliance in their patients. Compliance was defined as when a patient misses fewer than 20% of his or her medication doses, although the respondents preferred using a definition of missing less than 25% (Guideline 11A).

For patients who are perceived to be partially compliant, the experts consider psychosocial interventions the first choice. For patients who show evidence of noncompliance, the experts consider pharmacologic interventions

the first choice. Preferred psychosocial interventions were defined as patient education, family education and support, medication monitoring, and compliance therapy, which consisted of focused cognitive-behavioral therapy targeting compliance issues. Symptom and side effect monitoring and individual and group psychotherapy were also listed as options to be considered (Guideline 14B). The first-line pharmacologic strategy for partially compliant and noncompliant patients was switching to a long-acting atypical antipsychotic (Guideline 14C). It would be our preference to combine both psychosocial and pharmacologic interventions whenever possible, no matter what the level of compliance.

AGGRESSION, VIOLENCE, AND SUBSTANCE ABUSE

Aggression, violence, and substance abuse can complicate the course of mental illness. Although the experts seemed to assume that those complications were not due to noncompliance, this is an assumption that physicians should not necessarily make. Given the very strong possibility that partial compliance may be contributing to the emergence of aggressive or violent behavior, we would have liked to see long-acting injectable drugs play more of a role in the management of these problems, even though long-acting injectable atypical antipsychotics and olanzapine were only rated as high second-line options for aggression and violence. Clozapine and risperidone were the first-line choices for aggression and violence (Guideline 10A). Valproate and lithium were rated high second-line as adjunctive treatments for aggression and violence (Guideline 10B).

ADJUNCTIVE TREATMENT

Adjunctive treatment is an interesting topic because so many patients with psychotic disorders receive adjunctive treatments. However, the expert panel did not recommend any adjunctive treatments as first-line for complicating conditions, with the exception of selective serotonin reuptake inhibitors for dysphoria or depression.

CONCLUSION

Since the clinical trials literature can answer only some of the questions involved in the clinical decision-making process, *Expert Consensus Guidelines* can play an important role in filling in the gaps in the literature. The *Guidelines* also reveal expert opinions that are sometimes surprising concerning, for example, dosing and plasma levels, maintenance treatment, obesity, compliance, and the use of adjunctive treatment. We hope that the treatment recommendations presented in these *Guidelines*, which are based on an aggregate of expert opinion, when used in combination with the most up-to-date empirical data from clinical trials, will enable clinicians to provide the best treatment possible for their patients.

REFERENCES

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1. All of the following were recommended as first-line treatments for first-episode patients with predominantly positive symptoms *except*:

a. Risperidone
b. Olanzapine
c. Clozapine
d. Aripiprazole

2. For a first-episode patient with predominantly negative symptoms, the experts recommended use of oral conventional antipsychotics.

a. True
b. False

3. In a patient with a history of previous psychotic episodes, the experts did not recommend the use of _____ antipsychotics and gave only very limited support to the use of _____ antipsychotics.

a. Mid- or low-potency conventional; oral high-potency conventional
b. Oral atypical; mid- or low-potency conventional
c. Oral high-potency conventional; injectable atypical
d. Depot conventional; mid- or low-potency conventional

4. Clinicians recommended using slightly lower doses of antipsychotics during acute treatment than during maintenance treatment.

a. True
b. False

5. Over 50% of experts responded that they had plasma levels available to them only for:

a. Risperidone, ziprasidone, and haloperidol
b. Clozapine, quetiapine, and aripiprazole
c. Clozapine, haloperidol, and haloperidol decanoate
d. Aripiprazole, risperidone, and haloperidol decanoate

6. Adequate trial duration for a patient with little or no response to an initial antipsychotic was listed as:

a. 4 to 10 weeks
b. 1 to 2 weeks
c. 3 to 6 weeks
d. 5 to 11 weeks

7. Among clinicians, _____ would only sometimes consider a patient's weight in adjusting the dosage.

a. 75%
b. 45%
c. 15%
d. 89%

8. Before switching the antipsychotic, over 90% of experts said they would first increase doses of _____ and _____.

a. Clozapine and olanzapine
b. Quetiapine and risperidone
c. Aripiprazole and ziprasidone
d. Fluphenazine decanoate and haloperidol decanoate

9. All of the following were listed as the first medications that would be switched to after an inadequate response to another medication *except*:
   a. Risperidone
   b. Olanzapine
   c. Ziprasidone
   d. Perphenazine

10. Overlap and taper was listed as a first-line recommendation when switching to clozapine from another oral antipsychotic agent.
   a. True
   b. False

11. To manage relapse when the clinician has reason to believe the patient has been noncompliant with an oral antipsychotic regimen, the first-line recommendation is to:
   a. Switch to a long-acting conventional depot
   b. Switch to a long-acting injectable atypical antipsychotic
   c. Switch to a different oral antipsychotic
   d. Add an adjunctive agent

12. In treating complicating problems such as aggression and violence, all of the following were listed as first-line and high second-line recommendations *except*:
   a. Haloperidol
   b. Risperidone
   c. A long-acting injectable atypical antipsychotic
   d. Clozapine

13. In selecting adjunctive treatment for patients with complicating problems, physicians had no first-line treatment recommendations *except* ____ for depression:
   a. Electroconvulsive therapy
   b. Glutamatergic agent
   c. Selective serotonin reuptake inhibitor
   d. Another antipsychotic

14. When asked to rate compliance (missing < 20% of medication doses), physicians often rated their own patients' compliance as substantially higher than that of patients reported in literature.
   a. True
   b. False

15. Programmatic interventions were listed as the intervention of choice when treating noncompliant patients.
   a. True
   b. False

16. Preferred programmatic or psychosocial interventions to improve compliance included all of the following *except*:
   a. Patient education
   b. Family education and support
   c. Supervised residential services
   d. Medication monitoring

CME Registration Form

Optimizing Pharmacologic Treatment of Psychotic Disorders

Circle the one correct answer for each question.

1.	a	b	c	d	9.	a	b	c	d
2.	a	b			10.	a	b		
3.	a	b	c	d	11.	a	b	c	d
4.	a	b			12.	a	b	c	d
5.	a	b	c	d	13.	a	b	c	d
6.	a	b	c	d	14.	a	b		
7.	a	b	c	d	15.	a	b		
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Payment

No payment is necessary as this activity is free.

Please evaluate the effectiveness of this CME activity by answering the following questions.

1. Was the educational content relevant to the stated educational objectives? ❑ Yes ❑ No
2. Did this activity provide information that is useful in your clinical practice? ❑ Yes ❑ No
3. Was the format of this activity appropriate for the content being presented? ❑ Yes ❑ No
4. Did the method of presentation hold your interest and make the material easy to understand? ❑ Yes ❑ No
5. Achievement of educational objectives:
   A. Enabled me to review differences among atypical antipsychotics in terms of response to treatment. ❑ Yes ❑ No
   B. Enabled me to discuss recommended dosing guidelines for the atypical antipsychotics. ❑ Yes ❑ No
   C. Enabled me to describe several strategies for managing antipsychotic-treated patients with an inadequate response to first-line treatment. ❑ Yes ❑ No
6. Did this CME activity provide a balanced, scientifically rigorous presentation of therapeutic options related to the topic, without commercial bias? ❑ Yes ❑ No
7. Does the information you received from this CME activity confirm the way you presently manage your patients? ❑ Yes ❑ No
8. Does the information you received from this CME activity change the way you will manage your patients in the future? ❑ Yes ❑ No
9. Please offer comments and/or suggested topics for future CME activities.

   _____

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10. How much time did you spend completing this CME activity?

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Exhibit A
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B C D

DRUGDEX-EV 1728

MICROMEDEX
DRUGDEX® Evaluations

Database updated February 2007

OLANZAPINE

0.0 Overview

1) Class
   a) This drug is a member of the following class(es):
      Antipsychotic
      Thienobenzodiazepine
2) Dosing Information
   a) Adult
      1) Agitation - Bipolar I disorder - Mania
         a) initial, 10 mg INTRAMUSCULARLY; lower dose of 5 mg or 7.5 mg may be used if indicated. Usual effective dosage range is 2.5 mg to 10 mg
         b) subsequent doses may be given INTRAMUSCULARLY in doses up to 10 mg. Maximal dosing, three 10 mg doses given 2 to 4 hours apart (monitor for orthostatic hypotension prior to the administration of repeated doses)
      2) Agitation - Schizophrenia
         a) initial, 10 mg INTRAMUSCULARLY; lower dose of 5 mg or 7.5 mg may be used if indicated. Usual effective dosage range is 2.5 mg to 10 mg
         b) subsequent doses may be given INTRAMUSCULARLY in doses up to 10 mg. Maximal dosing, three 10 mg doses given 2 to 4 hours apart (monitor for orthostatic hypotension prior to the administration of repeated doses)
      3) Bipolar disorder, acute, Mixed or manic with or without psychotic features
         a) (monotherapy) 10-15 mg ORALLY once a day; may increase/decrease dosage by 5 mg/day at intervals of at least 1 day. Usual effective dosage range is 5-20 mg/day; the safety of doses above 20 mg/day has not been evaluated in clinical trials
      4) Bipolar disorder, acute - Bipolar disorder, manic episode
         a) (in combination with lithium or valproate) 10 mg ORALLY once a day; usual effective dosage range is 5-20 mg/day; the safety of doses above 20 mg/day has not been evaluated in clinical trials
      5) Bipolar disorder, Maintenance
         a) (monotherapy) 5 to 20 mg ORALLY per day (after achieving a responder status for an average duration of two weeks)
      6) Schizophrenia
         a) 5-10 mg ORALLY once a day (target dose of 10 mg/day within several days); may increase/decrease dosage by 5 mg/day at intervals of at least 1 week. Usual effective dosage range is 10-15 mg/day; the safety of doses above 20 mg/day has not been evaluated in clinical trials
   b) Pediatric

1) safety and effectiveness in pediatric patients have not been established
3) Contraindications
a) hypersensitivity to olanzapine products
4) Serious Adverse Effects
a) Tardive dyskinesia
b) Water intoxication syndrome
5) Clinical Applications
a) FDA Approved Indications
1) Agitation - Bipolar I disorder - Mania
2) Agitation - Schizophrenia
3) Bipolar disorder, acute, Mixed or manic with or without psychotic features
4) Bipolar disorder, acute - Bipolar disorder, manic episode
5) Bipolar disorder, Maintenance
6) Schizophrenia

1.0 Dosing Information

Drug Properties
Storage and Stability
Adult Dosage
Pediatric Dosage

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)
B) Synonyms
Olanzapine
C) Physicochemical Properties
1) Molecular Weight
a) 312.44 (Prod Info Zyprexa(R), 2004)
2) Solubility
a) Practically insoluble in water (Prod Info Zyprexa(R), 2004)

1.2 Storage and Stability

A) Oral route
1) Store at controlled room temperature, 20 to 25 degrees C (68 to 77 degrees F) (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004a). Protect from light and moisture
B) Extemporaneous Formulation - Oral route
1) Olanzapine is practically insoluble in water. A 1-milligram per milliliter (mg/mL) suspension prepared from crushed tablets in a pediatric mixture base (containing syrup, carboxymethylcellulose and parabens) was found to be stable for 14 days when stored in a refrigerator and protected from light (Harvey et al, 2000). Care in preparation and administration is advised as olanzapine may be irritating to the eye and can cause contact dermatitis. When breaking or crushing olanzapine tablets it is recommended to wear gloves and wash hands before and after exposure (Personal Communication, 2001).

