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

In The Matter of the Hospitalization of FAITH J. MYERS	)	Case No. 3AN 03-277 P/S
STATE OF NORTH CAROLINA	)	
_____ COUNTY	) ss	

An Analysis of the Olanzapine Clinical Trials – Dangerous Drug, Dubious Efficacy

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Sources of FDA Information:

Andreason, Paul. Review and Evaluation of Clinical Data, NDA 20-592, Reviewer Completion Date: July 29, 1996, pp 1-108, Appendices 7.2.1-7.2.4, Appendix 8.

Andreason, Paul. Statistical Review and Evaluation, NDA 20-592, February 14, 1996.

Efficacy of Olanzapine

- Four major studies were reviewed by the FDA for the purpose of establishing the efficacy of olanzapine in the treatment of chronic schizophrenia (acute exacerbation). These studies were identified with the following codes:
  HGAP, HGAD, E003, HGAJ.

  Two of these studies were rejected by the FDA and were thus omitted from the analyses of data used in validating the efficacy of the new drug relative to placebo:

  E003 - failed to establish any significant effectiveness for the drug in question
  HGAJ - poor trial design, with unacceptable biases in favor of experimental drug

The focus of this report is a methodical analysis of the experimental biases in both the clinical trials and the FDA evaluation process, leading to approval of the antipsychotic drug olanzapine (Zyprexa). A specific emphasis will be placed upon the two drug trials (HGAP, HGAD) used by the FDA to corroborate efficacy and safety of the experimental drug. These are the two trials which are referenced anonymously in the PDR and drug label. The goal of this paper is to clarify serious problems in the clinical study designs and statistical imputations of the olanzapine trials, so that the reader will emerge with an expanded capacity for critical reflection in psychopharmacological research and psycho-politics.

HGAP Trial

Multicenter, randomized, double-blind study
12 sites in US
Compared fixed doses of olanzapine (1.0 mg and 10.0 mg) vs. placebo
N - 152

Period I 4-9 day placebo lead-in period involving 152 patients meeting DSM-IIIR criteria for schizophrenia; patients had to have initial BPRS score of at least 24 (on scale of 0 to 6 for each of the 18 items in the scale), CGI of at least 4 (moderate severity)

Period II randomization of patients into one of three treatment groups.
Patients placed on olanzapine 10.0 mg were NOT titrated up to that dose from lower dose. This phase was six weeks in duration.

Subjects who had not responded to double-blind therapy after three weeks could enter **open-label phase of study at week four.**

73% of subjects dropped out of study after week four.

[What is NOT emphasized by the FDA or the sponsor is the fact that subjects were also eligible for **outpatient status after week four**, according to physician judgment.]

Period III Period II completers (six weeks) could enter open label phase of study at visit #8 (week six). Period II "changeovers" (non-responders who changed to open-label phase at week four, five, or six) were allowed to continue in open label extension

Concomitant medications:

Patients were allowed to *continue* a wide variety of medications which had been taken previously for pre-existing medical conditions. Patients were permitted to take lorezapam (Ativan) as needed or chronically, for sleep or agitation.

HGAP Trial

Study Design Problems

1) placebo washout: there is no mention of how many patients were taking neuroleptics (or other drugs) at the time of the placebo lead-in. We do not know how many of the patients in this study were actually exhibiting symptoms of medication discontinuation. **This turns the acute phase period (upon which efficacy has been established) into a comparison of drug withdrawal effects** – withdrawal on placebo, vs. withdrawal on olanzapine. The study, in effect, is a **comparison of supersensitivity psychosis in three different arms of subjects.**

2) failure of dose titration: again, patients were abruptly placed on 10.0 mg of Zyprexa in one arm of this study. This may have prejudiced results for that group in a favorable direction, as 10.0 mg may have had superior effects in protecting against withdrawal symptoms in those patients who had previously been taking neuroleptics for an extended period of time, or in subjects who may have been given high doses of potent drugs acutely.

3) concomitant medications: the allowance of concomitant medications for pre-existing medical conditions was an understandable part of the trial. However, it is unclear that the FDA or the drug sponsor has given adequate consideration to the impact of this variable. Concomitant medications given for pre-existing medical problems may be confounding factors in the trial for three reasons:
   a) many of the drugs permitted are known to have significant effects upon the brain (e.g., antihistamines, hormones, antihypertensives, cough medicines, and H2 blockers);
   b) many of the permitted drugs are known to induce or inhibit liver enzymes responsible for the metabolism of the experimental drug;

   and

   c) many of the pre-existing medical conditions for which concomitant drugs were allowed are, themselves, known risk factors for many of the symptoms which the trial was designed to track.

The use of lorazepam was allowed for acute or chronic insomnia or agitation. However, the FDA data do not present sufficient information to know which subjects were given lorazepam in each of the study arms, nor can it be determined to what degree the use of this drug may have contributed to patient outcomes according to responders and drop-outs.
The FDA database makes no reference to information which would permit a reasonable analysis of subject endpoints, based upon the possibility that "lack of efficacy" occurred in a higher proportion of those subjects who were not given lorazepam for neuroleptic-induced anxiety, neuroleptic withdrawal, or their pre-existing condition.
While Andreason contends that "there were no significant differences in the use of concomitant medications between groups" (meaning: olanzapine vs. placebo), this does not settle the question of the extent to which lorazepam use varied between RESPONDERS and COMPLETERS.

HGAP Trial

Study Design Problems

4) Drop-out rate: Period II was the "efficacy period," intended to last six weeks. Only 27% of the subjects completed Period II. This turned the HGAP study into a FOUR WEEK study. No results obtained after the four week mark can be generalized to the larger population, but results obtained at the six week mark are still interesting, as they demonstrate how closely placebo completers and olanzapine completers resembled each other in terms of SYMPTOM severity.

