Role of Active Controls for Risk:Benefit Analysis in Antipsychotic Clinical Trials: Clinical/Academic Considerations

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Disclosures of Interest

Interest	Name of organization
Research Support *	**AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Merck, Pfizer and Wyeth**
Advisor *	**Astra Zeneca, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Pfizer and Wyeth; and as a member of the Data Safety Management Board (DSMB) for Solvay and Wyeth**
Other involvement	**Holds a patent from Repligen**

*** Receives no personal financial remuneration for any of these activities**

We need new treatments !

Limitations of Antipsychotics:

Unmet Clinical Needs

- Symptom attenuation (not symptom remission) in majority of patients
- Significant minority (up to 30%) are unresponsive and up to two thirds residually symptomatic
- Little to no efficacy for negative symptoms and cognitive impairment
- Limited efficacy for functional impairment
- Limited efficacy for symptom exacerbation and relapse prevention
- Poor adherence to treatment

What do academic investigators and clinicians want ?

- To know all about the drug beginning with its efficacy and safety, clinical indications and its MOA
- To determine a treatment's comparative effectiveness to other treatments
- To determine a treatment's cost effectiveness

Goal of Phase II and III Clinical Trials

- To demonstrate the efficacy, safety, benefit/risk relationship of new treatments
  - by demonstrating superiority over placebo
  - by demonstrating that the new drug is similar, or not inferior, in efficacy to an established effective dose of a standard drug (active comparator)
- Relevant issues: patient sample, outcome measure(s), choice of comparator(s), dose, trial duration

Changing Clinical, Political and (Possibly) Regulatory Environment

- Increasing discomfort with placebo comparators particularly for outpatient and maintenance or relapse prevention trials

- Clinicians, administrators and policy makers want to know how new treatments, both mechanistically novel and precedented, compare to existing marketed treatments

Consequences of Untreated Psychosis/Relapse

- With each successive relapse symptom attenuation takes longer and may be less robust
- Substantially higher risk of suicide and dangerous behavior in patients with untreated vs. treated psychoses
- DUP predictive of more severe negative, positive, and cognitive symptoms, and grey matter loss in long-term follow-up studies.

Suggestive of toxic effects of untreated psychosis

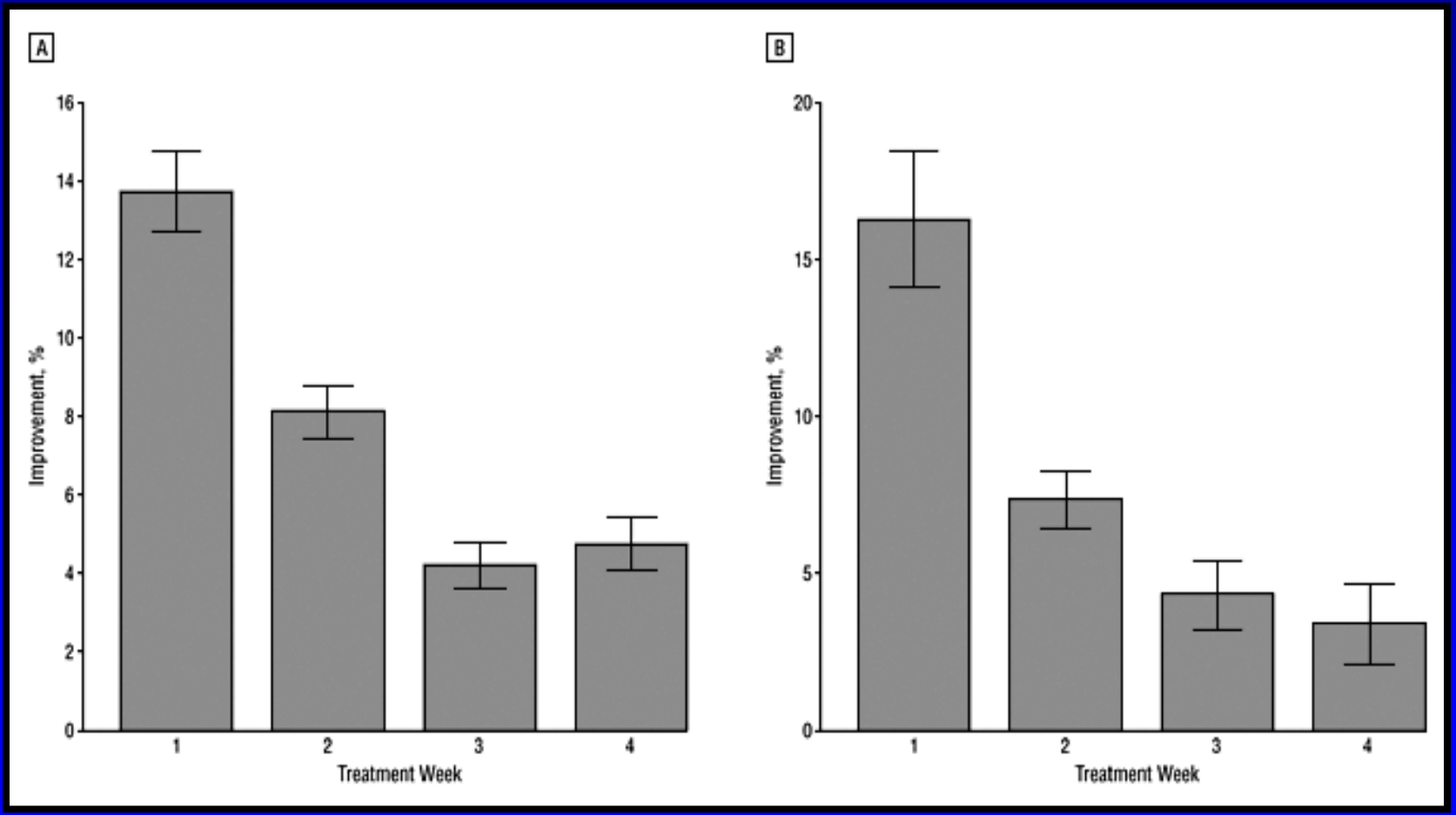
Loebel et al Am J Psychiatry 1991
Robinson, et al, *Arch Gen Psych* 1999
Perkins, et al, *Am J Psychiatry* 2005,
Marshall, et al, *Arch Gen Psych 2005,*
Lappin, et al, *Schiz Res 2006,*

Response to Antipsychotic Treatment Over Time

(Meta-analysis of 42 DB, PC Trails involving 7450 patients)

Overall clinical improvement

Psychotic symptom improvement



Agid, et al, *Arch Gen Psychiatry* 2003; 60:1228-1235.