1.3 Adult Dosage

1.3.1 Normal Dosage

1.3.1.A Intramuscular route

1.3.1.A.1 Agitation - Manic bipolar I disorder - Schizophrenia

20 mg/day
83%
4) D(2) receptor occupancy was measured at 88% in a single patient taking olanzapine 40 mg/day.

B) REVIEW ARTICLES
1) A review of the side effects of antipsychotic medications, including olanzapine, in the elderly is available. Of particular importance in this population is the high incidence of sedation and abnormal gait which can lead to falls and other accidents (Masand, 2000).
2) Reviews of the adverse effects related to olanzapine are available. The management of these side effects, including sedation, tremor, dry mouth, increased appetite, and weight gain is discussed (Zarate, 2000). Safety data from comparative clinical trials is also available (Conley & Meltzer, 2000).
3) Comprehensive reviews on olanzapine have been published (Tollefson & Kuntz, 1999; Falsetti, 1999; Bever & Perry, 1998a; Kando et al, 1997a).
4) The pharmacologic properties and therapeutic efficacy of olanzapine in the management of psychoses are reviewed (Fulton & Goa, 1997).
5) An indepth overview of the efficacy of olanzapine in clinical trials has been published (Beasley et al, 1997).
6) A review of clinical trails evaluating olanzapine dosing is available (Nemeroff, 1997).
7) A study reviewing the safety profile of olanzapine has been published (Beasley et al, 1997a).
8) The use of atypical antipsychotic medications in adults (Markowitz et al, 1999; Brown et al, 1999), older adults (Chan et al, 1999), and children (Malone et al, 1999; Lewis, 1998; Toren et al, 1998) has been reviewed.
9) The mechanisms of neuroleptic-induced extrapyramidal symptoms and tardive dyskinesia and their relationship to atypical antipsychotic agents was reviewed (Glazer, 2000).
10) A review of atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease was completed (Friedman & Factor, 2000).

4.5 Therapeutic Uses

4.5.A Adverse reaction to cannabis - Induced psychotic disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
As effective as haloperidol

3) Adult:
a) Olanzapine was as effective as haloperidol in the treatment of cannabis-induced psychotic disorder (Berk et al, 1999). In a double-blind study, patients with a psychotic episode associated with cannabis use were randomized to receive either olanzapine 10 milligrams (n=15) or haloperidol 10 mg (n=15). After 4 weeks there was a significant improvement in both groups as compared to baseline measured on the Brief Psychiatric Rating Scale (p=0.0002 for olanzapine, p=0.0001 for haloperidol). There was no significant difference between the 2 groups. Olanzapine was associated with fewer extrapyramidal side effects.

4.5.B Agitation - Manic bipolar I disorder - Schizophrenia

FDA Labeled Indication
1) Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Intramuscular olanzapine is indicated for the treatment of AGITATION ASSOCIATED WITH SCHIZOPHRENIA OR BIPOLAR I MANIA
Oral olanzapine has been used for the treatment of acute agitation in patients with schizophrenia or bipolar disorder

3) Adult:
a) Intramuscular olanzapine effectively reduced symptoms of agitation in patients with schizophrenia or bipolar disorder in 3 short-term, placebo-controlled trials. The primary efficacy measure in these trials was the change in the Positive and Negative Syndrome Scale (PANSS) Excited Component from baseline to 2 hours post-injection. The mean baseline PANSS Excited Component score was 18.4 (range, 13 to 32) out of a maximum score of 35, suggesting mostly moderate levels of agitation. The first trial included agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270). Four fixed intramuscular olanzapine doses (2.5 mg, 5 mg, 7.5 mg and 10 mg) were evaluated and all doses were significantly better as compared with placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the 5 mg, 7.5 mg, and 10 mg doses. In a second placebo-controlled trial, agitated inpatients with schizophrenia (n=311), received a fixed 10 mg dose of intramuscular olanzapine or placebo. Again, olanzapine was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. In the third trial, agitated inpatients with Bipolar I Disorder (and acute manic or mixed episode with or without psychotic features) (n=201), received one fixed intramuscular olanzapine dose of 10 mg or placebo. Olanzapine was significantly better as compared with placebo on the primary outcome measure. Examination of population subsets such as age, race, and gender did not show any differential responsiveness on the basis of these sub-groupings (Prod Info Zyprexa(R) IntraMuscular, 2004).
b) Rapid initial dose escalation (RIDE) of olanzapine was effective in the treatment of acute agitation in patients with schizophrenia or bipolar disorder. In a randomized, double-blind, multicenter study, acutely agitated patients (n=148) received either RIDE therapy (olanzapine 20 to 40 milligrams (mg)/day for 2 days, then 20 to 30 mg/day for 2 days) or "usual clinical practice" (UCP) therapy (olanzapine 10 mg/day plus lorazepam as needed) for 4 days of blinded treatment before entering an open-label phase in which all patients received olanzapine 5 to 20 mg/day for 3 days. Both the RIDE and UCP therapies produced significant mean reductions in the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) score from baseline to 24 hours (mean reduction, -7.01 and -5.51, respectively, p less than 0.001, both values). However, patients in the RIDE group showed greater improvements in agitation those in the UCP group on days 2, 3, and 4 as measured by mean changes in PANSS-EC scores (p=0.03, p=0.08, p=0.001, respectively). Adverse events were similar in both groups with headache, somnolence, dizziness, nervousness, and insomnia being reported most frequently reported (Baker et al, 2003).

4.5.C Alzheimer's disease - Psychotic disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Olanzapine doses of 5 or 10 mg daily were safe and effective in decreasing behavioral and psychotic symptoms associated with Alzheimer's disease in elderly patients
Somnolence and gait disturbances increased in olanzapine-treated patients

3) Adult:
a) Low doses of olanzapine (5 milligrams (mg) or 10 mg daily (QD)) were safe and significantly superior to placebo in the treatment of behavioral and psychotic symptoms associated with Alzheimer's disease in elderly patients. In a 6-week, multicenter, double-blind, placebo-controlled trial, 206 nursing home residents were randomized to receive a fixed daily dose of olanzapine 5, 10, or 15 mg or placebo. Efficacy was measured using the sum of scores for agitation, aggression, hallucinations, and delusion items ("Core Total") of the Neuropsychiatric Inventory-Nursing Home scoring system and

the Occupational Disruptiveness score, to assess patient-related caregiver distress. Core Totals were significantly improved in patients receiving 5 mg and 10 mg doses, while Occupational Disruptiveness scores were significantly reduced in those receiving 5 mg doses. Somnolence occurred significantly more often in patients receiving olanzapine than placebo. Gait disturbances were more common in those receiving olanzapine 5 or 15 mg daily. Frequencies of significant cognitive impairment, increased extrapyramidal symptoms, and central anticholinergic effects in olanzapine-treated patients were similar to those of placebo-treated patients (Street et al, 2000). In an 18-month, open extension of this trial with 105 patients, behavioral and psychotic symptoms continued to decrease, with the final average Core Total score having decreased to 6 from 7.9 at the start of the open trial (p=0.002). Nearly half of the patients showed a 50% or greater additional reduction in Core Total score. Measures of cognitive status showed no change. Levels of akathisia continued to improve (p=0.018); extrapyramidal symptoms and parkinsonian symptoms did not increase. Although weight did not change significantly for the group overall, some individuals had significant weight gain (average, 4.3 kilograms) or weight loss (average, 4.4 kilograms). Somnolence and accidental injury continued to be the most common adverse events. Five milligrams was the modal dose (the dose prescribed for a patient for the most number of days) for two-thirds of the patients during the open trial (Street et al, 2001).

4.5.D Anorexia nervosa

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effective treatment in small, open-label trial in patients with anorexia nervosa
Effective in 1 case report of anorexia nervosa with obsessive-compulsive symptoms
See Drug Consult reference: ANOREXIA NERVOSA - DRUG THERAPY

3) Adult:
a) Weight gain occurred in patients with anorexia nervosa when treated with olanzapine. In a small, open-label trial, patients with anorexia nervosa (restricting or binge/purge subtype) without schizophrenia, schizoaffective disorder or bipolar disorder received olanzapine 10 milligrams (mg) once daily for 10 weeks (n=18). Patients attended weekly group psychoeducational sessions. Of the 14 patients that completed the study, 10 patients had a mean weight gain of 8.75 pounds and 4 patients lost an average of 2.25 pounds. Of these patients, those that gained weight had significantly different mean weights at day 1 as compared to both week 5 and week 10 (p=0.0195 and p=0.0092, respectively). Three patients attained their ideal body weight. The most common adverse event was sedation. Controlled studies are needed to substantiate these findings (Powers et al, 2002).

b) Body weight, appetite, and self-image were restored with olanzapine 5 milligrams (mg) daily in 3 women. Patients with a 12 year or more history of anorexia nervosa gained 9 to 19 kilograms over several months. At the time of publication, patients continued to receive olanzapine 5 mg daily. Because it takes a few weeks before a full antipsychotic effect is achieved, patients should be encouraged to continue with olanzapine therapy within the first 2 months (Jensen & Mejlhede, 2000).

c) A 49-year-old woman with anorexia nervosa and obsessive- compulsive symptoms improved with olanzapine therapy (Hansen, 1999). The woman's obsessive-compulsive problems were mainly fear of food contamination, preoccupation with nutritional issues, confusion, and seriously disturbed body image. She had no insight into her problems and was depressed. She weighed 31.2 kilograms when she was started on olanzapine 5 milligrams daily. Over the following months, her confusion cleared and her insight changed markedly. Approximately 6 months later her weight had increased to 53.1 kg.