The implication is that there was NO DIFFERENCE between olanzapine and placebo in those who continued treatment.

** Results obtained AFTER the four-week mark cannot be used for the purpose of generalization to the larger population, as the study is underpowered (not enough subjects) to meet statistical requirements [80% power, > or = 40% reduction in BPRS scores, assumption of standard deviation = 14.56].

To find size needed to treat (past week four)
Take standardized effect size = desired mean change on BPRS / standard deviation
then locate sample size for that standardized ES at 80% power:

standardized effect size = 10 / 14.56 = 0.68
for 80% power (B – 0.20, alpha – 0.05), sample size = 26 in each arm
None of the treatment arms had 26 subjects or more past week four.

5) Reasons for the large drop-outs across all treatment groups after week FOUR

(Statistical Review and Evaluation, pp1-3)

Andreason acknowledges in his Statistical Review and Evaluation that physicians were free to qualify subjects for open-label participation at the four-week mark of the study, based upon "patient performance ...and physician judgment." The FDA was appropriately concerned about the cause(s) of the 73% drop-out rate after four weeks. When queried, the sponsor's representative (Dr. Charles Beasley) stated that many investigators had worried about the study design, in which they presumed that 2/3 of the subjects would invariably be harmed (greater risk of relapse) by treatment with placebo, or a dose of olanzapine believed to be non-active (ersatz placebo).

According to Beasley, subjects were disenrolled from the study at week four in order to spare them the "possibility of being continued in a group which investigators believed would be more prone to relapse." This makes little sense, based upon a trial design process which permitted physicians to transfer non-responders into the open label phase after week three.

Also, numerically speaking, 20 of the olanzapine 10 mg subjects dropped out of the study after week four, but we do not know how many of these subjects did so because of side effects or lack of efficacy. **Given the large number of drop-outs occurring even within the assumed "effective" treatment arm,** one must consider additional reasons for the poor completion rate in this study.

HGAP Trial

Study Design Problems

One potential source of experimental bias, apparently neglected by the FDA, is the fact that patients first became eligible for conversion to outpatient status based upon their week four assessment. This suggests (although by no means confirms) a bias in the study, whereby patients desirous of discharge from the hospital may have inflated their answers on rating instruments at weeks five and six.

As the data that are reported do not distinguish endpoints on the basis of "inpatient" vs. "outpatient" reporting in weeks five and six, **we cannot determine the extent to which patient "improvement" may have been compromised by a patient's overriding desire to obtain or continue outpatient status**. Similarly, we cannot know the extent to which physicians themselves were influenced (consciously or otherwise) in their assessments of subjects, due to the possible impact of such ratings upon treatment locale.

HGAP

Efficacy Results

1) "Dropouts were OVERWHELMING" (Andreason, Statistical Review and Evaluation pg 2).

2) **Completers in the placebo and olanzapine arms "not only did not differ at the end of the trial, but also hardly varied from each other during the whole course of the trial."** (Andreason, Statistical Review p2)

3) Percentage of Responders:

Responders were those subjects who demonstrated a change in BPRS of 40% or more, following a minimum completion of two weeks in the study

	Responders
Placebo arm	4/ 43 subjects = 9.5%
Olanzapine 10.0 mg	12/42 subjects · 27.9%

4) Comparison of the average slopes for BPRS over time (a form of repeated measures analysis, considered by many statisticians to be superior to LOCF) demonstrated NO statistical significance between treatment groups (p =.345).

5) Re: possibility that negative symptoms caused by neuroleptics or neuroleptic withdrawal confounded endpoints

The FDA report (Statistical and Evaluation Review, pg 3) reveals that the sponsor performed a covariate analysis for the negative PANSS, using as covariates the changes from baseline in positive PANSS, PANSS depression item, and parkinsonian symptoms (Simpson-Angus Scale total). The FDA does not supply these data. However, the FDA states that this analysis demonstrated "no statistical differences" in any arm. This failure to obtain statistical significance may have been a reflection of the poor study power, due to high drop-out rates. It would be especially important for the FDA to confirm the extent to which parkinsonian symptoms may have confounded efficacy and drop-out rates in both placebo and experimental drug groups.

6) LOCF vs. OC data:

Endpoint data (efficacy results) were collected by assessing scores on several rating scales commonly used by RESEARCHERS (but not by everyday clinicians) to assess psychotic symptoms. Results were reported in two ways:

LOCF = last observation carried forward
wherever a subject dropped out of the study, the last measured score was used as the endpoint for that individual.

OC = observed cases
wherever a subject remained in the study (27% at end of six weeks), the most current rating was used as the endpoint

HGAP Trial

Efficacy Results

6) LOCF vs. OC data:

The FDA concedes that "**OC data at week six did not support olanzapine as being effective**" (Review and Evaluation of Clinical Data, p17).

Dr. Andreason is apologetic for this finding, but then sides with the manufacturer by suggesting that Observed Case data should be dismissed. Per Andreason, "OC data reflect the high drop-out rate of placebo treated patients who could not remain in the study... this left the least symptomatic patients in all groups to compare against each other. It is for this reason that LOCF and not OC data represent a clearer picture of the true efficacy of olanzapine in this patient population."
[Review and Evaluation of Clinical Data, p 18]

In fact, at the six week mark of the study, almost EQUAL numbers of subjects remained in EACH group – particularly if the placebo pool is combined with the olanzapine 1.0 mg pool:

Subjects Remaining at Six Weeks

Placebo	N – 50	at six weeks: N = 10	20%
Olanzapine 1.0 mg	N = 32	at six weeks: N = 12	23%
Olanzapine 10.0 mg	N = 50	at six weeks: N = 19	38%

Thus, at the end of the six week acute phase, OC data demonstrate a comparison between 22 subjects taking either placebo or the lowest dose of olanzapine, and 19 subjects taking 10.0 mg of olanzapine.
This suggests that OC data provide a very good gauge of six-week outcomes, for those subjects willing or able to remain in the study for the full six weeks.
If Andreason wants to suggest that six-week data unfairly reflect "less symptomatic placebo subjects" due to previous drop-outs, then he must logically concede that six-week data similarly reflect "less symptomatic olanzapine subjects" due to previous drop-outs.