Early Onset of Treatment Effects with Oral Risperidone

	PANSS Total	PANSS Positive	PANSS Negative	PANSS Gen. Psychopath.
Day 0 (n = 48)	100%	100%	100%	100%
Mean ± SD	110.9 ± 20.4	30.4 ± 5.2	25.3 ± 7.3	55.1 ± 11.8
Day 1 (n = 43)	96.7% ± 6.7%	97.7% ± 9.3%	96.8% ± 9.7%	96.3% ± 6.7%
Day 3 (n = 37)	87.3% ± 12.9%	85.1% ± 14.3%	91.1% ± 19.5%	88.0% ± 14.3%
Day 7 (n = 32)	76.6% ± 17.5%	69.6% ± 21.8%	83.6% ± 25.8%	79.0% ± 17.5%

Raedler, et al, *BMC Psychiatry* 2007; 7: 4

Efficacy-Effectiveness Gap

- Medical and Psychiatric Co-Morbidities
- Polypharmacy
- Variation in clinical settings, provider behavior, psychosocial treatments and living environment
- **Effectiveness Trials**

Role of Comparators

- Placebo – to distinguish effect of active agent from non-specific effects

- Active (Standard) Comparator
  - Assay sensitivity
  - Superiority
  - Non-inferiority
  - Equivalence

Justification for Placebo-Comparator

- Known high placebo response rate
- Therapy available but disease not serious
- Therapy available but has little benefit
- Adjunctive Treatments: Proven therapy + new therapy or placebo ("add-on trials" e.g., for negative symptoms, cognitive deficits)

Dropout Rates in Placebo-Comparator and Active-Comparator Trials of Antipsychotic Drugs

Table 2. Comparison of Dropout Rates in Active Treatment Arms of Placebo-Controlled Trials (PCTs) and Active-Control Trials (ACTs)

Type of Active Treatment	Mean Dropout Rate, %*		Odds Ratio (95% Confidence Interval), PCT vs ACT	Statistics
	PCTs	ACTs		
Second-generation antipsychotic	48.1	28.3	2.34 (1.58-3.47)	$t_{28} = 4.42$, $P<.001$
Classical antipsychotic	55.4	37.2	2.10 (1.29-3.40)	$t_{18} = 3.19$, $P = .005$
All antipsychotics	48.9	30.3	2.20 (1.46-3.33)	$t_{28} = 3.92$, $P<.001$

*Weighted mean using the weights of the random-effects meta-regression.

Table 3. Comparison of Dropout Rates in Placebo-Controlled Trials (PCTs) With Placebo Arms and With Active Treatment Arms

Type of Antipsychotic	No. of Trials	Mean Dropout Rate, %*		Odds Ratio (95% Confidence Interval), Placebo Arm vs Active Treatment Arm	Statistics
		Placebo Arms	Active Treatment Arms		
Second-generation antipsychotic	11	60.2	48.1	1.63 (1.37-1.94)	$t_{10} = 6.18$, $P<.001$
Classical antipsychotic	5	63.3†	55.4	1.39 (1.14-1.69)	$t_4 = 4.65$, $P = .01$
All antipsychotics	11	60.2	48.9	1.58 (1.36-1.84)	$t_{10} = 6.76$, $P<.001$

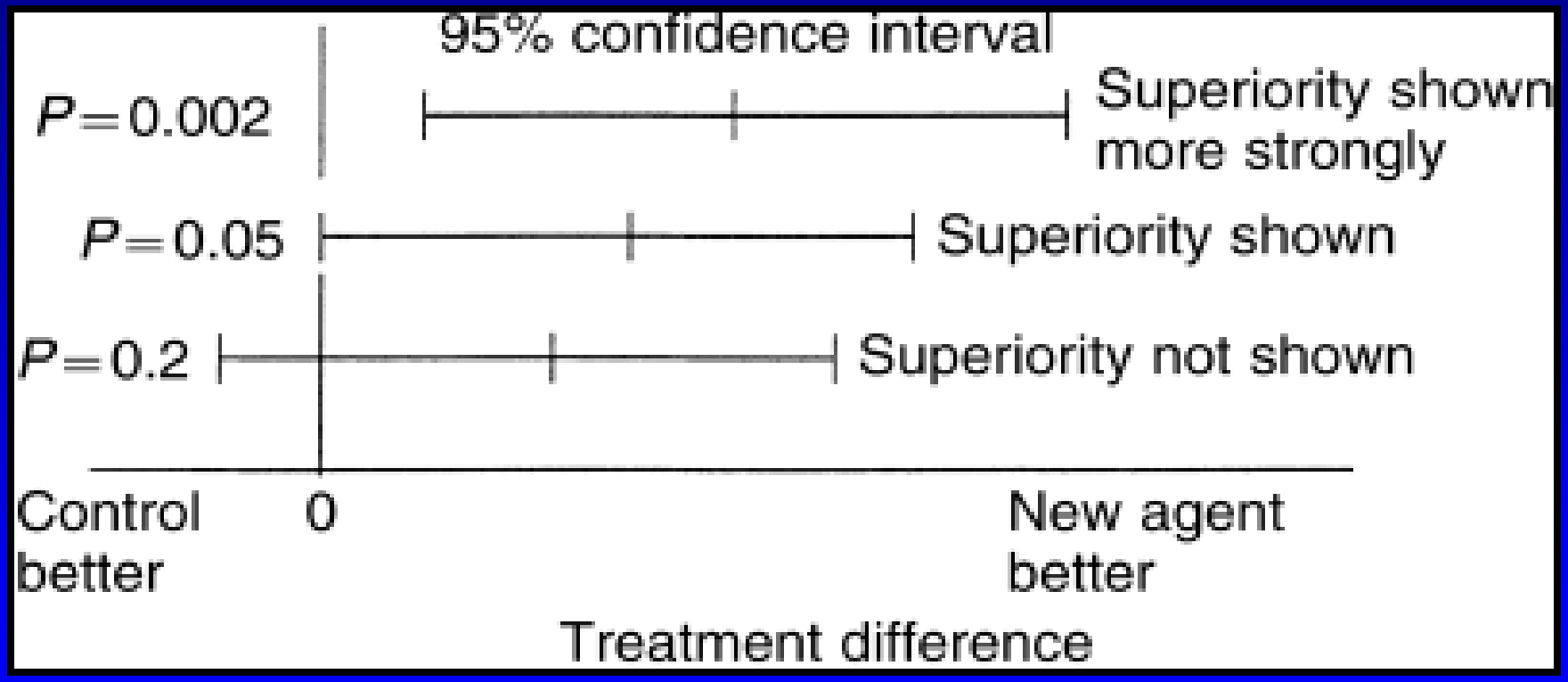
*Weighted mean using the same weights as in Table 2.
†Weighted mean dropout rate for the placebo arms of the 5 PCTs that included an arm with a classical antipsychotic.