4.5.E Anxiety - Dementia

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Reduced anxiety in elderly dementia patients

3) Adult:
a) Olanzapine treatment reduced anxiety in elderly patients with Alzheimer's-type dementia independently of improvement in hallucinations, treatment-caused somnolence, or benzodiazepine use. A post hoc analysis was performed on a subset of patients (n=120) from a larger, randomized, double-blind trial that evaluated the efficacy of olanzapine (3 dosages) versus placebo for 6 weeks for the treatment of psychosis and agitation/aggression due to Alzheimer's disease. The subgroup (mean age 83 years) was selected for exhibiting clinically significant anxiety, defined as a score of 2 or higher on the anxiety item of the Neuropsychiatric Inventory/Nursing Home instrument (NPI/NH). Anxiety scores of patients receiving olanzapine 5 milligrams (mg) per day improved significantly more than scores of patients receiving placebo (p=0.034). Improvement in anxiety with olanzapine 5 mg/day remained statistically superior even after controlling for improvement in hallucinations. With higher doses of olanzapine (10 and 15 mg/day), improvement in anxiety scores was not significantly different from that with placebo. Somnolence was the only adverse effect that occurred significantly more frequently with olanzapine than with placebo. None of the individual peripheral or central potential anticholinergic adverse events occurred more frequently with olanzapine than with placebo. However, peripheral anticholinergic effects collectively occurred more frequently with olanzapine 15 mg/day than with placebo (26% vs 6%, p=0.008). There was no difference between olanzapine and placebo treatments in the occurrence of extrapyramidal symptoms (Mintzer et al, 2001).

4.5.F Bipolar disorder, Maintenance

FDA Labeled Indication
1) Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Indicated for maintenance monotherapy in bipolar patients who have responded to initial treatment with olanzapine

3) Adult:
a) Continuation olanzapine therapy was more effective than placebo in delaying the time to relapse in patients with bipolar disorder. In a randomized, double- blind, placebo-controlled trial, bipolar patients with a mixed or manic episode who responded to initial, open-label olanzapine therapy (5 to 20 milligrams (mg)/day for approximately two weeks) received either continuation of olanzapine at their same dose (n=225) or placebo (n=136) for observation of relapse. Response during the initial phase of the study was defined as a decrease in the Young Mania Rating Scale (Y-MRS) total score to 12 or less and a decrease in the Hamilton Depression Rating Scale (HAM-D) score to 8 or less. Relapse was defined as an increase of the Y-MRS or HAM-D total score to 15 or greater, or hospitalization for either mania or depression. Patients treated with olanzapine showed a significantly longer time to relapse as compared with patients given placebo (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

4.5.G Bipolar disorder, manic episode

FDA Labeled Indication
1) Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIa; Pediatric, Class IIa

Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Indicated for the treatment of acute manic or mixed episodes associated with bipolar I disorder
The combination of olanzapine with lithium or valproate is indicated for the short-term treatment of acute manic episodes associated with bipolar I disorder

3) Adult:
a) MONOTHERAPY
1) In a small open-label study, olanzapine was found to be somewhat effective as an adjunctive treatment of patients with bipolar disorder (BPD) Twenty-three, severely ill, BPD patients (10 men) with a history of poor response or intolerance to therapeutic concentrations of lithium, valproate or carbamazepine were enrolled in this long-term study (mean 303 days). The Clinical Global Impressions Scale for use in bipolar illness (CGI-BP) was used to assess olanzapine effectiveness. The depression subscale decreased by 0.9 (p less than 0.006), the mania subscale by 1.6 (p less than 0.001), and the general score decreased by 1.3 (p less than 0.0003). Ten of the 23 patients had a decrease of at least 2 points on the CGI-BP at endpoint, but only 2 patients were rated as in remission. There were 6 dropouts in the study, 2 due to adverse effects, 2 due to lack of response, 1 because of overdose, and one lost to follow-up. The mean final dose of olanzapine was 8.2 milligrams (mg) per day with 16 patients taking lithium, 8 taking carbamazepine, 3 receiving valproate and one each taking gabapentin and lamotrigine concurrently. The most common adverse events were somnolence (17%) and weight gain (13%). No new cases of tardive dyskinesia were reported during the study (Vieta et al, 2001).
2) Olanzapine was more effective than placebo in the treatment of patients with acute bipolar mania. In a randomized, double-blind, parallel study, 115 patients were assigned to receive olanzapine 5 to 20 milligrams (mg) daily (QD) (n=55) or placebo (n=60) for 4 weeks. Olanzapine-treated patients demonstrated significantly greater mean improvement in symptoms over placebo, as determined by the total Young-Mania Rating Scale (YMRS). Improvement was clinically evident within the first week of treatment and was maintained throughout the study. Significantly more olanzapine-treated patients demonstrated a 50% or more decrease in total YMRS score from baseline (65% versus 43%, p=0.02) and euthymia as measured by a total YMRS score of 12 or higher at endpoint) (61% versus 36%, p=0.01). The incidence of extrapyramidal symptoms was similar between olanzapine- and placebo-treated patients. However, weight gain, treatment-emergent somnolence, and elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) occurred significantly more often in olanzapine-treated patients (Tohen et al, 2000).
3) Olanzapine exhibited superior efficacy over placebo in the treatment of acute mania (Tohen et al, 1999; Prod Info Zyprexa(R), 2000a). In a double-blind study, patients with manic or mixed episodes associated with bipolar disorder were randomized to receive either olanzapine 10 milligrams (mg) (n=70) or placebo (n=69). The olanzapine dose could be adjusted between a range of 5 to 20 mg daily. At the end of 3 weeks the mean modal dose of olanzapine was 14.9 mg daily. The olanzapine group had a significantly greater improvement in total scores on the Young Mania Rating Scale at week 3 (p less than 0.02). Olanzapine was well-tolerated with no drop-outs due to adverse effects.
4) In 2 case reports, olanzapine effectively augmented mood stabilizers in 2 patients with nonpsychotic bipolar mixed mood states (Ketter et al, 1998). The first was a 34-year-old male with bipolar I disorder that entered a nonpsychotic mixed mood state after increased occupational and familial stress. He had previously been euthymic on lithium and divalproex. Olanzapine 10 milligrams (mg) was added at bedtime and, with the initial dose, the patient slept well for the first time in over 2 weeks. He reported complete remission of his symptoms by the next morning. A 47-year-old woman with bipolar I disorder escalated to a mixed mood state after previously taking divalproex, lorazepam, and levothyroxine. Olanzapine 10 mg was added at bedtime and she slept well for the first time in 10 days. Her mood was also improved by the next morning. Both of these patients had rapid improvements which the authors admit may have been an indirect benefit of improved sleep with olanzapine or may have actually been due to a direct mood stabilization effect.

b) COMBINATION THERAPY
1) In patients with bipolar manic or mixed episodes who do not respond adequately to lithium or valproate, addition of olanzapine increases efficacy of treatment. In a randomized, double-blind, placebo-controlled trial, patients with bipolar disorder who had responded inadequately to 2 or more

C D

weeks of therapy (ie, maintaining a score of 16 or more on the Young Mania Rating Scale (YMRS)) received either olanzapine (flexible dose range of 5, 10, 15 or 20 milligrams/day)(n=229) or placebo (n=115). Both groups improved during the course of treatment, but the olanzapine group showed a 59% improvement in YMRS score from baseline, while the monotherapy group improved by 40% (p=0.003). Particular items of the YMRS that improved more with cotherapy were irritability, speech, language/thought disorder, and disruptive/aggressive behavior. Sixty-eight percent of the cotherapy group were responders (50% or greater improvement in YMRS score), compared to 45% of the montherapy group (p=0.01). Median time to response was 18 days with cotherapy and 28 days with monotherapy. Patients in the cotherapy group showed significantly greater improvement in depression scores than did those in the monotherapy group (p less than 0.001). Among patients experiencing a mixed episode with moderate to severe depression, the mean decrease in the Hamilton Depressive scale from baseline to 6 weeks was 10.3 for cotherapy and 1.6 for monotherapy (p less than 0.001). The most frequently reported adverse events in the cotherapy group were somnolence, dry mouth, weight gain, increased appetite, tremor, and speech disorder. No statistically significant changes from baseline were observed in extrapyramidal symptoms (Tohen et al, 2002a).

2) Combination therapy with olanzapine and lithium or valproate was effective in the treatment of acute manic episodes in patients with bipolar disorder with manic or mixed episodes. In two 6-week, randomized, placebo-controlled trials, patients (n=175, n=169) on lithium or valproate therapy with uncontrolled manic or mixed symptoms and with a score of 16 or higher on the Young Mania Rating scale (Y-MRS) received either olanzapine (dose range of 5 to 20 milligrams (mg) once daily, starting at 10 mg/day) or placebo, in combination with their original lithium (in a therapeutic range of 0.6 milliequivalents/liter (mEq/L) to 1.2 mEq/L) or valproate (in a therapeutic range of 50 micrograms/milliliter (mcg/mL) to 125 mcg/mL) therapy. In both trials, olanzapine in combination with lithium or valproate was more effective than either lithium or valproate alone in reducing the total Y-MRS score (Prod Info Zyprexa(R), Zyprexa(R) Zydis(R), Zyprexa(R) IntraMuscular Olanzapine, 2004b).

4) Pediatric:

a) MONOTHERAPY

1) Olanzapine monotherapy effectively treated symptoms of psychosis, depression, and mania in a group of 23 youths diagnosed with pediatric bipolar disorder (BPD). In this open-label, 8-week study, 23 youths, 5 to 14 years old, discontinued their current BPD treatments and were started on olanzapine 2.5 milligrams (mg) per day. Olanzapine was increased by 2.5 mg/day every 3 days to a maximum dose of 20 mg/day (mean dose at endpoint was 9.6 +/- 4.3 mg per day). Lorazepam (up to 4 mg/day) and benztropine (up to 2 mg/day) were allowed as needed for rescue medication and for extrapyramidal symptoms respectively. Patients taking guanfacine or clonidine for attention deficit hyperactivity disorder (ADHD) were allowed to continue their medications, but could not adjust the dose during the study. Psychiatric symptoms were assessed at baseline and once weekly using the Young Mania Rating Scale (YMRS), the Clinical Global Impressions Severity Scale (CGI-S), the Brief Psychiatric Rating Scale (BPRS), and the Children's Depression Rating Scale (CDRS). Extrapyramidal symptoms were assessed on the same schedule using the Simpson-Argus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale (AIMS). Significant improvement from baseline to endpoint was noted on YMRS (62%, p less than 0.001), CGI-S (38%, p less than 0.001), and BPRS (62%, p less than 0.001). The most frequently reported adverse effects were increased appetite (n=14), somnolence (n=10), abdominal pain (n=7) and weight gain (n=7). There was no significant difference in extrapyramidal symptoms during the study, although 2 patients had treatment-emergent akathisia. There were small statistically significant decreases in hematocrit, hemoglobin, and mean cell volume and statistically significant increases in alanine transferase (ALT) and prolactin levels. One patient dropped out of the study after 6 weeks due to worsening of depressive symptoms (Frazier et al, 2001).