HGAP Trial

Efficacy Results

Andreason contends that LOCF gives a truer picture of medication efficacy. What LOCF PROBABLY gives is a truer picture of how the **active** forms of any drug (compared to placebo) are able to eclipse **drug withdrawal or rebound symptoms** in study subjects, as we can assume that most of these individuals were abruptly removed from their previous medication regimens during the placebo lead- in phase.

Andreason implies that placebo patients "left the study" in a disproportionate fashion *due to lack of efficacy*. In fact, the number of patients who left the study for "lack of efficacy" was impressive BUT **NOT STATISTICALLY significant** across all three groups of subjects:

HGAP drop-outs due to lack of efficacy

74%	of placebo patients
62 %	of 1.0 mg olanzapine patients
56%	of 10.0 mg olanzapine patients

A final concern about "efficacy" as measured by the FDA in all of the trials pertains to effect size. This means that statistics are presented, and conclusions drawn, relative to reductions in symptoms on the BPRS, PANSS (positive and negative), or CGI rating scales. What is not emphasized by Dr. Andreason (FDA) is the fact that there is much debate about the *meaning* of these changes in scores. Thus, while statistically significant differences in rating scales may be obtained across studies, there is no consensus that any of these observed differences are of CLINICAL import (that is to say, a change of 5 points might be just as clinically meaningful, or meaningless, as a change of 10-20 points). The FDA side-steps this very important philosophical and clinical issue, although Dr. Paul Leber is at least decent enough to mention this problem in a memo addressed to Dr. Robert Temple on AUG 18 1996. It is also possible that many patients experience a temporary regression as a part of recovery from an acute psychotic episode. To the extent that this results in changes in rating scales, there may be a false assumption that early reductions in symptoms portend the best long-term prognosis.

- Note: BOTH of these interpretive problems occur throughout the FDA analysis of the olanzapine trials:

  1) preference for LOCF data instead of OC data to establish efficacy
  2) acceptance of statistically significant "mean changes" (on rating scales) despite lack of evidence that these measures are in any way clinically meaningful

HGAD Trial

Multicenter, randomized, double blind study
23 sites in US and Canada
Compared multiple fixed doses of olanzapine (5.0 mg +/- 2.5, 10 mg +/- 2.5, 15 mg +/- 2.5) against ONE fixed dose of Haldol (15.0 mg +/- 5.0 mg) and placebo.

N = 335

Period I 4-9 day placebo lead-in period (neuroleptic washout) involving **419 inpatients** meeting DSM-IIIR criteria for schizophrenia (experiencing acute exacerbation of their illness: initial BPRS score of at least 24 and CGI of at least four)

Note: **84 patients were not continued in the study**. Reasons are not given in the FDA record, but these drop-outs may have been due to unfavorably high rate of placebo response in some of these subjects (i.e., investigators elected not to continue individuals who demonstrated too much improvement in BPRS while taking placebo during the lead-in phase).

Period II Randomization of 335 patients into one of three treatment groups for six weeks (multiple dose olanzapine, fixed dose Haldol, placebo).
At visit #5 (week two), subjects could switch over to open-label arm as OUTPATIENTS depending upon performance in trial and physician judgment.

Period III continuation of double blind for up to one year in subjects who were positive responders in period II.

Period IV open ended continuation of period III in subjects who wanted to continue in double blind therapy

Period V open label extension for patients who had previous exposure to olanzapine who wanted to continue

- Note: principal investigator at study site #2 (Dr. Richard L. Borison) was indicted for research misconduct. While FDA dismisses the relative importance of Borison's data (number of patients contributed to database -- 17), the results from his center were nonetheless reviewed and included for the purposes of determining olanzapine's efficacy.

Concomitant medications:

Patients were allowed to *continue* a wide variety of medications which had been taken previously for pre-existing medical conditions. Patients were permitted to take lorezapam (Ativan) as needed or chronically, for sleep or agitation.

HGAD Trial

Problems in Study Design

1) placebo washout and abrupt neuroleptic withdrawal syndromes:
there is no mention of how many patients were taking neuroleptics (or other drugs) immediately prior to the placebo lead-in phase, but it is presumed that this number was high (all patients were inpatients at the start of the study, experiencing an exacerbation of symptoms).

   Thus, we can assume that many of the subjects randomized to the placebo or low dose olanzapine arms of the study manifested the symptoms of neuroleptic WITHDRAWAL in addition to, or instead of, symptoms of their pre-existing schizophrenia. [In fact, we do not know how many of these same subjects were experiencing the "exacerbation" of their psychoses because of an *earlier* withdrawal from neuroleptics. In that case, the trial simply extended or repeated those previous experiences.] Thus, the trial was designed in such a way as to induce, or worsen, symptoms of schizophrenia in the study groups who were not exposed to the experimental drug at medium or higher doses.
   HGAD is a clinical trial that *compares neuroleptic withdrawal syndromes* (supersensitivity psychosis and/or tardive phenomena) in three different arms of subjects.