Kemmler, et al, *Arch Gen Psychiatry* 2005; 62:1305-1312

Active Comparators:
Possible Reasons for Poor Assay Sensitivity

- High placebo response rate
- High rate of spontaneous improvement
- Poorly responsive study population
- Poor compliance
- Poor study quality
  - Inadequate patient sample
  - Poor protocol fidelity, violations of protocol
  - Poor quality of assessments

Superiority of New Treatment

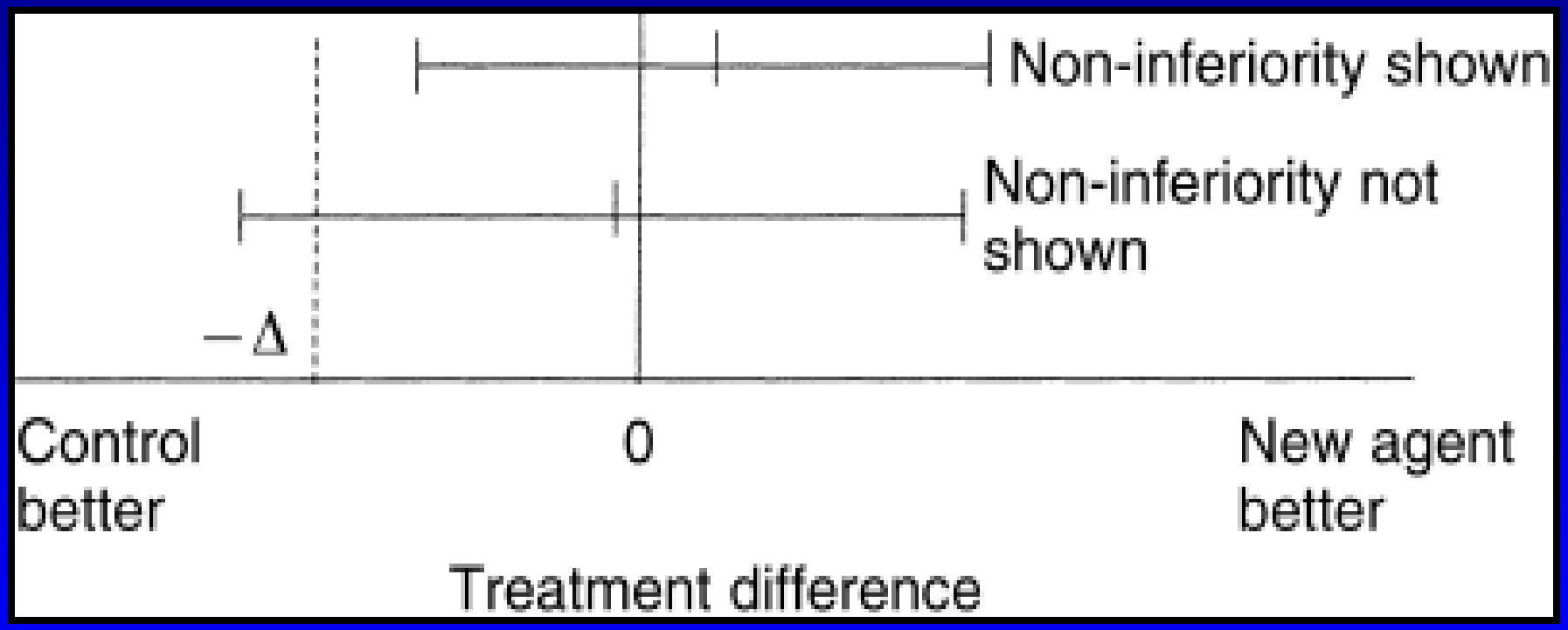


Committee for Proprietary Medicinal Products (CPMP)

"Points to consider on switching between superiority and non-inferiority"

***Br J Clin Pharm 2001;* 52(3):223**

Non-inferiority of New Treatment



Committee for Proprietary Medicinal Products (CPMP)

"Points to consider on switching between superiority and non-inferiority"

***Br J Clin Pharm 2001;* 52(3):223**

Advantages/Disadvantages of Active Comparators

- No subject exposed to known inactive treatment
- Facilitates approval from IRB's
- Easier recruitment
- Lower drop-out rate compared to PBO-controlled trials

BUT

- "No evidence of difference is not evidence of no difference"
- No direct assessment of effect size
- May require larger sample and more expensive