4.5.H Borderline personality disorder

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb

study, treatments with both olanzapine and olanzapine-fluoxetine combination produced significantly greater reductions in depressive symptoms (as measured by the MADRS) as compared with placebo (p less than 0.001, all values). Also, a significantly greater improvement in the mean MADRS score at weeks 4, 6, and 8 were observed with olanzapine-fluoxetine combination therapy as compared with olanzapine monotherapy (p=0.01, p=0.02, p=0.01, respectively). The rate of response (defined as at least a 50% improvement in the MADRS total score and completion of at least 4 weeks of study) was significantly higher in olanzapine-treated patients as compared with placebo (39% vs 30.4%, respectively; p=0.02). Additionally, the response rate was significantly higher in the olanzapine-fluoxetine group as compared with both the placebo (56.1% vs 30.4%, respectively; p less than 0.001) and olanzapine groups (56.1% vs 39%, respectively; p=0.006). There were no statistically significant differences between groups with regard to rates of treatment-emergent mania. Adverse events were similar between the combination therapy and monotherapy groups, however, the olanzapine-fluoxetine group had a significantly higher rate of nausea and diarrhea (Tohen et al, 2003).

4.5.O Depression, Treatment-resistant

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Ineffective as a single agent in resistant depression
Possibly effective as augmentation therapy with antidepressants

3) Adult:
a) Some patients experiencing a recurrence of depression while under medical treatment responded very quickly to addition of olanzapine to their existing regimen. In a case series of 10 patients, 4 patients, all of whom had unipolar depression, were judged to be non-responders after 1 week of olanzapine treatment. Of the 6 responders, 5 had bipolar conditions and were receiving venlafaxine, desipramine, anafranil and citalopram, with 2 also taking epilim and 1 taking lithium. Each received olanzapine augmentation of 2.5 milligrams (mg) or 5 mg each night. Daily rating scores kept by the patients improved by 52% in the first day, 73% by day 4, and 89% by day 6. Anxiety and insomnia scores, in particular, showed notable improvement in the first 24 hours. Depressed mood showed linear improvement over the week. Two patients emerged with what they described as a "high." Because of the bipolar nature of the illness of the majority, it is uncertain whether the improvement with olanzapine was through an effect on a switching mechanism, leading to mild mania (Parker, 2002).
b) Patients with treatment-resistant, nonpsychotic, unipolar depression treated with olanzapine combined with fluoxetine showed significantly greater improvement than either agent alone across a variety of measures. In an 8-week, double-blind study, 28 patients (mean age 42 years) were randomized into 3 treatment groups: olanzapine plus placebo, fluoxetine plus placebo or olanzapine plus fluoxetine. The mean modal dose of olanzapine was 12.5 milligrams (mg) and 13.5 mg for the monotherapy and combined therapy groups, respectively. The mean modal dose of fluoxetine was 52 mg QD for both the monotherapy and combination group. Patients receiving combination therapy experienced greater improvements over baseline in Montgomery-Asberg Depression Rating Scale scores than with either agent alone and in total Hamilton Depression scale scores than olanzapine treatment alone. The proportion of patients responding (at least 50% improvement in Montgomery-Asberg Depression Rating Scale score) in the combination therapy group was significantly greater those receiving olanzapine alone (60% versus 0%). Both drugs were well tolerated alone or in combination. Adverse effects included somnolence, increased appetite, asthenia, weight gain, headache, dry mouth, and nervousness. Increased appetite and weight gain occurred significantly more often in patients treated with olanzapine (Shelton,et al, 2001).

4.5.P Drug-induced psychosis - Methamphetamine adverse reaction

1) Overview

4.5.Y Pervasive developmental disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Some improvement in one small open-label study in patients with autism or pervasive developmental disorder not otherwise specified
Only 3 of 12 pediatric patients benefited in a small open-label trial

3) Adult:
a) In a 12-week open-label pilot study of eight children, adolescents, and adults with pervasive developmental disorders, six patients treated with olanzapine were rated as much improved or very much improved on the Clinical Global Impression Scale. Patients ranged in age from 5 to 42 years and met DSM-IV criteria for pervasive developmental disorder (autistic disorder, N=5; not otherwise specified, N=3). Mean olanzapine doses were 8 milligrams per day. Significant changes from baseline were observed on the Vineland Maladaptive Behavior Scale, Rivto-Freeman Real-life Rating Scale, Self-Injurious Behavior Questionnaire, and portions of the Clinician-Rated Visual Analog Scale (all p less than 0.001). One patient dropped out at week 9 due to lack of efficacy, six patients experienced weight gain, and three patients reported sedation (Potenza et al, 1999).

4) Pediatric:
a) A retrospective chart review demonstrated that olanzapine therapy (2.5 to 15 milligrams per day (mg/d)) was effective in reducing hyperactivity, aggression, and hallucinations in only 3 of 12 pediatric patients (aged 5 to 17 years) with developmental disabilities or psychotic disorders. Teachers or parents determined efficacy reporting improvement or worsening of symptoms. Ten of the 12 studied had previously failed other psychotropic medications. Seven patients were mentally retarded. Eight of the 12 children discontinued olanzapine after a mean duration of 50 days due to adverse effects (6), lack of positive effects (5), and exacerbated target symptoms or a combination of these issues (2). The most frequent side effects were an increased appetite and sedation. Slurred speech, tremulousness, drooling, and suicidal ideation were also reported (Demb & Roychoudhury, 2000). In another short-term study, 2 of 4 children discontinued olanzapine due to weight gain despite a positive response to therapy, while adult responders continued therapy without incident, suggesting that different age groups may exhibit diverse responses to olanzapine treatment (Potenza & McDougle, 2001).
b) In a 12-week open-label pilot study of eight children, adolescents, and adults with pervasive developmental disorders, six patients treated with olanzapine were rated as much improved or very much improved on the Clinical Global Impression Scale. Patients ranged in age from 5 to 42 years and met DSM-IV criteria for pervasive developmental disorder (autistic disorder, N=5; not otherwise specified, N=3). Mean olanzapine doses were 8 milligrams per day. Significant changes from baseline were observed on the Vineland Maladaptive Behavior Scale, Rivto-Freeman Real-life Rating Scale, Self-Injurious Behavior Questionnaire, and portions of the Clinician-Rated Visual Analog Scale (all p less than 0.001). One patient dropped out at week 9 due to lack of efficacy, six patients experienced weight gain, and three patients reported sedation (Potenza et al, 1999).

4.5.Z Posttraumatic stress disorder

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Improved all types of symptoms of PTSD in combat veterans

4.5.AD Schizophrenic prodrome

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
May be effective in the treatment schizophrenic prodromal syndrome

3) Adult:
a) The results of one study suggest that olanzapine may be effective in the treatment of patients experiencing prodromal symptoms of schizophrenia. In a randomized, double-blind, placebo-controlled, multicenter study, patients with prodromal syndrome received olanzapine 5 to 15 milligrams (mg) daily (n=31; mean dose, 8 mg/day) or placebo (n=29) for 8 weeks. Results of the study were inconsistent across analyses. In a mixed effects analysis of the data, olanzapine-treated patients showed a significant improvement from baseline to endpoint in total score for the Scale of Prodromal Symptoms (SOPS) (treatment x time interaction), as compared with placebo (p less than 0.005). However, when a last observation carried forward (LOCF) analysis was done, the trend favored olanzapine but did not reach statistical significance. Significantly more patients taking olanzapine experienced a weight gain of more than 7% of their baseline body weight as compared with placebo (56.7% vs 3.4%, respectively, p less than 0.001). Larger, longer-term studies are needed in order to establish clinical efficacy (Woods et al, 2003).

4.5.AE Senile dementia of the Lewy body type

1) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Effective in low doses (5 milligrams/day) but not at high doses (15 mg/day)

3) Adult:
a) Olanzapine at low doses significantly reduced delusions and hallucinations in patients with dementia with Lewy bodies (DLB). The patients with DLB (n=29) were a subset of patients with Alzheimer's disease being treated for psychosis with various doses of olanzapine in a randomized, double- blind, placebo-controlled trial. Within the DLB subset, 10 patients were treated with placebo, 5 with olanzapine 5 milligrams (mg) per day, 7 with olanzapine 10 mg/day, and 7 with olanzapine 15 mg/day. In comparison to scores with placebo treatment, final scores on the delusions subscale of the Neuropsychiatry Inventory-Nursing Home (NPI/NH) after 12 weeks of olanzapine treatment were significantly better for the 5 mg group (p=0.009) and the 10 mg group (p=0.018) but not for the 15 mg group. Scores on the hallucinations subscale were significantly better for the 5 mg group only. Olanzapine did not cause any significant exacerbation of symptoms of parkinsonism or any decrease in cognition. The 5-mg dose also diminished disruptiveness of patients (Cummings et al, 2002).
b) Olanzapine (2.5 to 7.5 milligrams daily) showed little advantage over conventional neuroleptics in 8 patients diagnosed with Dementia with Lewy bodies (DLB). Only 2 patients demonstrated clear improvement in psychotic and behavioral symptoms. Three patients gained only minimal clinical benefit and the remaining 3 patients could not tolerate olanzapine, even at the lowest dose. The data suggests that benzodiazepines, antidepressants, and sociopsychological methods should be considered prior to olanzapine for treatment of DLB (Walker et al, 1999).

4.5.AF Severe major depression with psychotic features

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

PLAINTIFF'S RESPONSES TO DEFENDANT'S FIRST SET OF INTERROGATORIES

Pursuant to Rule 33 of the Alaska Rules of Civil Procedure, Plaintiff provides the following Responses to Defendant's First Set of Interrogatories. Plaintiff specifically reserves the right to supplement and amend these responses as provided by the applicable rules of procedure.

INTERROGATORIES

INTERROGATORY NO. 1: Identify each Medicaid State Plan in effect for the State of Alaska since 1996, and for each plan:

a. state whether pharmacy benefits are offered as part of the coverage;

b. state whether pharmacy benefits are offered for Zyprexa prescriptions; and

c. describe in detail any rules and/or restrictions relating to the pharmacy benefits offered for Zyprexa.