2) placebo lead-in and removal of early placebo responders: 419 subjects were enrolled in the study, based upon selection criteria. **84 of these subjects were disenrolled during the first 4-9 days of the study.** No reasons are given by the FDA for this large drop-out, but one can assume that these subjects were removed from the study in order to maxmize comparative efficacy of the experimental drug. **In other words, subjects who responded to placebo early in the study were simply not counted in the final results, so that the overall pool of placebo responders was reduced.**

3) Comparison of non-equieffective doses:
Patients on olanzapine were given doses ranging from 5.0 mg (+/- 2.5 mg) up to 15 mg (+/- 2.5 mg). Patients on haloperidol were given a fixed dose in range of 15.0 mg (+/- 5.0 mg).

   In terms of BINDING affinity, the comparative doses for each level of olanzapine used in this study would have been as follows:

   (This information is taken from Bezchlibnyk-Butler and Jeffries (2002), Clinical Handbook of Psychotropic Drugs, Seattle: Hogrefe & Huber Publishers, pp 90-91)

   olanzapine 10 mg (based on D2 affinity and pharmacokinetics)
   55-80% D2 Receptor occupancy

   haloperidol 2 mg (based on D2 affinity and pharmacokinetics)
   75-89% of D2 Receptor occupancy

HGAD Trial

Study Design Problems

4) Non-equieffective Doses

In terms of receptor binding and D2 occupancy, 10 mg of olanzapine would have been equieffectively dosed with 2 mg of haloperidol.

In THIS study (as in all the other studies with Haldol), we see the following comparisons:

Olanzapine 2.5 mg - 7.5 mg	vs.	Haldol 10 – 20 mg
Olanzapine 7.5 – 12.5 mg	vs.	Haldol 10 – 20 mg
Olanzapine 12.5 – 17.5 mg	vs.	Haldol 10 – 20 mg

Equieffective DOSING would have been:

Olanzapine 2.5 - 7.5 mg	vs. Haldol	0.5mg - 2.5 mg
Olanzapine 7.5 mg – 12.5 mg	vs. Haldol	1.5 mg – 2.5 mg
Olanzapine 12.5 mg – 17.5 mg	vs. Haldol	2.5 mg 3.5 mg

This means that patients in olanzapine HIGH arm of study received 4-6 TIMES the equivalent dose of Haldol (OVERDOSED on HALDOL four- to six-fold). Patients in olanzapine MEDIUM arm received 7-8 TIMES the equivalent dose of Haldol (overdosed on Haldol seven- to eight-fold). Patients in olanzapine LOW arm of study received 8 to 20 times the equieffective dose of Haldol (OVERDOSED eight- to TWENTYfold).
This HAD to have prejudiced DROPOUT from study in favor of olanzapine, due to side effects or lack of efficacy.

Why OVER-DOSING Haldol contributes to DIMINISHED efficacy on Rating Scales Used in the Study

Due to the use of such high levels of a potent, typical neuroleptic (Haldol), it is likely that Haldol subjects experienced more parkinsonian symptoms (and possibly more TD) than olanzapine subjects. This would necessarily contribute to elevations in negative symptoms of schizophrenia, reflected in both total BPRS scores, PANSS (negative), and CGI. There is a substantial body of literature documenting the phenomena of NEUROLEPTIC INDUCED DEFICITS, Tardive Dysmentia, and Tardive Anosognosia.

Without testing specifically for the variance in negative symptoms associated with EPS or TD in the olanzapine vs. Haldol subjects, the FDA cannot conclude that olanzapine has superior efficacy (compared to Haldol) in treating schizophrenia. Eli Lilly has unfairly prejudiced the outcome results by INDUCING or EXACERBATING pre-existing negative symptoms in Haldol subjects, while giving comparatively low doses (D2 receptor occupancy) in the olanzapine subjects.

It is important to remember that negative parkinsonian symptoms seem to be linked closely to D2 receptor blockade; thus, it is significant that the study compares 55-80% receptor occupancy in olanzapine against 75-89% receptor occupancy in haloperidol. One must wonder what kinds of EPS or TD might emerge in olanzapine patients maintained on doses that result in 75-89% receptor occupancy.

[SEE references on NIDS, Tardive Dysmentia, Tardive Frontal Lobe Syndromes]

HGAD Trial

Study Design Problems

5) Drop-out: **Only 42% of 335 subjects completed six weeks of this study.**

Andreason (Statistical Review and Evaluation, pg 3) concedes: **"Dropouts were overwhelming due to lack of efficacy."**

HGAD Completion Rates (at six weeks) were as follows:

Placebo	N = 22	32.4%
olanzapine low	N = 27	41.5%
olanzapine med	N = 26	40.6%
olanzapine high	N = 34	49.3%
Haldol	N = 30	43.5%

HGAD Drop-Out Rates

	Lack of Efficacy		Adverse Event		Patient Decision	
Placebo	N = 32	47%	N = 7	10.3%	N = 2	2.9%
Olz low	N = 22	33.8%	N = 5	7.7%	N = 7	10.8%
Olz med	N = 24	37.5%	N = 1	1.6%	N = 7	10.9%
Olz high	N = 18	26.1%	N = 4	5.8%	N = 7	10.1%
Haldol	N = 19	27.5%	N = 6	8.7%	N = 7	10.1%

RE: Drop-out for lack of efficacy:

Placebo patients dropped out more frequently for lack of efficacy than olanzapine and Haldol, but this is what one would expect given the fact that these were patients in the midst of placebo-washout from previous neuroleptics (all patients had been in hospital for at least 4-9 days, presumably on neuroleptics and/or other drugs).

RE: Drop-out for adverse events:

Adverse events were higher in the placebo and Haldol patients. Placebo events may have been attributable to neuroleptic withdrawal. Haldol events may have been attributable to non-equieffective (HIGH) doses used for that arm of the study.