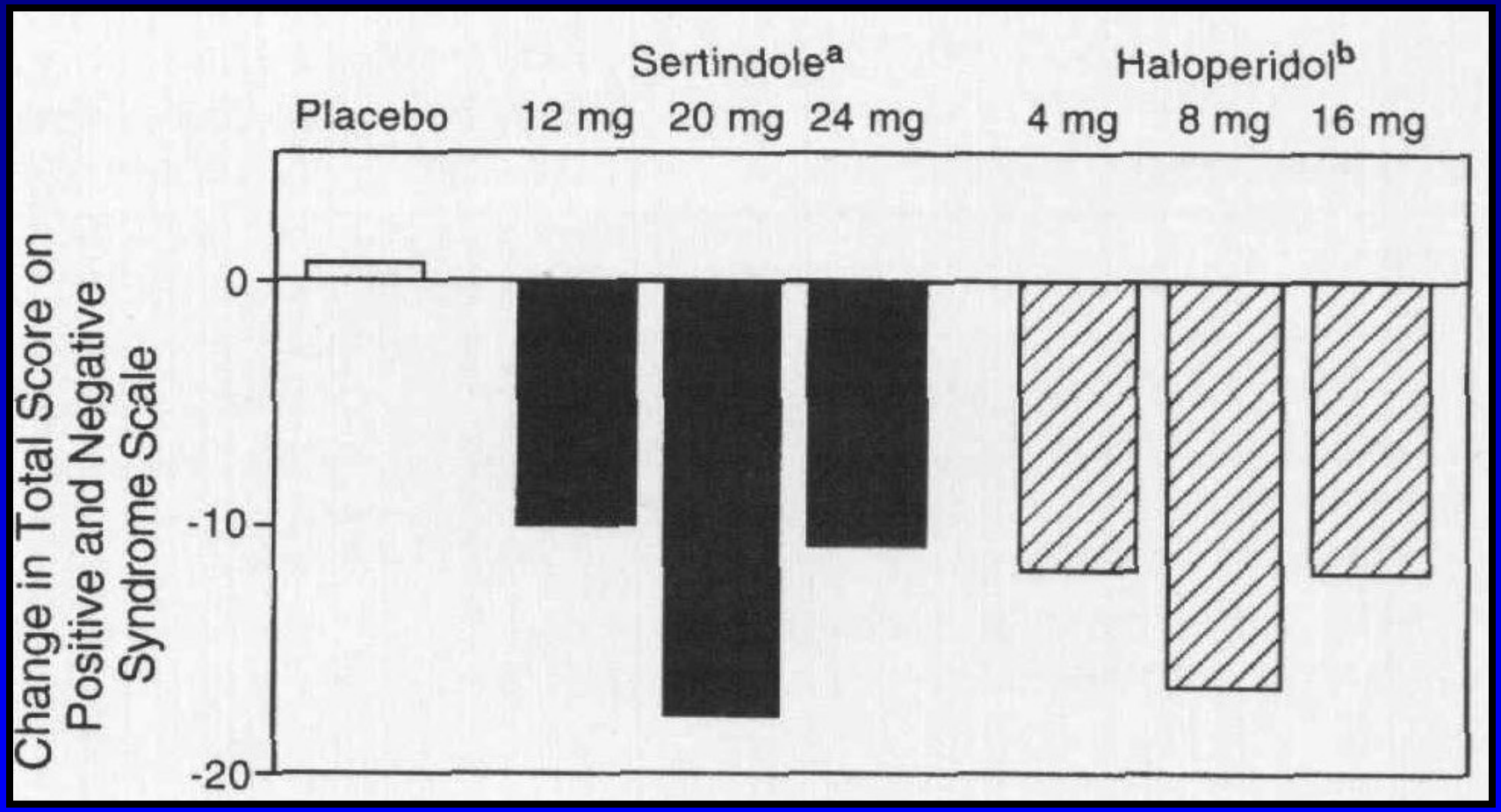
Choosing an Antipsychotic to Serve as Active Control

- Most extensively studied and commonly used
- Most effective
- Best tolerated
- Least expensive

- Based on available data risperidone and olanzapine (excepting clozapine) appear to be the most effective antipsychotics (Leucht et al Lancet and AJP 2009)
- Consistent separation from placebo in registration trials across broad dose range
- Large historical clinical trial database
- Well defined dose-response curve in acute trials
- Little or no titration to therapeutic dose
- Risperidone preferable from side effect profile and

Precedented and Novel Mechanism Drugs

Controlled, Dose-Response Study of Sertindole and Haloperidol in the Treatment of Schizophrenia

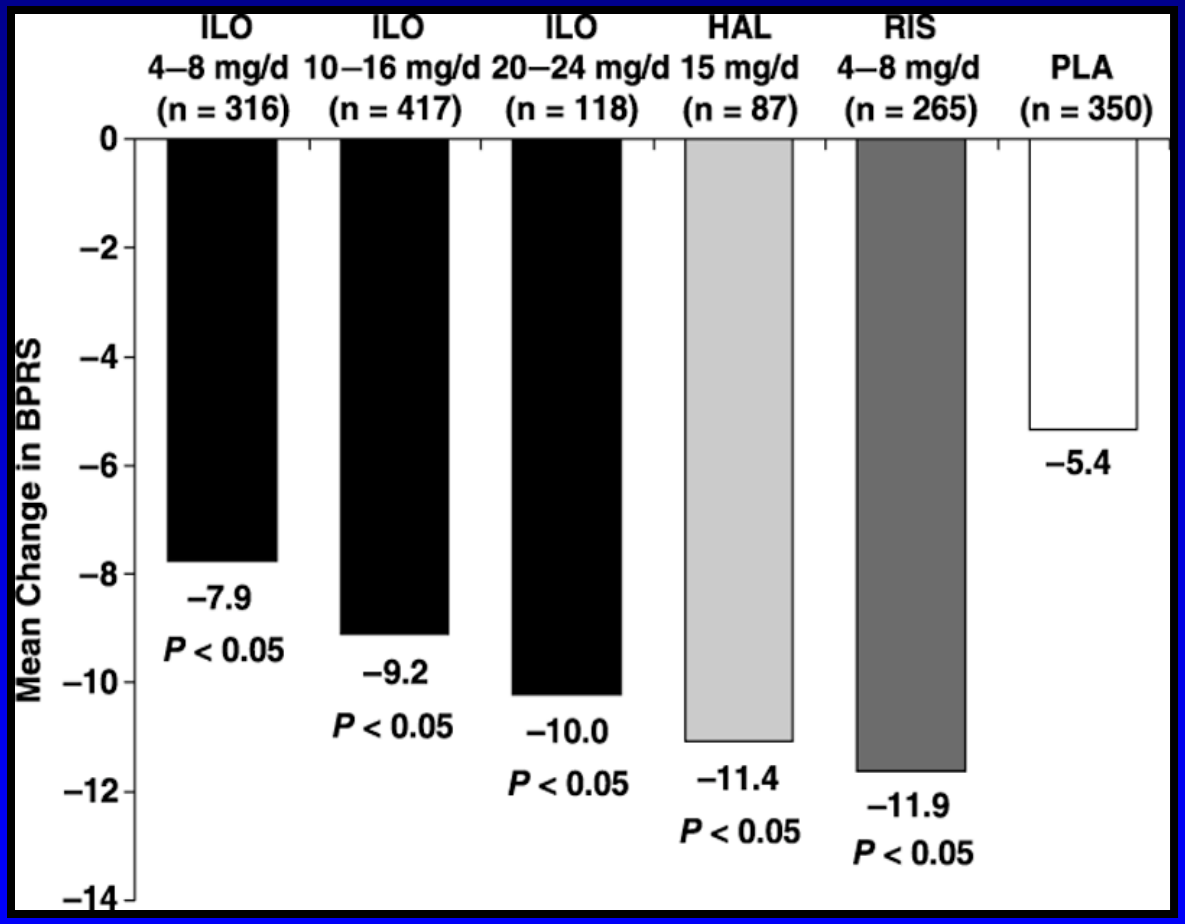


[a]Comparison with placebo: ANOVA F=7.59, df=3, 233, p<0.001; adjusted p values for the 12-, 20-, and 24-mg groups were 0.01, <0.001, and 0.008, respectively (Dunnett's test).