ANSWER: The current Medicaid plan in effect for the State is on the State Health Department website and may be accessed at:

http://www.hss.state.ak.us/commissioner/medicaidstateplan/default.htm. The State will produce

copies of all responsive plans in its possession as soon as possible. Upon information and belief, the following has been true from 1996 to the present:

a. Pharmacy benefits are offered.

b. Pharmacy benefits are offered for Zyprexa prescriptions.

c. Zyprexa benefits are available for "medically necessary" prescriptions. To be "medically necessary," a prescription must comply with FDA approved uses or be for a use found within standard medical or pharmaceutical compendia.

INTERROGATORY NO. 2: Identify each formulary and/or Preferred Drug List (PDL) in effect for the State of Alaska's Medicaid State Plan since 1996, and for each formulary and/or PDL:

a. state whether Zyprexa is on the formulary and/or PDL;

b. describe in detail any rules and/or restrictions on the formulary and/or PDL relating to Zyprexa; and

c. state whether any other atypical antipsychotic is on the formulary and/or PDL.

ANSWER: See response to Request for Production No. 3. The State has had a formulary since approximately 1995. The State has had a PDL since approximately 2004. The PDL does not include any atypical antipsychotic medications.

a. Zyprexa is on the formulary but it is not on the PDL.

b. There are no rules, regulations and/or restrictions on the prescription of Zyprexa except the general requirement that the prescription be "medically necessary."

c. Other atypical antipsychotic medications are on the formulary but there are no atypical antipsychotics on the PDL.

INTERROGATORY NO. 3: Did you ever modify the formulary and/or PDL for any antipsychotic drug? If so, explain why.

ANSWER: Neither the PDL nor the formulary has ever been modified for any antipsychotic drug.

INTERROGATORY NO. 4: Identify the Alaska employees or representatives who communicated with Lilly about Zyprexa since 1996.

ANSWER: David Campana, Lynda Walsh, and Tom Porter, M.D.

INTERROGATORY NO. 5: Identify each employee of Alaska that had supervisory or management responsibility for any of the pharmacy benefits offered to Medicaid recipients, or any role in selecting drugs for the formulary and/or PDL, since 1996. For all employees identified in response to this interrogatory, identify all documents they considered regarding Zyprexa.

ANSWER: Upon information and belief, the individuals most knowledgeable about the selection of drugs for the formulary are David Campana and Tom Porter, M.D. Plaintiff objects to the request to identify all documents these individuals "considered" regarding Zyprexa on the grounds that it is overbroad, vague and burdensome.

INTERROGATORY NO. 6: Identify each of Alaska's committees, including its P&T Committees, and its constituent members, that have had supervisory or management responsibility for any of the pharmacy benefits offered to Medicaid recipients, or any role in selecting drugs for the formulary and/or PDL, since 1996. For all committees and members identified in response to this interrogatory, identify all documents they considered regarding Zyprexa.

ANSWER: Upon information and belief, the State has not organized a P & T committee since 1996 that had any management or supervisory role in the selection of pharmacy benefits offered to Medicaid recipients or any role in selecting drugs for the formulary or PDL.

INTERROGATORY NO. 7: Did Alaska retain a PBM to assist in the development or administration of its Medicaid pharmacy benefit? If the answer is yes, identify the PBM(s), the

Alaska employees with any supervisory or management responsibility for the relationship between Alaska and Alaska's PBM(s) since 1996, and the individuals at Alaska's PBM(s) with whom Alaska communicated regarding Zyprexa since 1996, and any documents exchanged with the PBM(s) regarding Zyprexa since 1996.

ANSWER: The State of Alaska has engaged the services of a PBM, First Health Services, Corporation. First Health's services have been limited to administrating the pharmacy program. It has had no responsibility for selecting drugs to include on the formulary or PDL. David Campana and Lynda Walsh are the State's employees with responsibility for communicating with First Health. Plaintiff objects to the interrogatory to the extent it requests Plaintiff to identify any documents exchanged with the PBM(s) regarding Zyprexa since 1996 on the grounds that the request is overbroad, vague, and burdensome.

INTERROGATORY NO. 8: Identify any false or misleading statements alleged to have been made to Alaska by Lilly.

ANSWER: The State reserves the right to supplement this response as discovery progresses in this case. The following is a general description of the types of false or misleading statements made by Lilly regarding Zyprexa. As discovery has only begun in this case, it is neither intended to be exhaustive nor exclusive.

Lilly's false and misleading statements regarding Zyprexa span a decade beginning with the launch of the drug in 1996 and continuing through the FDA mandated label change for all atypical antipsychotics in 2003.

In 1995, a prelaunch analysis by Lilly of data from its HGAJ study of Zyprexa showed a statistically significant increased incidence of high blood glucose in Zyprexa patients as compared to patients using Haldol. This analysis has never been disclosed to prescribing

physicians. In October 1996, Lilly began its Zyprexa marketing campaign by characterizing weight gain on Zyprexa as "therapeutic" instead of an adverse event. By 1998, despite Lilly's knowledge of significant numbers of post-marketing adverse event reports related to weight gain and hyperglycemia, Lilly continued to refer to these adverse events as "infrequent" events seen in clinical studies and made no mention of them in post-marketing reports. Also, by 1998 Lilly employees were internally discussing the link between atypical antipsychotics, weight gain and diabetes, but declined to notify physicians or the public of their concerns.

In 1999, Lilly knew there was a reasonable association between Zyprexa and treatment-emergent hyperglycemia, yet it refused to provide any such information to physicians or the public because it would be damaging to Zyprexa. In early 2000, however, Lilly's Global Product Labeling Committee was reviewing information in consideration of a labeling change regarding hyperglycemia. The information indicated that analyses of Lilly's clinical trial data showed an incidence of treatment-emergent hyperglycemia in Zyprexa patients that was 3 ½ times higher than in patients treated with placebo. Rather than providing this information to physicians, however, Lilly engaged in a tortured reanalysis of the data and in May of 2000 issued a label change without prior FDA approval claiming there was no significant difference in treatment-emergent hyperglycemia rates between Zyprexa and placebo. Lilly had its sales force actively promote this tortured data nationwide. Five months later, in October 2000, FDA demanded that Lilly remove the language from the label claiming there was no difference in the rates of treatment-emergent hyperglycemia, noting that the changed label inappropriately implied that Zyprexa was safe.

In 2000, while trumpeting the supposedly superior efficacy of Zyprexa and falsely stating that it carried no significant risk of treatment-emergent hyperglycemia, Lilly additionally began a

nationwide campaign to promote Zyprexa to primary care physicians for non-indicated or off-label uses. Lilly not only falsely promoted Zyprexa as safe and effective, it promoted it for a wide array of intentionally broad and vague mental disorders. At the same time, outside Lilly consultants were warning the company to "come clean" on the hyperglycemia issue, yet Lilly failed to do so. Instead, in 2001 Lilly tripled its direct-to-physician promotion of Zyprexa using a "sell sheet" which featured its tortured clinical trial data analysis and a "comparable rates" message claiming Zyprexa patients had rates of hyperglycemia and diabetes comparable to those treated with other antipsychotics. Internally, however, Lilly acknowledged that appropriate analysis of clinical trial data showed that Zyprexa treatment resulted in statistically significant mean increases in random glucose compared with both placebo and other antipsychotics.

Regardless, in 2002 Lilly's position was that diabetes occurred at comparable rates across antipsychotics. While it knew this position was false, it believed that advancing it would help eliminate diabetes concerns from the risk-benefit equation. Further, Lilly advanced the position that weight gain on Zyprexa was manageable for most patients even though it knew that position was false. Lilly instructed its sales force to avoid the issue of hyperglycemia altogether if possible, and if confronted with it, to use the "comparable rates" story.

In July 2003, Lilly intensified its efforts to influence the public that Zyprexa did not cause diabetes and that if diabetes occurred with Zyprexa use it did so at "comparable rates" with other antipsychotics. While admitting internally that weight gain caused by Zyprexa could be a substantial contributing factor pushing some patients into diabetes, Lilly falsely represented to the public that there was no causal link, that weight gain was manageable, and that diabetes occurred at "comparable rates" across all antipsychotics. Even after the September 2003 label change mandated by the FDA, Lilly continued to trumpet its "comparable rates" message, even

though subsequent pronouncements by the ADA Consensus Conference and the Veterans Healthcare Administration clearly demonstrated that the consensus of the medical community most knowledgeable on this issue was that use of Zyprexa resulted in more weight gain and a higher risk of diabetes than most other atypical antipsychotics.

INTERROGATORY NO. 9: Identify any false or misleading statements alleged to have been made to Alaska's PBM(s) by Lilly.

ANSWER: See response to Interrogatory No. 8 above.

INTERROGATORY NO. 10: Identify every on-label Zyprexa prescription that you reimbursed or paid for as a result of Lilly's alleged wrongful conduct.

ANSWER: The State objects to this interrogatory to the extent it seeks information and/or documents, the disclosure of which would violate the privacy or confidentiality rights of non-parties including, but not limited to, those privacy rights guaranteed by the Federal and state constitutions as well as Federal and state statutes and regulations. Subject to and without waiving this objection, upon the execution of a proper confidentiality agreement, Alaska will provide in electronic form data which does not identify individuals from which Alaska is extracting the comparative data which will substantiate its claim.

INTERROGATORY NO. 11: For each Zyprexa prescription identified in response to Interrogatory No. 10:

a. identify the patient;

b. identify the age of the patient;

c. identify the patient's diagnosis for which Zyprexa was prescribed;

d. identify the period of time the patient took Zyprexa;

e. state whether the patient is still being prescribed Zyprexa;

f. state what treatment, if any, you contend the patient would have received if the Zyprexa prescription you allege was the result of Lilly's wrongful conduct was not prescribed;

g. identify the prescriber;

h. state whether the prescriber continues to prescribe Zyprexa;

i. state whether you contend that Zyprexa was not efficacious for the patient;

j. state whether you contend that Zyprexa caused a physical injury(ies) to the patient, and if so, what injury(ies) were caused; and

k. state the dollar amount Alaska is seeking to recover from Lilly for that prescription.

ANSWER: See response to Interrogatory No. 10 above. The State further objects to this interrogatory in that it seeks information that is irrelevant to the claims and defenses of the parties and is not reasonably calculated to lead to the discovery of admissible evidence. As the State noted in its Memorandum Describing its Claims and Proofs, because the State seeks compensation for increased costs within a population, its burden is to establish generic causation in that population (i.e., the rate by which Alaska Medicaid recipients who took Zyprexa show an increased incidence of diabetes compared to the background rate of the disease in matched controls). The State does not need to prove specific causation in any particular individual.