RE: Drop-out for "patient decision":

- Note: no discussion or clarification is offered to explain the content of these patient decisions, but it is reasonable to suspect that withdrawal syndromes in the placebo arm, and side effects in the active drug arms (especially weight gain or sedation in olanzapine; akathisia, EPS, and/or TD in Haldol) may have been contributing factors.

HGAD Trial

Study Design Problems

6) cross-over to outpatient status: investigators were permitted to switch subjects into the **OPEN label OUTPATIENT phase of the study after two weeks** of observation. This decision removed the "double blind" of the investigation at a very early point in the trial. **In effect, this was NOT a double-blinded study after two weeks (if it ever was).** Furthermore, it is highly likely that outpatient status – once attained · was not likely to be jeopardized by patients who might otherwise have communicated more openly about deterioration or plateau in symptoms. The decision to permit olanzapine patients to continue their medications in a non-blinded, outpatient status after TWO weeks may have substantially favored outcomes for the experimental drug.

HGAD Trial

Efficacy Results

1) BPRS baselines used in this study were slightly higher in olanzapine subjects than in Haldol or placebo subjects. That is to say, the study examined multiple fixed doses of olanzapine in a "sicker" group of patients at the start of the study. This may have made it easier to demonstrate larger RELATIVE improvements in olanzapine patients (vs. placebo).

2) **No dose effect was revealed in this study.** Olanzapine-MED showed improvement over placebo in Observed Case BPRS *positive* scale, but NOT in BPRS *negative* scale. **In general, Observed Case data failed to prove that olanzapine is more effective than placebo.**

3) No endpoints in the Observed Case SANS or CGI Severity scales attained statistical significance. BPRS total score change in Observed Cases did attain statistical significance in olanzapine medium and olanzapine high (relative to placebo), but the clinical significance of these changes is uncertain. That is to say, it is unclear that a mean change in total BPRS of ten is clinically more meaningful than a mean change of five.

4) Dr. Andreason again gives preference to LOCF data, suggesting that OC data reflect "less symptomatic placebo subjects." Andreason implies that Observed Case data are invalid because they reflect the symptom level of a subject pool that remains following a large number of drop-outs for low efficacy. In fact, the statistics demonstrate that **LACK OF EFFICACY was a common occurrence across all arms of the trial.**

   The FDA decision to validate olanzapine efficacy using LOCF methodology compels a closer consideration of the limitations of this approach:

   a) LOCF improperly assumes that all subjects who drop out will remain stable (i.e., last observed endpoint will neither improve, nor deteriorate) This is an especially dangerous assumption to make in psychiatry, where many conditions may actually improve over time

   b) LOCF artificially inflates the advantages of the experimental DRUG by assuming that placebo (or comparison drug) drop-outs are occurring primarily for lack of efficacy. However, it is just as likely that placebo or comparison drug subjects drop out because of intolerable *side effects* associated with the respective treatment conditions (in other words, placebo subjects may drop out because of symptoms of neuroleptic withdrawal, rather than schizophrenia

   c) LOCF fails to make appropriate use of ALL data points BEFORE the last visit. By simply taking the last available data point, and by projecting it forward in time, LOCF loses the trajectory of how each subject may have been improving or deteriorating over time.

HGAD Trial

Efficacy Results

5) Responder analysis demonstrates that there was **NO statistically significant difference** between the PROPORTION of subjects in each arm of the study who RESPONDED to treatment, for purpose of any pairwise comparison.

Olanzapine High	32/65 subjects or	49.2% responded
Placebo	21/62 subjects or	33.9% responded

E003 Trial

Not used for efficacy evaluation due to negative findings
No placebo arm.
Providers allowed to titrate doses up/down farily liberally for clinical effect.

Highlights of this study
Multicenter, randomized, double blind study
50 sites in Europe, South Africa, Australia, Israel
431 patients.

Compared several fixed dose RANGES of olanzapine (5.0 mg, 10.0 mg, 15.0 mg +/- 2.5) vs.
Fixed dose olanzapine (1.0 mg) vs. fixed dose RANGE of Haldol (15.0 mg +/- 5.0)

Only 47% of the subjects completed six weeks.

***No significant improvement was noted in olanzapine (low / medium / high) doses vs. Haldol or "homeopathic" fixed dose of Olanzapine (1.0 mg).**

FDA was at a loss as to what they should do with this study, which suggested that 1.0 mg of olanzapine was having a beneficial effect in a significant number of patients. Andreason called this a "failed study" but did not explain what he meant by the word: failed. For thoughtful students of placebo effects, this study was a marked VICTORY.

It appears that the FDA buried this study, out of embarrassment or panic that it showed **NO dose effect:** and worse, **it implied that 1.0 mg of olanzapine was inducing a placebo benefit in patients.** After all, if a 1.0 mg dose of olanzapine could produce benefits ("active" placebo ?), then clinicians might have to consider the possibility that 2.5 mg, 5 mg, or 10 mg doses might also exert their salutary effects through placebo mechanisms in the body, rather than D2 receptor occupancy.

HGAJ Trial

Not used for efficacy evaluation due to poor design
Multicenter, randomized, double blind
186 sites in US and Europe
N = 1996 patients
Compared olanzapine RANGE (5 – 20 mg) vs. Haldol range (5 20 mg).
NO placebo arm.
Broader inclusion criteria: schizophrenia, schizophreniform, and schizoaffective.
Included subjects who had experienced adverse event on recent or current neuroleptic, or subjects who were "not tolerating their pre-study treatments."