[b]Comparison with placebo: ANOVA F=6.50, df=3, 226, p<0.001; adjusted p values for the 4-, 8-, and 16-mg groups were 0.008, <0.001, and 0.005, respectively (Dunnett's test).

Zimbroff et al, *Am J Psychiatry* 1997; 154(6): 782-791

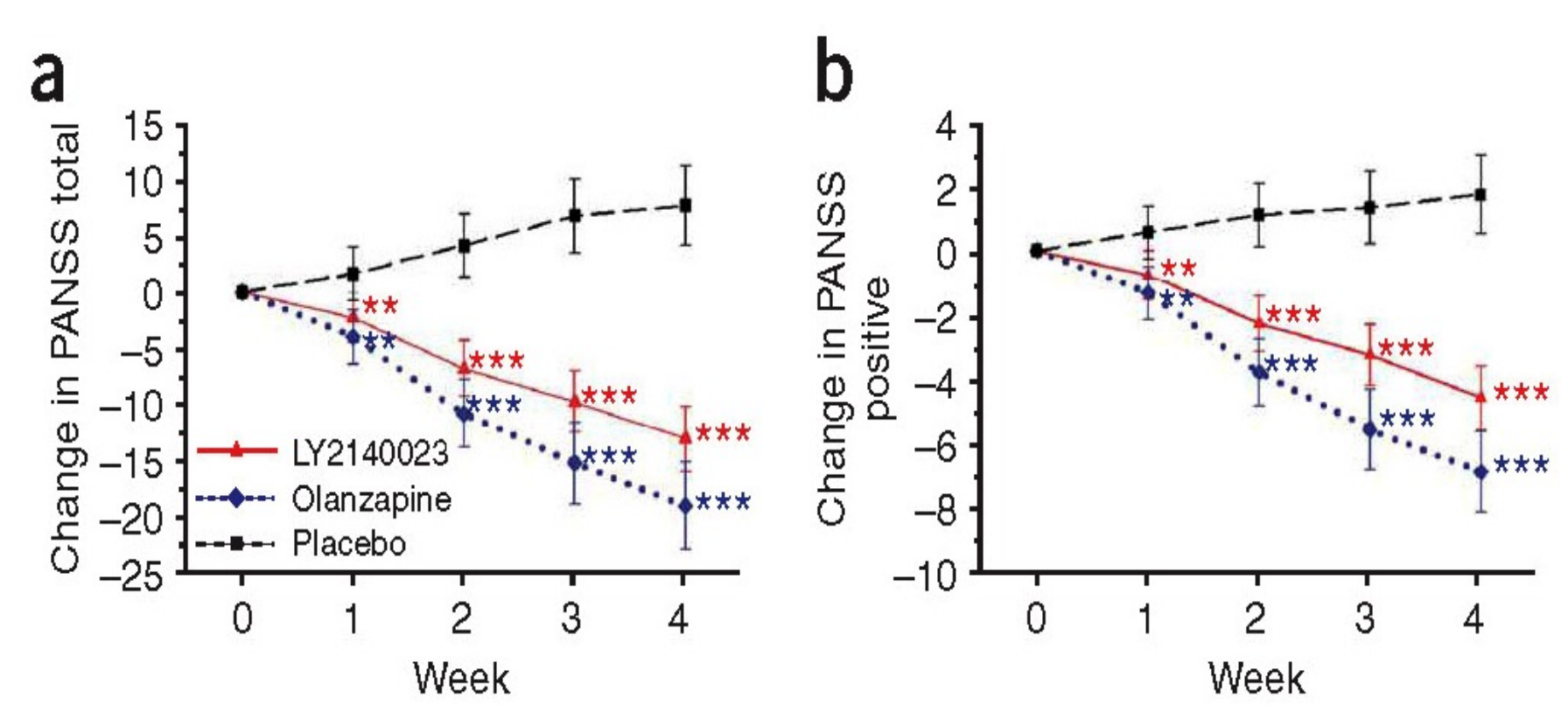
Efficacy of Iloperidone in the Treatment of Schizophrenia: Initial Phase 3 Studies



Combined mean change from baseline in BPRS scores for patients who remained in Studies 1, 2, and 3 for at least 2 weeks.

Potkin, et al, *J Clin Psychopharm* 2008; 28(2) Suppl. 1:S4-S11

Activation of mGlu2/3 Receptors as a New Approach to Treat Schizophrenia: A Randomized Phase 2 Clinical Trial