Subject to and without waiving these objections, the State will provide in electronic form the data described in Interrogatory No. 10 above. Further, to the extent this interrogatory seeks information related to the State's damages, this response will be supplemented and made as part of the expert disclosures and accompanying reports related to its proof of damages in this case.

INTERROGATORY NO. 12: Identify every off-label Zyprexa prescription you reimbursed or paid for as a result of Lilly's alleged wrongful conduct.

ANSWER: See response to Interrogatory No. 10 above. Subject to and without waiving this objection, the State will provide in electronic form the data described in Interrogatory No. 10 above.

INTERROGATORY NO. 13: For each Zyprexa prescription identified in response to Interrogatory No. 12:

a. identify the patient;

b. identify the age of the patient;

c. identify the patient's diagnosis for which Zyprexa was prescribed;

d. identify the period of time the patient took Zyprexa;

e. state whether the patient is still being prescribed Zyprexa;

f. state what treatment, if any, you contend the patient would have received if the Zyprexa prescription you allege was the result of Lilly's wrongful conduct was not prescribed;

g. identify the prescriber;

h. state whether the prescriber continues to prescribe Zyprexa;

i. state whether you contend that Zyprexa was not efficacious for the patient;

j. state whether you contend that Zyprexa caused a physical injury(ies) to the patient, and if so, what injury(ies) were caused; and

k. state the dollar amount Alaska is seeking to recover from Lilly for that prescription.

ANSWER: See responses to Interrogatory Nos. 10 and 11 above. Subject to and without waiving these objections, the State will provide in electronic form the data described in Interrogatory No. 10 above. Further, to the extent this interrogatory seeks information related to the State's

damages, this response will be supplemented and made as part of the expert disclosures and accompanying reports related to its proof of damages in this case.

INTERROGATORY NO. 14: Describe in detail how Lilly's alleged wrongful conduct caused you to reimburse or pay for each of the Zyprexa prescriptions identified in response to Interrogatories 10 and 12.

ANSWER: Lilly's wrongful conduct, the general nature of which is described in response to Interrogatory No. 8 above, caused the State to pay for numerous Zyprexa prescriptions when there were safer, equally efficacious treatments available which could have been used if the physicians and the public had known the true risks and benefits of Zyprexa. Additionally, Lilly's wrongful conduct described generally in Interrogatory No. 8 caused the State to pay for numerous prescriptions of Zyprexa that were not medically necessary.

INTERROGATORY NO. 15: Identify every person whose alleged deception by Lilly caused your reimbursement or payment for a Zyprexa prescription identified in response to Interrogatories 10 and 12.

ANSWER: The State objects to this interrogatory in that it is vague, ambiguous, and unintelligible. To the extent this interrogatory seeks the identities of specific Lilly employees or representatives who made misrepresentations; the State reserves the right to respond as discovery progresses.

INTERROGATORY NO. 16: Identify each physician that has written a prescription for Zyprexa the cost of which was reimbursed or paid for by Alaska, that you allege was deceived by Lilly and that but for the deception would not have prescribed Zyprexa to some or all of his/her patients.

ANSWER: See responses to Interrogatory Nos. 10 and 11 above.

INTERROGATORY NO. 17: For each physician identified in response to Interrogatory No. 16, identify any false or misleading statements made to him or her by Lilly.

ANSWER: See responses to Interrogatory Nos. 10 and 11 above.

INTERROGATORY NO. 18: Do you contend that the price to you of Zyprexa would have been lower but for Lilly's alleged wrongful conduct? If so, identify each fact that forms the basis of that contention, identify the amount at which you contend Zyprexa should have been priced, and set forth your methodology and data for calculating the difference in price.

ANSWER: The State objects to this interrogatory in that it seeks information that is irrelevant to the claims and defenses of the parties, is not reasonably calculated to lead to the discovery of admissible evidence, and is vague and ambiguous. The State contends it paid for unnecessary Zyprexa prescriptions, regardless of price, because it was deceptively and illegally marketed.

INTERROGATORY NO. 19: Do you contend that Lilly's alleged wrongful conduct increased the number of on-label Zyprexa prescriptions you reimbursed or paid for? If so, identify each fact that supports that contention.

ANSWER: Yes, the State alleges that Lilly's wrongful conduct increased the number of on-label Zyprexa prescriptions. Had Lilly appropriately warned the State, physicians and the public about the true efficacy and side effects of Zyprexa, there would have been fewer prescriptions. The State intends to provide proof, as described in its Memorandum Describing Claims and Proofs, that a reasonable physician would have instead prescribed equally efficacious and safer alternatives to Zyprexa. While the State reserves the right to supplement this response with more specific facts as discovery progresses, see generally the facts discussed in response to

Interrogatory No. 8 above. Additionally, the number of prescriptions has declined since the FDA mandated label change.

INTERROGATORY NO. 20: Please quantify the number of additional on-label prescriptions you contend were caused by Lilly's alleged wrongful conduct and set forth your methodology and data for calculating the increased number of on-label Zyprexa prescriptions and the excess dollar amount that you reimbursed or paid as a result of Lilly's alleged wrongful conduct.

ANSWER: The State's response to this interrogatory will be part of its expert disclosures and accompanying reports related to its proof of damages in this case.

INTERROGATORY NO. 21: Do you contend that Lilly's alleged wrongful conduct increased the number of off-label Zyprexa prescriptions you reimbursed or paid for? If so, identify each fact that supports that contention.

ANSWER: Yes, the State of Alaska maintains that Lilly's wrongful conduct increased the number of off-label Zyprexa prescriptions. The State intends to provide proof, as described in its Memorandum Describing Claims and Proofs, that Lilly promoted Zyprexa for numerous non-indicated or off-label uses which resulted in prescriptions which were not medically necessary. While the State reserves the right to supplement this response with more specific facts as discovery progresses, see generally the facts discussed in response to Interrogatory No. 8, above.

INTERROGATORY NO. 22: Please quantify the number of additional off-label prescriptions you contend were caused by Lilly's alleged wrongful conduct and set forth your methodology and data for calculating the increased number of on-label Zyprexa prescriptions and the excess dollar amount that you reimbursed or paid as a result of Lilly's alleged wrongful conduct.

ANSWER: The State's response to this interrogatory will be supplemented and made as part of its expert disclosures and accompanying reports related to its proof of damages in this case.

INTERROGATORY NO. 23: Identify all payments for medical treatment of injuries you allege were caused by Zyprexa for which you seek damages in this matter.

ANSWER: The State's response to this interrogatory will be supplemented and made as part of its expert disclosures and accompanying reports related to its proof of damages in this case.

INTERROGATORY NO. 24: For each payment identified in response to Interrogatory No. 23:

a. identify the patient;

b. identify the age of the patient;

c. identify the patient's diagnosis for which Zyprexa was prescribed;

d. identify the period of time the patient took Zyprexa;

e. state whether the patient is still being prescribed Zyprexa;

f. state what treatment, if any, you contend the patient would have received if the Zyprexa prescription you allege was the result of Lilly's wrongful conduct was not prescribed;

g. identify the prescriber;

h. state whether the prescriber continues to prescribe Zyprexa;

i. identify any misrepresentations you allege caused the physician to prescribe Zyprexa;

j. identify the injury you allege was caused by Zyprexa for which you seek damages;

k. identify the physician that diagnosed the injury;

l. identify all physicians that treated the injury; and

m. state the dollar amount that Alaska is claiming against Lilly in damages.

ANSWER: See responses to Interrogatory Nos. 10 and 11 above.

INTERROGATORY NO. 25: Identify any communications since 1996 by Alaska to Medicaid recipients concerning Zyprexa.

ANSWER: The State has no documents or communications responsive to this request.

INTERROGATORY NO. 26: Identify any communications since 1996 by Alaska to physicians concerning Zyprexa.

ANSWER: The State objects to this interrogatory in that it seeks information that is irrelevant to the claims and defenses of the parties, is not reasonably calculated to lead to the discovery of admissible evidence, and is vague and ambiguous. Subject to and without waiving these objections, the State has no documents or communications responsive to this request.

INTERROGATORY NO. 27: Identify any Drug Utilization Reviews and/or Drug Class Reviews done by Alaska since 1996 concerning Zyprexa.

ANSWER: The State did a review of atypical antipsychotic medications in approximately 2005 with respect to their propensity to cause diabetes. The minutes of this review meeting are being produced with the State's responses to Lilly's Requests for Production.

INTERROGATORY NO. 28: Identify any algorithms or protocols adopted by Alaska for treatment of schizophrenia, bipolar disorder, and/or any other algorithms or protocols that include Zyprexa.

ANSWER: The State of Alaska has used a protocol for the use of atypical antipsychotic medications, although it does not specifically address Zyprexa. This protocol was developed by

a grant from Eli Lilly. It is generally known as the BPMS program and is run by a contractor, CNS.

INTERROGATORY NO. 29: Identify any studies or analyses performed by Alaska to assess the effect on overall costs to the state of prescribing atypical anti-psychotics to mental health patients.

ANSWER: The State objects to this interrogatory in that it is vague and ambiguous. Subject to and without waiving this objection, and assuming this interrogatory is limited to the Medicaid program, cost reports were prepared in response to a request from the Anchorage Daily News in approximately 2005. These reports are produced in the State's responses to Lilly's Requests for Production.

INTERROGATORY NO. 30: Identify all employees of Alaska with knowledge of the events alleged in the Complaint.

ANSWER: David Campana, Lynda Welch and Tom Porter, M.D.

INTERROGATORY NO. 31: Identify any lawsuits filed by plaintiff against any manufacturer of atypical anti-psychotics other than Lilly.

ANSWER: The State objects to this interrogatory in that it seeks information that is irrelevant to the claims and defenses of the parties and is not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving these objections, the State has filed no other such lawsuits.

INTERROGATORY NO. 32: Identify all Alaska Medicaid recipients who have filed lawsuits or otherwise asserted claims against Lilly on their own behalf in connection with their ingestion of Zyprexa.

ANSWER: The State objects to this interrogatory to the extent it seeks information and/or documents, the disclosure of which would violate the privacy or confidentiality rights of non-parties including, but not limited to, those privacy rights guaranteed by the Federal and state constitutions as well as Federal and state statutes and regulations. The State further objects to this interrogatory in that it seeks information that is irrelevant to the claims and defenses of the parties and is not reasonably calculated to lead to the discovery of admissible evidence.