FDA DECLINED to use this study for efficacy (but did use it for safety database), due to problems with selection bias. **38% of Haldol patients enrolled in study had FAILED Haldol previously.**

In discussing the HGAJ study, Andreason expresses for the first time some concerns about:

a) "non-comparable dose ranges"

without elaborating, Andreason suggests that dosing the two drugs on a "mg. for mg basis" biased the study "against Haldol." He suggested that dosing at lower doses, or slower dose increases would have similarly disfavored olanzapine (Review and Evaluation of Clinical Data, p. 33)

b) rating scale results (mean rating scores): Andreason raises for the first time some concerns that difference in mean scores had attained statistical significance, but that this significance (of dubious clinical significance · see pg 33) had been reached only *after* increasing the size of the study to very large numbers. He concludes that the study was OVERPOWERED, in order to obtain statistical significance on the rating scales

While it is encouraging that Andreason finally acknowledges some of these problems in the HGAJ study, it is worrisome that he is not similarly able to apply the same limitations to the two studies (HGAP, HGAD) whose data were used to establish the efficacy of the experimental drug. [i.e., HGAD also suffered from non-comparable dose ranges; HGAD and HGAP both suffered from rating scales whose clinical significance remains dubious]

Summary – Problems in Olanzapine Clinical Trials

Study Design and Efficacy Results

1) **No mention of previous drugs taken by patients in all arms of studies.**

We do not know how many drugs were being consumed by subjects before or during the trials. We do not know to what extent symptoms tracked during the studies were manifestations of an underlying condition, rather than manifestations of neuroleptic induced deficits or neuroleptic discontinuation syndromes.

2) **Failure to maintain "double blind".**

A number of the studies used for the purposes of establishing clinical efficacy broke the double blind intentionally, by permitting investigators to remove subjects into the open phase of the study. It is also possible that the "blinded" nature of the studies was further compromised by the adverse reactions present in many patients who received active neuroleptics (for example: weight gain and sedation with olanzapine; akathisia with Haldol).

3) **Concomitant medications:**

Despite the efforts of investigators to limit the use of centrally active medications in these studies, it appears that patients were permitted to continue using a wide variety of chemicals with known neuropsychiatric effects. These include hormonal therapies, antihypertensives, and H2 blockers. No data appear in the FDA report to explain treatment differences in subject arms according to the use of "permitted" concomitant medications. As lorazepam (Ativan) was allowed in many studies for the treatment of anxiety and insomnia, it would be important to know how many placebo vs. olanzapine subjects had endpoints which were influenced by the use of the benzodiazepine.

4) **High drop-out rates:**

HGAP 73% drop-out rate in four weeks
HGAD 68% drop-out rate in six weeks

Even the FDA analysts themselves refer on numerous occasions to the "overwhelming drop-out rates" present in the olanzapine studies. The loss of so many subjects presents two problems: first, it prevents the generalization of findings to a larger population. Second, it creates methodological problems in the evaluation of treatment differences. (see below)

Based upon these drop-out rates in the acute phases of the studies, the FDA appropriately refused to approve olanzapine as a maintenance therapy for schizophrenia, arguing that its long term effectiveness had not been demonstrated.

Summary of Problems – Study Design / Efficacy

5) **Placebo Washout:**

In one study (HGAD), the FDA refused to address the large number of drop-outs (84) which occurred in the first four to nine days of the study. As this was the placebo "lead-in" phase of the study, it is possible that these 84 individuals were removed because they demonstrated an unacceptably favorable response to the early placebo treatment. **By removing these 84 subjects from the overall data pool, the investigators biased the results in favor of the experimental drug (removing the placebo responders necessarily raised the comparative efficacy of olanzapine – particularly in LOCF analysis).**

6) **LOCF (last observation carried forward) to validate efficacy:**

In order to compensate for the missing data created by large numbers of drop-outs, the FDA used the LOCF technique. This method involved taking the last observed clinical findings in each subject who disenrolled, then carrying those ratings forward to each successive evaluation period as though each subject in question had NOT CHANGED over time.

LOCF data fail to capture the possible improvement of subjects, who might be lost to follow-up or who might withdraw from a study when they are feeling improved. LOCF data also assume that drop-outs occur primarily for lack of efficacy, when in fact, many subjects disenroll from a study because of adverse events or side effects (tolerability) – temporary conditions which may make the last observed endpoint inaccurate.

When Observed Cases (OC) data were compared in the olanzapine studies, olanzapine was not found to be effective. OC data revealed no significant difference between placebo and olanzapine. **Using OC rather than LOCF data, the FDA report consistently revealed that subjects in all treatment arms looked quite similar to each other in terms of symptom severity, not only at study endpoint, but also at each evaluation interval along the way.**

7) **Transition to outpatient care:**

Each of the studies used to establish efficacy permitted the transition of subjects from their initial treatment setting (inpatient) into outpatient status, depending upon "patient performance and physician judgment." In the HGAP study, this transition was permitted after four weeks. In the HGAD study, this transition was permitted after two weeks. **The FDA analysts fail to consider the proportion of placebo vs. olanzapine subjects in the outpatient setting at each interval of evaluation.** Failure to consider the effect of treatment milieu upon subjective symptom assessments may have favored the experimental drug. **It is likely that subjects in the open label portions of the study, and all outpatient settings, may have inflated their responses to treatment solely for the purpose of avoiding re-admission.** It is unknown if subjects involved in the research protocol were compensated monetarily for their participation, but this may have introduced another source of bias in favor of the experimental drug.

Although Andreason makes note of the sponsor's explanation of the high drop-out rate in the HGAP trial, he accepts that accounting with limited scrutiny. It was the sponsor's contention that 73% of the subjects dropped out because the physicians themselves were concerned about a study design which randomized 2/3 of the subjects into non-effective treatment arms (the physicians believed that placebo and low dose olanzapine would be equally useless). However, a closer examination of the study design reveals that physicians were free to place all non-responders into the open label arm of the study after three weeks. The large drop-out from the study occurred at week FIVE rather than week FOUR. Either the FDA has communicated unclear information about the timing of open-label changeovers in this particular study, or the sponsor has presented a limited rationalization of the high drop-out rate.