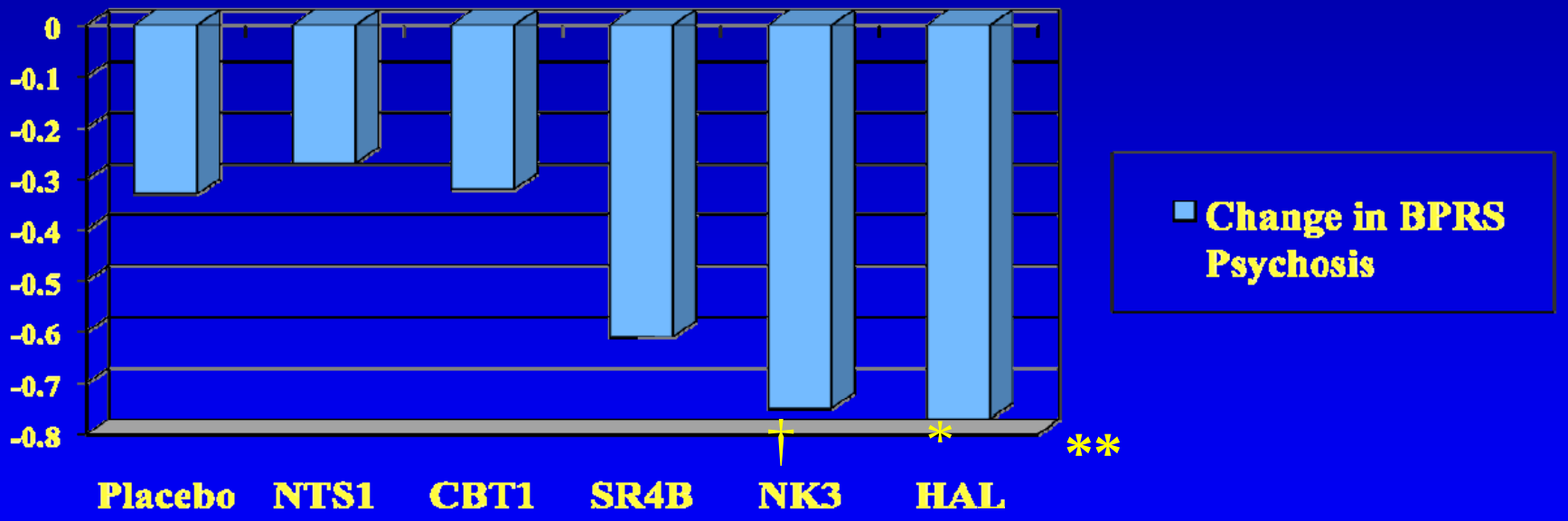


(**a**) PANSS total score

(**b**) PANSS positive score

Patil, et al, *Nature Medicine* 2007; 13(9):1102-1107

Effectiveness of Five Compounds on Core Psychotic Items in Acute Schizophrenia



*P<0.01**P<0.003; †P=0.08

Meltzer, et al, *Am J Psychiatry* 2004; 161: 975-84

Residual Psychosis, Negative Symptoms and Cognition

No active comparators

A Randomized, Placebo-Controlled Study of Memantine as Adjunctive Treatment in Patients with Schizophrenia

Jeffrey A Lieberman*[,1,2], Kelly Papadakis[3], John Csernansky[4], Robert Litman[5], Jan Volavka[6], Xinwei Daniel Jia[3] and Allyson Gage[3], for the MEM-MD-29 Study Group

[1]Department of Psychiatry, Columbia University, College of Physicians and Surgeons, New York, NY, USA; [2]Department of Psychiatry, New York State Psychiatric Institute, New York, NY, USA; [3]Forest Research Institute, Jersey City, NJ, USA; [4]Division of Biology and Biomedical Sciences, Conte Center for the Neuroscience of Mental Disorders, Washington University School of Medicine, St Louis, MO, USA; [5]CBH Health, LLC, Rockville, MD, USA; [6]Department of Psychiatry, New York University School of Medicine, New York, NY, USA

Memantine, an uncompetitive antagonist of glutamate receptors of the *N*-methyl-D-aspartate type is approved for the treatment of moderate to severe Alzheimer's disease. A growing body of evidence supports a link between the glutamatergic neurotransmission and schizophrenia. The purpose of this study (MEM-MD-29) was to examine the efficacy and safety of memantine as an adjunctive treatment to atypical antipsychotics in patients with persistent residual psychopathology of schizophrenia. In this double-blind, placebo-controlled study, participants were assigned to receive 20 mg/day memantine ($n = 70$) or placebo ($n = 68$), in addition to continuing treatment with atypical antipsychotics, for 8 weeks. The primary efficacy measure was the total score on the Positive and Negative Symptom Scale (PANSS). Secondary measures were positive and negative PANSS scores, PANSS responders, Calgary Depression Scale for Schizophrenia (CDSS), Clinical Global Impression of Severity (CGI-S), Clinical Global Impression of Improvement (CGI-I), and Brief Assessment of Cognition in Schizophrenia (BACS). Missing data were imputed using the last observation carried forward (LOCF) approach. Safety was assessed by means of physical examination, clinical laboratory evaluation, recording of adverse events (AEs), and measures of extrapyramidal symptoms. At end point, total PANSS scores did not differ between the memantine and the placebo group ($p = 0.570$, LOCF). A similar outcome was observed for all secondary measures. The frequency of serious AEs in the memantine *vs* placebo group was 8.7 *vs* 6.0%; treatment discontinuations because of AEs occurred in 11.6 and 3.0% of patients in these groups, respectively. Memantine showed no efficacy as an adjunctive therapy in schizophrenia patients with residual psychopathology and was associated with a higher incidence of AEs than placebo.

Neuropsychopharmacology advance online publication, 12 November 2008; doi:10.1038/npp.2008.200

Change of Scores of Secondary Measures from Baseline at Week 8

Parameter	Group	Baseline		Week 8 (LOCF)			
		N	Score[a]	N	Change[a]	LSMD[b]	p value[c]
PANSS positive score	Placebo	66	18.4 ± 4.5	66	−1.5 ± 2.7	0.2 (−0.9, 1.2)	0.746
	Memantine	69	18.9 ± 4.2	69	−1.4 ± 3.4		
PANSS negative score	Placebo	66	19.9 ± 5.6	66	−1.0 ± 4.3	−0.7 (−1.9, 0.5)	0.233
	Memantine	69	18.6 ± 6.3	69	−1.2 ± 3.3		
PANSS hostility factor score	Placebo	66	6.4 ± 2.5	66	−0.1 ± 1.4	0.2 (−0.5, 0.8)	0.583
	Memantine	69	6.7 ± 2.0	69	0.0 ± 2.3		
CDSS	Placebo	64	12.5 ± 3.5	64	−0.3 ± 4.1	−0.6 (−1.6, 0.4)	0.246
	Memantine	62	12.3 ± 3.0	62	−0.7 ± 2.6		
CGI-S	Placebo	64	4.0 ± 0.9	64	3.7 ± 0.9	N/A	0.917
	Memantine	66	3.9 ± 0.9	66	3.7 ± 0.9		
CGI-I[d]	Placebo	N/A	N/A	65	3.6 ± 0.8	N/A	0.772
	Memantine	N/A	N/A	68	3.6 ± 0.8		
BACS composite *z*-score	Placebo	62	0.01 ± 0.67	62	−0.01 ± 0.37	−0.06 (−0.19, 0.07)	0.372
	Memantine	61	0.19 ± 0.71	61	−0.08 ± 0.42		
BACS total construct score	Placebo	63	193.9 ± 44.5	63	17.7 ± 22.7	−0.4 (−8.8, 7.9)	0.916
	Memantine	62	207.8 ± 44.9	62	17.2 ± 24.3		

Lieberman, et al, *Neuropsychopharm* 2008; 1-8

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Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

Jeffrey A. Lieberman, M.D., T. Scott Stroup, M.D., M.P.H., Joseph P. McEvoy, M.D., Marvin S. Swartz, M.D., Robert A. Rosenheck, M.D., Diana O. Perkins, M.D., M.P.H., Richard S.E. Keefe, Ph.D., Sonia M. Davis, Dr.P.H., Clarence E. Davis, Ph.D., Barry D. Lebowitz, Ph.D., Joanne Severe, M.S., and John K. Hsiao, M.D., for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators*

Hypotheses for Primary Outcomes:

1. There are differences between APDs (olanzapine, quetiapine, risperidone, ziprasidone and perphenazine) in measures of effectiveness.