INTERROGATORY NO. 33: Did you ever take any steps to reduce the amount you were paying or reimbursing for any anti-psychotic drug? If the answer is anything but an unqualified "no," describe in detail what steps you took.

ANSWER: The State is and has been working on a formulary aimed at reducing the amount paid for all pharmaceuticals, including atypical antipsychotics. The State participated in the BPMS program sponsored by Lilly. Additionally, the State has investigated the possibility of joining with other states to negotiate further rebates. Further, the State limits the prescription of pharmaceuticals as set out in the answer to interrogatory 1(c).

INTERROGATORY NO. 34: Did Alaska impose the maximum allowable charges pursuant to Alaska Stat. §47.07.042 or any predecessor statute for purchases of Zyprexa? If the answer is anything but an unqualified "yes," explain the reason why not.

ANSWER: The maximum allowable charge is $3.00 per co-payment. The State has chosen to impose a co-payment of $2.00 as being more reasonable given the finances of Alaska Medicaid recipients.

INTERROGATORY NO. 35: Has Alaska involuntarily medicated any Alaska citizens with Zyprexa? If the answer is yes, please state when such involuntary medications have occurred,

the conditions for which Zyprexa was prescribed, and identify any court filings relating to the involuntary medications.

ANSWER: See response to Interrogatory No. 10 above. The State further objects to this interrogatory in that it seeks information that is irrelevant to the claims and defenses of the parties, is not reasonably calculated to lead to the discovery of admissible evidence.

INTERROGATORY NO. 36: State when you first became aware that:

a. Lilly advertised and sold Zyprexa for non-approved or "off-label" uses as alleged in paragraph 12 of the Complaint, and what actions, if any, you took upon discovering those facts.

b. Beginning in 1998, scientific journals began to publish studies that established a causal association between using Zyprexa and developing or exacerbating diabetes mellitus and development of dangerously high blood sugar levels, also known as hyperglycemia, as alleged in paragraph 14 of the Complaint, and what actions, if any, you took upon discovering those facts.

c. In April 2002, the British Medicines Control Agency warned about the risk of diabetes for patients prescribed Zyprexa, of diabetes, hyperglycemia, diabetic ketoacidosis, diabetic coma, and one death among and required Lilly to warn consumers about the risk of diabetes and diabetic ketoacidosis, and further required Lilly to instruct patients who were using Zyprexa to monitor their blood sugar levels, as alleged in paragraph 15 of the Complaint, and what actions, if any, you took upon discovering those facts.

d. In April 2002, the Japanese Health and Welfare Ministry issued emergency safety information regarding the risk of diabetes, diabetic ketoacidosis, and diabetic coma for users of Zyprexa, as alleged in paragraph 16 of the Complaint, and what actions, if any, you took upon discovering those facts.

e. Lilly had failed to warn consumers in this country, including Alaska, about the serious risks of diabetes, hyperglycemia, diabetic ketoacidosis, and other serious conditions associated with the use of Zyprexa, as alleged in paragraph 17 of the Complaint, and what actions, if any, you took upon discovering those facts.

f. Lilly failed to warn consumers, including Alaska, its physicians, and Medicaid recipients, of the dangerous and permanent health consequences caused by the use of Zyprexa, and instructed its representatives to minimize and misrepresent the dangers of Zyprexa, as alleged in paragraph 19 of the Complaint, and what actions, if any, you took upon discovering those facts.

g. Beginning in the 1990s, Lilly's strategy has been to aggressively market and sell Zyprexa by willfully misleading potential users about serious dangers resulting from the use of Zyprexa and that Lilly advertised the use of Zyprexa for off-label uses, including geriatric dementia, pediatric symptoms, and for general depression, as alleged in paragraph 20 of the Complaint, and what actions, if any, you took upon discovering those facts.

h. Lilly engaged in an advertising program that purposefully disguised the risks associated with Zyprexa use, including serious illness and death, as alleged in paragraph 22 of the Complaint, and what actions, if any, you took upon discovering those facts.

i. Lilly in making Zyprexa available to Medicaid patients, knowingly misrepresented to the State of Alaska that Zyprexa was safe and effective, as alleged in paragraph 25 of the Complaint, and what actions, if any, you took upon discovering those facts.

ANSWER: The general answer to all subparts is that when the State of Alaska became aware of Lilly's misrepresentations, it filed a lawsuit. This general awareness took place in the summer of 2005.

However, Lilly took affirmative actions to hide the true nature of Zyprexa and its side effects from the State. For example in 2002, Lilly's representative Kevin Walters met with David Campana to discuss Lilly products. He focused upon diabetic products. With respect to atypical medications, he introduced the BPMS system but did not disclose the evidence connecting Zyprexa with diabetes. In approximately the same time period, Alaska joined a group of other States, led by Missouri, to negotiate manufacturer rebates. At no time did Lilly or its representatives disclose the connection between Zyprexa and diabetes.

Lilly consistently concealed important safety information regarding Zyprexa from plaintiff, physicians and the public. When such information surfaced in the popular or scientific press, Lilly took steps to blunt the information or spin available data to its purposes, primarily further concealing the risks of Zyprexa. Thus, Lilly falsely maintained that weight gain due to Zyprexa was manageable for most patients, that there was no association between Zyprexa and hyperglycemia, and that even if hyperglycemia occurred in patients taking Zyprexa, it occurred at rates comparable to other antipsychotics.

INTERROGATORY NO. 37: Identify all witnesses you intend to call to testify at the trial of this matter.

ANSWER: The State will designate witness at the time called for under the pre-trial order.

INTERROGATORY NO. 38: Identify all expert witnesses you intend to call to testify at the trial of this matter.

ANSWER: The State will designate expert witness, provide reports and make those experts available for deposition in accordance with the pre-trial report.

Respectfully SUBMITTED and DATED this 23rd day of April, 2007

FELDMAN, ORLANSKY & SANDERS
Counsel for Plaintiff

BY _____

Eric T. Sanders
Alaska Bar No. 7510085
500 L Street
Suite 400
Anchorage, AK 99501
(907) 272-3538

GARRETSON & STEELE
Matthew L. Garretson
Joseph W. Steele
5664 South Green Street
Salt Lake City, UT 84123
(801) 266-0999
Counsel for Plaintiff

RICHARDSON, PATRICK, WESTBROOK
& BRICKMAN, LLC
H. Blair Hahn
Christiaan A. Marcum
P.O. Box 1007
Mt. Pleasant, SC 29465
(843) 727-6500
Counsel for Plaintiff

CERTIFICATE OF SERVICE

Plaintiff, State of Alaska, hereby certifies that it has caused to be served upon the below listed individuals copies of Plaintiff's Answers to Defendants First set of Interrogatories by placing copies of same in a Federal Express envelope, postage prepaid, on April 23, 2007.

Respectfully submitted,

Eric T. Sanders
Feldman, Orlansky & Sanders
500 L Street, Suite 400
Anchorage, AK 99501
(907) 272-3538

COUNSEL FOR PLAINTIFF

Defendant's Counsel

Brewster Jamieson
Lane Powell
301 West Northern Lights Blvd, Ste 301
Anchorage, AK 99503-2648

Andrew Rogoff
Pepper Hamilton
3000 Two Logan Square
Eighteenth and Arch Streets
Philadelphia, PA 19103-2799

Dated: April 23, 2007

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

STATE OF ALASKA,

Plaintiff,

v.

ELI LILLY AND COMPANY,

Defendant.

Case No. 3AN-06-05630 CI

PLAINTIFF'S RESPONSES TO DEFENDANT'S FIRST SET OF REQUESTS FOR PRODUCTION OF DOCUMENTS

Pursuant to Rule 34 of the Alaska Rules of Civil Procedure, Plaintiff provides the following Responses to Defendant's First Set of Requests for Production of Documents. Plaintiff specifically reserves the right to supplement and amend these responses as provided by the applicable rules of procedure.

REQUESTS FOR PRODUCTION

REQUEST FOR PRODUCTION NO. 1: Any charts that identify the State of Alaska's Department of Health and Social Services organizational structure from 1996 to the present, including but not limited to, charts that set forth the organization of the various departments and the heads and/or employees of each such department.

RESPONSE: See ZYP-AK-00001-00002.

REQUEST FOR PRODUCTION NO. 2: Each Medicaid State Plan in effect for the State of Alaska since 1996.

RESPONSE: See the website referred to in the State's response to Interrogatory No. 1. The State will produce copies of all Medicaid Plans in its possession as soon as possible.

REQUEST FOR PRODUCTION NO. 3: Each formulary and/or Preferred Drug List (PDL) in effect for the State of Alaska's Medicaid State Plan since 1996.

RESPONSE: See ZYP-AK-00003-00166. The State will supplement this response with additional documents as soon as possible.

REQUEST FOR PRODUCTION NO. 4: Any manuals provided to Medicaid providers from 1996 to the present that relate to Zyprexa or reimbursement for prescription drugs.

RESPONSE: The pharmacy provider manual is found on the Medicaid website and can be located at http://Alaska.fhsc.com. See also ZYP-AK-00167-00892. The State will supplement this response with additional documents as soon as possible.

REQUEST FOR PRODUCTION NO. 5: Any documents demonstrating payments Alaska made for Zyprexa since 1996 for which Alaska seeks reimbursement from Lilly in this litigation, including the documents that reflect the amount that Alaska has paid, to whom it made payments, and for whose prescription it has made payments.

RESPONSE: The State objects to this request to the extent it seeks information and/or documents, the disclosure of which would violate the privacy or confidentiality rights of non-parties including, but not limited to, those privacy rights guaranteed by the Federal and state constitutions as well as Federal and state statutes and regulations. The State further objects to this request in that it seeks information that is irrelevant to the claims and defenses of the parties and is not reasonably calculated to lead to the discovery of admissible evidence.

Subject to and without waiving these objections, the State will provide in electronic form the data described in the State's response to Interrogatory No. 10. Further, to the extent this request seeks information related to the State's damages, this response will be supplemented and

made as part of the expert disclosures and accompanying reports related to its proof of damages in this case.

REQUEST FOR PRODUCTION NO. 6: All medical records from the birth of the patient to the present for any patient whose Zyprexa prescription(s) were paid for by Alaska, and which Alaska seeks reimbursement for in this litigation.

RESPONSE: See response to Request for Production No. 5 above. As the State noted in its Memorandum Describing its Claims and Proofs, because the State seeks compensation for increased costs within a population, its burden is to establish general causation in that population (i.e., the rate by which Alaska Medicaid recipients who took Zyprexa show an increased incidence of diabetes compared to the background rate of the disease in matched controls). The State does not need to prove specific causation in any particular individual.