8) Statistically significant results may not be clinically significant:

The FDA approved olanzapine based upon studies which demonstrated statistically significant differences in treatment arms (placebo vs. varying doses of olanzapine). However, at no point did the FDA establish proof of statistically different *clinical relevance.*

In the HGAP study, investigators sought to obtain a mean change of 10 points on the BPRS rating scale, using LOCF analysis (Andreason, Statistical Review and Evaluation, p. 1). In the HGAD study, investigators sought to obtain a mean change of 8 on the BPRS rating scale (LOCF analysis) by week four (Andreason, Statistical Review and Evaluation p. 2).

While both studies suggest that olanzapine was successful in contributing to the attainment of these desired goals, the cutoffs themselves were arbitrary. There may be no clinically significant difference between a subject whose BPRS score improves by 5 or 15 points. **Furthermore, it is important to recall that OC data sets suggest NO difference in outcome between olanzapine and placebo. Particularly for those individuals who were capable of tolerating the active drug or placebo through the end of the acute study periods, the experimental drug offered no advantage to placebo.**

For reasons elaborated above, the LOCF data should have been rejected by the FDA, in favor of OC endpoints.

9) Dosing methods biased studies in favor of olanzapine:

In several studies, olanzapine subjects were placed abruptly on higher levels of the medication, rather than "titrating up" from 5 mg. This may have biased results in favor of the higher dose levels of the active drug. In other words, the relative efficacy of olanzapine in some subjects may have reflected the influence of increased D2 receptor occupancy (blockade) in off-setting the disabling symptoms of neuroleptic withdrawal or rebound.

Non-equieffective doses of Haldol in the HGAD study necessarily biased that trial in favor of olanzapine, due to a four- to twenty-fold comparative OVERDOSING of the older drug. This megadosing of Haldol may have guaranteed the creation of side effects, poor compliance, and negative deficits (parkinsonian and/or tardive). In the LOCF analyses, these drop-outs would have been especially prejudicial to comparative outcomes.

Regardless of the aforementioned biases, efficacy results were remarkable for the finding of **no dose effect** in olanzapine. **There was no consistent difference in symptom reduction based upon olanzapine doses (medium or high). This finding was present in both the LOCF and OC analyses of the relevant trials (HGAD, E003, HGAJ).** Furthermore, the FDA rejected study E003, but that trial was significant for the implication that low doses of olanzapine (1.0 mg) should not be dismissed as clinically irrelevant. If olanzapine 1.0 mg doses are included in the consideration of dose effects, then the implication of "no dose effect" broadens, and one must consider how much of any drug effect may be due to placebo mechanisms.

10) FDA failure to consider confounding variables impacting the metabolism of olanzapine:

Like many other psychotropic drugs whose metabolism depends upon hepatic clearance (the cytochrome P450 system), the effectiveness of olanzapine may have been heavily influenced by diet, concomitant medications, and smoking - the latter, a behavior which lowers olanzapine levels by inducing the drug's metabolism by the 1A2 cytochrome. Without knowing the percentage of smokers in each of the subject arms, one cannot fully appreciate the extent to which outcomes may have been influenced by these behaviors. In this case, lower doses of olanzapine may have been especially vulnerable to the influence of nicotine. Alternatively, patients who used smoking as a means of side effect control (nicotinic stimulation may or may not reduce parkinsonian symptoms) may have experienced better outcomes or better compliance.

11) Olanzapine trials failed to study efficacy in new onset psychosis:

None of the olanzapine trials assessed the impact of the drug in neuroleptic naïve patients. FDA approval was thus limited to the treatment of chronic schizophrenia, based upon trials which failed to establish long term effectiveness (efficacy beyond four to six weeks).

Safety of Olanzapine

- Data from five major studies were pooled for the purposes of evaluating safety. Results are summarized in the FDA report in a cryptic fashion. That is to say, the FDA report identifies a "primary database" and "secondary database" for safety. However, it does not clearly state the dates (durations of follow-up) which were used in evaluating outcomes for each of five component studies.

  Serious adverse reactions and deaths are reported from a pooled database (N = 3139), with **no *breakdown according to duration of drug exposure* associated with each kind of adverse reaction or fatality.** This aspect of the FDA summary report seems poorly constructed.

Of particular concern is the handling of the most serious adverse reactions (Andreason, Review and Evaluation of Clinical Data, pp 42-3):

Deaths: Olanzapine 20 (of 3139 subjects)

Suicide: Olanzapine 12 (of 3139 subjects)

HOWEVER, NO DATA are furnished for SUICIDE ATTEMPTS in the complete database (presumably, because the FDA or the sponsor failed to provide that information for the HGAP and HGAD trials).

As if to compensate for the missing suicide attempt data in toto, the FDA presents some specific information from the rejected HGAJ trial (Review and Evaluation of Clinical Data, p. 47):

Completed Suicides - HGAJ

for Olanzapine subjects:	9/2500	= 0.4%
for Placebo subjects:	1/236	= 0.4%
for Haldol subjects:	1/810	= 0.1%

At the very most, this data suggest that olanzapine is no more effective than placebo in reducing suicide. At the very least, there is the suggestion that olanzapine may be associated with a four-fold rate of suicide in patients, relative to older neuroleptics.

Information about suicide attempts is presented only for the HGAJ trial (page 47):

Suicide attempts - HGAJ

Olanzapine	3.4%
Placebo	4.0 %

These results were not found to be statistically significant.