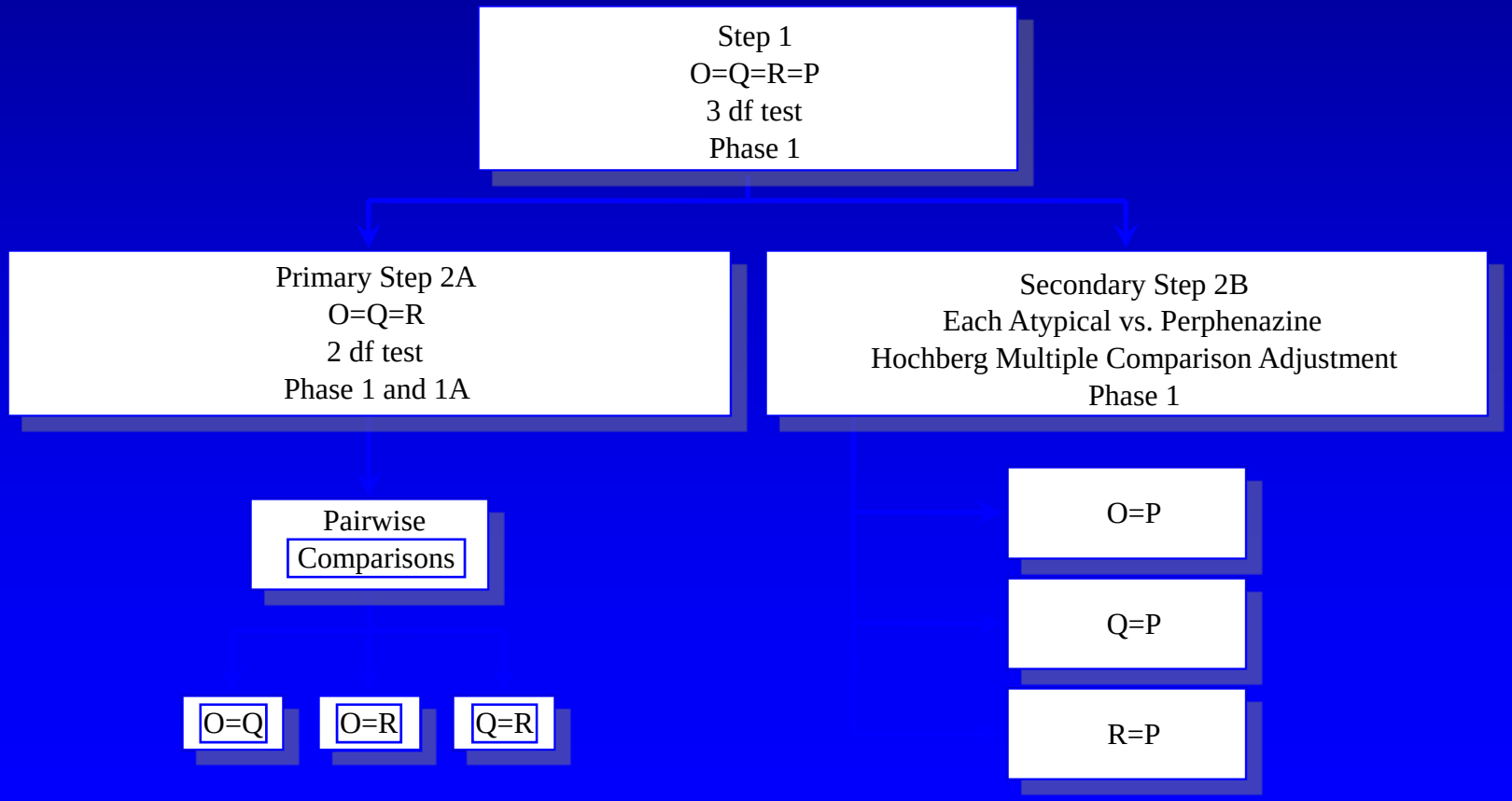
2a. The FGA (perphenazine) is less effective than SGA medications (olanzapine, quetiapine, risperidone and ziprasidone).

2b. There are differences between SGAs in effectiveness measures (olanzapine, quetiapine, risperidone and ziprasidone).