REQUEST FOR PRODUCTION NO. 7: Any documents demonstrating payments Alaska made for treatment of injuries allegedly caused by Zyprexa for which Alaska seeks reimbursement from Lilly in this litigation, including the documents that reflect the amount that Alaska had paid, to whom it made payments, and for whose treatment it has made payments.

RESPONSE: See response to Request for Production No. 5 above.

REQUEST FOR PRODUCTION NO. 8: All medical records from birth of the patient to the present for any patient whose treatment for medical injuries was paid for by Alaska, and for which Alaska seeks reimbursement in this litigation.

RESPONSE: See responses to Requests for Production Nos. 5 and 6 above.

REQUEST FOR PRODUCTION NO. 9: Any documents reflecting communications or transactions relating to Zyprexa between Alaska and Alaska's PBM(s) including (a) agreements, (b)

pharmacy benefit design records, (c) drug utilization reviews, (d) formulary management programs, (e) records relating to mental health disease management, and (f) communications to physicians.

RESPONSE: The State will produce the minutes of a Drug Utilization Review concerning the connection between Zyprexa and diabetes. Because those minutes contain patient health information, they cannot be produced until the entry of an appropriate protective order. See responses to Request for Production Nos. 5 and 6 above. Upon information and belief, the State has no other documents responsive to this request.

REQUEST FOR PRODUCTION NO. 10: Any documents reflecting the agreements concerning Zyprexa between Alaska and Alaska's PBM(s) (including those related to rebate sharing arrangement).

RESPONSE: The State has no documents responsive to this request.

REQUEST FOR PRODUCTION NO. 11: Any formularies and/or Preferred Drug Lists (PDLs) relating to Zyprexa.

RESPONSE: See response to Request for Production No. 3 above.

REQUEST FOR PRODUCTION NO. 12: Any documents concerning Zyprexa considered by any Pharmacy & Therapeutics ("P&T") Committee, or similar committee or individual, or by any individual with supervisory or management responsibility for any of the pharmacy benefits offered to Medicaid recipients, or any role in selecting drugs for the formulary and/or PDL.

RESPONSE: The State objects to this request as vague, ambiguous, and unintelligible. Subject to and without waiving this objection, upon information and belief, the State has no documents responsive to this request.

REQUEST FOR PRODUCTION NO. 13: Any documents concerning clinical summaries of Zyprexa performed by Alaska, or Alaska's PBM(s).

RESPONSE: See response to Request for Production No. 12 above. Subje

without waiving this objection, see response to Request for Production No. 9 above.

REQUEST FOR PRODUCTION NO. 14: Any documents concerning Alaska's

or proposed changes to, any formulary or PDL relating to Zyprexa.

RESPONSE: The State has no documents responsive to this request.

REQUEST FOR PRODUCTION NO. 15: Any documents concerning Alaska's decision to include or not to include Zyprexa on its formulary, or PDL, to place restrictions on Zyprexa, or any other decision concerning the formulary or PDL status of Zyprexa.

RESPONSE: The State has no documents responsive to this request.

REQUEST FOR PRODUCTION NO. 16: Any documents reflecting misrepresentations by Lilly to Alaska.

RESPONSE: The State has in its possession documents produced by Lilly in the MDL collection. Discovery in this case has just begun, thus the list of documents provided is neither intended to be all-inclusive nor exhaustive, but merely illustrative of the types of documents the State intends to use to prove its claims. The State reserves its right to supplement this response as discovery progresses. See generally the documents produced by Lilly in the MDL and listed on ZYP-AK-00893-00970.

REQUEST FOR PRODUCTION NO. 17: Any documents reflecting misrepresentations by Lilly to Alaska's PBMs.

RESPONSE: See response to Request for Production No. 16 above.

REQUEST FOR PRODUCTION NO. 18: Any documents reflecting misrepresentations by Lilly to physicians that prescribed to Alaska Medicaid recipients.

RESPONSE: See response to Request for Production No. 16 above.

REQUEST FOR PRODUCTION NO. 19: Any documents reflecting misrepresentations by Lilly to Alaska's Medicaid recipients.

RESPONSE: See response to Request for Production No. 16 above.

REQUEST FOR PRODUCTION NO. 20: Any documents concerning communications or transactions between Alaska and any consultant related to pharmacy benefits for Alaska's Medicaid recipients.

RESPONSE: The State objects to this request in that it seeks information that is irrelevant to the claims and defenses of the parties, is not reasonably calculated to lead to the discovery of admissible evidence, and is overly broad. Subject to and without waiving these objections, the State has no documents responsive to this request.

REQUEST FOR PRODUCTION NO. 21: Any documents concerning transactions or communications between Alaska or Alaska's PBMs and Lilly regarding Zyprexa.

RESPONSE: The State has no documents responsive to this request.

REQUEST FOR PRODUCTION NO. 22: Any documents concerning communications between Alaska and physicians regarding Zyprexa.

RESPONSE: The State has no documents responsive to this request.

REQUEST FOR PRODUCTION NO. 23: Any documents concerning communications by Alaska to Medicaid recipients regarding Zyprexa.

RESPONSE: The State has no documents responsive to this request.

REQUEST FOR PRODUCTION NO. 24: Any documents concerning transactions or communications between Alaska and any anti-psychotic manufacturer other than Lilly regarding Zyprexa.

RESPONSE: The State has no documents responsive to this request.

REQUEST FOR PRODUCTION NO. 25: Any documents concerning the pricing of Zyprexa.

RESPONSE: Such documents are contained in the pharmacy benefits manual. See the administrative code, Medicaid website and pharmacy benefits manual provided in response to Request for Production No. 4 above.

REQUEST FOR PRODUCTION NO. 26: Any documents concerning communications to any other states relating to Zyprexa.

RESPONSE: The State objects to this request in that it seeks information that is irrelevant to the claims and defenses of the parties and is not reasonably calculated to lead to the discovery of admissible evidence. The State further objects that this request seeks information which is beyond the scope of permissible discovery and which is protected from disclosure by the attorney-client privilege and/or the attorney work product doctrine.

REQUEST FOR PRODUCTION NO. 27: Any Drug Utilization Reviews and/or Drug Class Reviews by Alaska concerning Zyprexa.

RESPONSE: See response to Request for Production No. 9 above.

REQUEST FOR PRODUCTION NO. 28: Any treatment algorithms or protocols concerning Zyprexa, schizophrenia, or bipolar disorder recommended to physicians or required for physicians by Alaska.

RESPONSE: The only protocol in use in Alaska is the BPMS program provided by a grant from Eli Lilly.

REQUEST FOR PRODUCTION NO. 29: Any documents concerning any involuntary medications by Alaska using Zyprexa.

RESPONSE: The State objects to this request to the extent it seeks information and/or documents, the disclosure of which would violate the privacy or confidentiality rights of non-parties including, but not limited to, those privacy rights guaranteed by the Federal and state constitutions as well as Federal and state statutes and regulations. The State further objects to this request in that it seeks information that is irrelevant to the claims and defenses of the parties and is not reasonably calculated to lead to the discovery of admissible evidence.

REQUEST FOR PRODUCTION NO. 30: Any documents concerning lawsuits filed by Alaska against any manufacturer of atypical anti-psychotics other than Lilly.

RESPONSE: The State has no documents responsive to this request.

REQUEST FOR PRODUCTION NO. 31: Any studies or analyses performed by Alaska to assess the effect of prescribing atypical antipsychotics to mental health patients on overall costs to the state.

RESPONSE: See ZYP-AK-00971-00984.

REQUEST FOR PRODUCTION NO. 32: Any documents provided to or developed by your expert witnesses.

RESPONSE: The State objects to this request in that it seeks information which is beyond the scope of permissible discovery and which is protected from disclosure by the attorney-client privilege and/or the attorney work product doctrine. Subject to and without waiving this objection, this response will be supplemented and any non-privileged materials made available as part of the expert disclosures and accompanying reports in this case.

REQUEST FOR PRODUCTION NO. 33: Any documents provided to the Garretson Law Firm for the purpose of developing liability or damages models.

RESPONSE: See response to Request for Production No. 32 above.

REQUEST FOR PRODUCTION NO. 34: Any liability or damages models developed by the Garretson Law Firm for this matter.

RESPONSE: See response to Request for Production No. 32 above.

REQUEST FOR PRODUCTION NO. 35: Any claims profiles or damages profiles concerning Alaska Medicaid recipients, and any documents used to develop those profiles.

RESPONSE: See response to Request for Production No. 7 above.

REQUEST FOR PRODUCTION NO. 36: Any documents identified in, or consulted in preparing, your response to Defendant's First Set of Interrogatories.

RESPONSE: See documents provided with the State's responses to these Requests for Production.

REQUEST FOR PRODUCTION NO. 37: Any documents that you intend to rely upon to prove your claims in this matter.

RESPONSE: As discovery has just begun in this case, the State reserves the right to supplement this response as discovery progresses. Generally, the State may rely upon any documents produced by any party or non-party in discovery in this matter, and any documents produced by any party or non-party in the MDL litigation.

Respectfully SUBMITTED and DATED this 23rd day of April, 2007

FELDMAN, ORLANSKY & SANDERS
Counsel for Plaintiff

BY _____

Eric T. Sanders
Alaska Bar No. 7510085
500 L Street
Suite 400
Anchorage, AK 99501
(907) 272-3538

GARRETSON & STEELE
Matthew L. Garretson
Joseph W. Steele
5664 South Green Street
Salt Lake City, UT 84123
(801) 266-0999
Counsel for Plaintiff

RICHARDSON, PATRICK, WESTBROOK
& BRICKMAN, LLC
H. Blair Hahn
Christiaan A. Marcum
P.O. Box 1007
Mt. Pleasant, SC 29465
(843) 727-6500
Counsel for Plaintiff

CERTIFICATE OF SERVICE

Plaintiff, State of Alaska, hereby certifies that it has caused to be served upon the below listed individuals copies of Plaintiff's Responses to Defendants Request for Production by placing copies of same in a Federal Express envelope, postage prepaid, on April 23, 2007.

Respectfully submitted,

Eric T. Sanders
Feldman, Orlansky & Sanders
500 L Street, Suite 400
Anchorage, AK 99501
(907) 272-3538

COUNSEL FOR PLAINTIFF

Defendant's Counsel

Brewster Jamieson
Lane Powell
301 West Northern Lights Blvd, Ste 301
Anchorage, AK 99503-2648

Andrew Rogoff
Pepper Hamilton
3000 Two Logan Square
Eighteenth and Arch Streets
Philadelphia, PA 19103-2799

Dated: April 23, 2007