Summary – Problems with Safety

1) **suicide / suicide attempts:**

Olanzapine does not appear to be any more or less effective than placebo in terms of completed suicide. Olanzapine may be associated with a higher rate of suicide than older neuroleptics.

The FDA provides no information about suicide attempts in the two trials which were used to establish efficacy

2) **liver injury**
(Review and Evaluation of Clinical Data, pp 101-102)

In light of the potential consequences of poorly monitored LFTs (liver function tests), it would seem that the FDA may have been cavalier in its summary. **Evidence existed in the trials for significant and early elevation of transaminases at levels that were 8 to 20 TIMES the upper limit of normal** (Review and Evaluation of Clinical Data, p 102). **In the acute phase, the percentage of patients with marked elevations in AST, ALT, and GGT was 2.9% for olanzapine; 0 % in placebo. For long term exposure (primary integrated database), rates were 6.6% for olanzapine; 3.6% for Haldol; and 3.7% for placebo** (Review and Evaluation of Clinical Data, p 102).

Precaution section of PDR label vastly understates these risks –
(Compare Andreason document – pp 101-102 with PDR)

3) **weight gain**
(Review and Evaluation, p 103)

In the acute phase placebo controlled study pool, 5.6% of olanzapine patients experienced weight gain. Average gain was 6.2 pounds (2.80 kg) in 6 weeks. In 29.3% of THESE patients, (vs. 2.7% of placebo) patients gained MORE than 7% of their baseline weight.

NO LONG TERM data (weight gain over time) are furnished by the FDA.

Andreason recommended that weight gain be listed under the PRECAUTIONS section of the product label. This did not occur. Instead, the FDA honored the wishes of the drug sponsor and moved weight gain information to the adverse effects section of the label.

Note: The issue of weight gain is significant for at least two reasons: phase IV of the drug development (post-trial) phase has revealed serious problems with hyperlipidemia, glucose dysregulation, diabetes, and in some cases, diabetic ketoacidosis.
The precise mechanism of these endocrinopathies has not yet been determined, but the issue of weight gain --- while not sufficient to explain the rapid development of type II diabetes in these patients – points to an underlying disturbance in homeostasis and catabolism.
Clinical trial data presented by the sponsor offer no evidence of glucose dysregulation, and no evidence that investigators monitored subjects regularly for any such possible disorders.

Summary – Problems with Safety

4) **prolactin level**
(Andreason, Review and Evaluation of Clinical Data, p 103)

The acute phase study pool demonstrated that 34% of the olanzapine subjects experienced elevated prolactin levels, compared to 13.1% of the placebo subjects. Although long term extension phases of each trial demonstrated that prolactin levels declined after the first 2-4 weeks of treatment, these levels remained at a plateau that was still approximately 50% above baseline.

Andreason conceded his concerns by acknowledging the fact that "the clinical significance of changes in serum prolactin is not clearly known," with many scientists hypothesizing a connection between hyperprolactinemia and hormonally sensitive cancers (such as breast cancer).

FORTUNATELY, Andreason's considerations were honored, and hyperprolactinemia was added to the PRECAUTIONS section of the olanzapine label.

OTHER REASONS why a psychiatrist should care about OLANZAPINE and PROLACTIN

Prolactin releasing peptide or PrRP (a protein in the central nervous system) is now felt to be one of several stress hormones in the body. Chronic elevations in PrRP may impair cognition and memory indirectly, by contributing to a cascade of events which leads to high levels of cortisol.

(SEE article and abstract about PROLACTIN RELEASING PEPTIDE)

a) new research suggests that PROLACTIN RELEASING PEPTIDE may act as a stress hormone in mammals, via a cascade of events between the midbrain and diencephalon

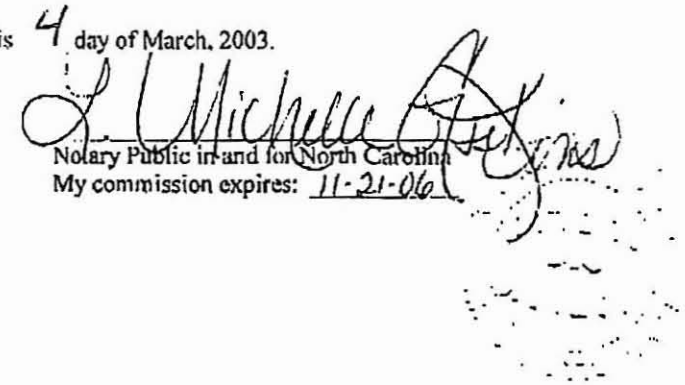
Complicated circuits in the hypothalamus lead ultimately to the production of elevated levels of cortisol. Hypercortisolemia can then have harmful effects upon immune function and memory (elevated cortisol is associated with hippocampal atrophy).

b) animal models suggest that OLANZAPINE may elevate cortisol levels via Prolactin Releasing Peptide. Olanzapine stimulates norepinephrine in the brainstem (midbrain, pons). These noradrenergic neurons then synapse with cells in the paraventricular nucleus of the hypothalamus, leading to the synthesis and release of prolactin releasing peptide. Prolactin Releasing Peptide stimulates hypothalamic neurons which produce corticotrophin releasing hormone (CRH). CRH then induces pituitary secretion of ACTH, with subsequent effects upon the adrenal glands (increasing cortisol levels in the body).

Consequently, it is highly likely that there are SEVERAL mechanisms through which neuroleptics modulate prolactin levels -- not all of those being direct effects upon the hypothalamus or pituitary; but rather, many of those effects occurring in the brainstem.

Grace E. Jackson, MD

SUBSCRIBED AND SWORN TO before me this 4 day of March, 2003.



Notary Public in and for North Carolina
My commission expires: 11-21-06