Primary Treatment Comparisons

Ziprasidone analyzed separately

Primary Phase 1 Treatment Comparisons

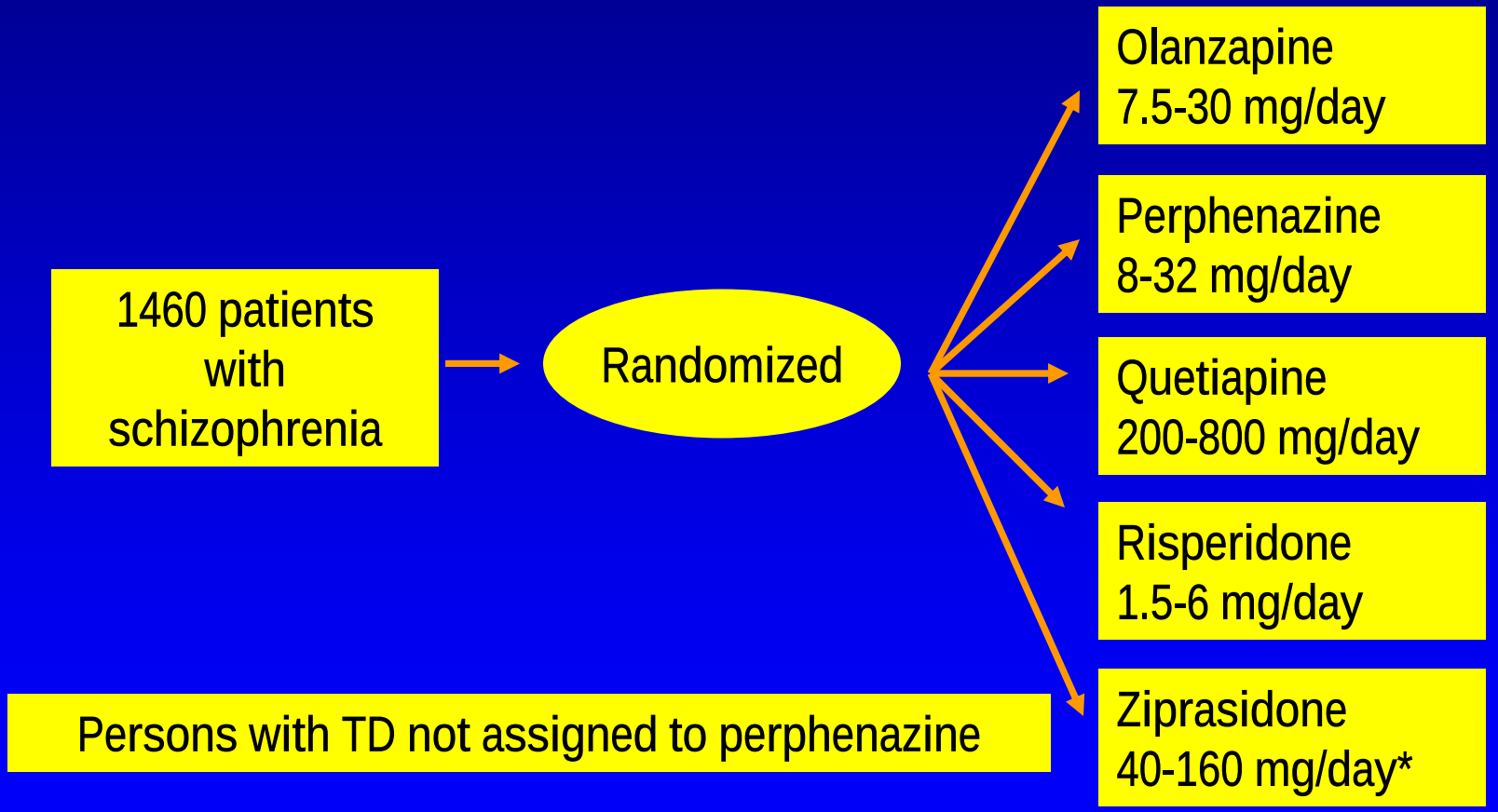


Corrections for multiple comparisons

Power for Pairwise Comparisons of Discontinuation Rate

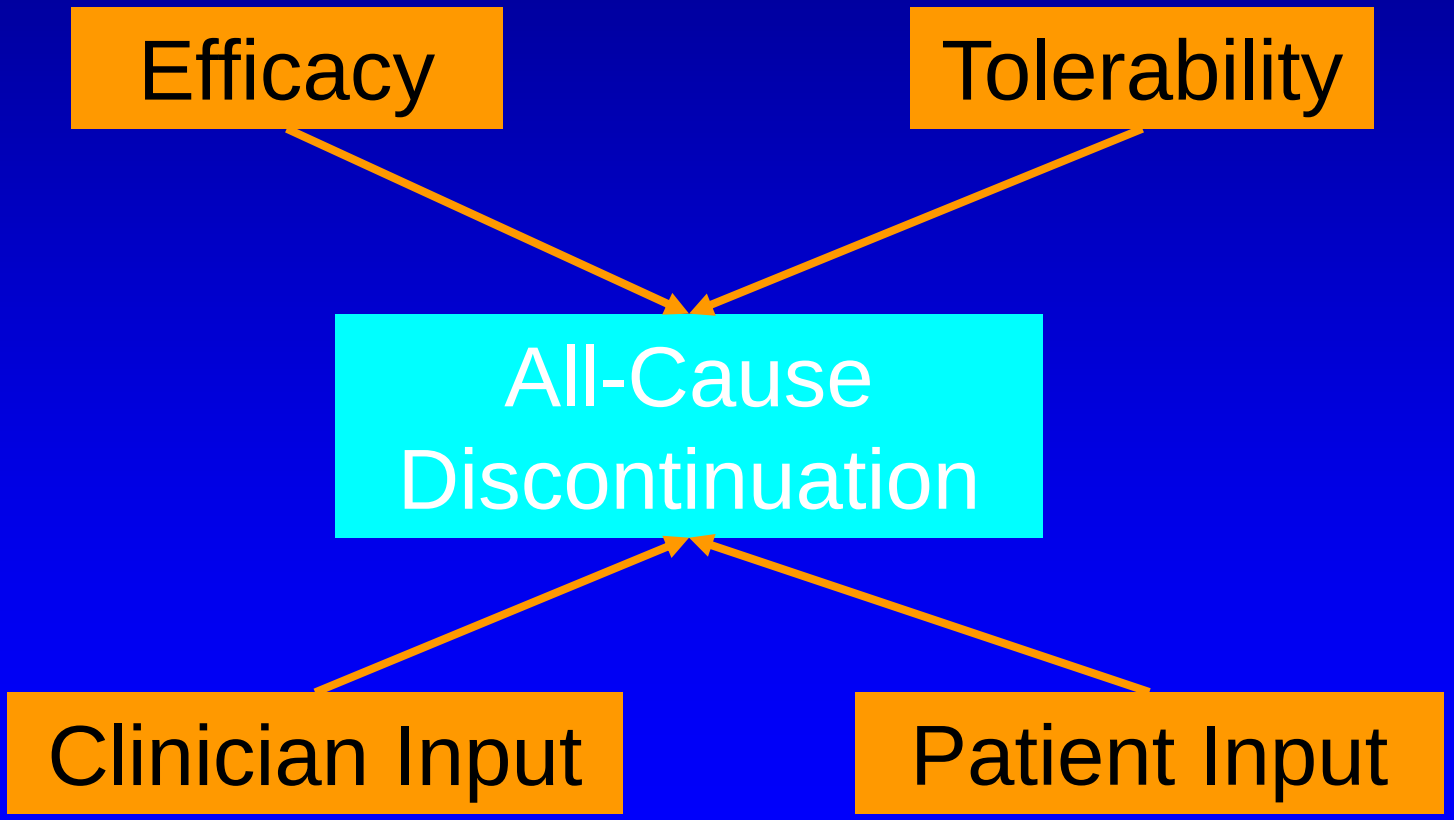
- 85% power to identify a 12% difference between two atypicals (olanzapine, quetiapine, risperidone)
- 76% power to identify a 12% difference between perphenazine and an atypical (olanzapine, quetiapine, risperidone)
- Not powered for non-inferiority

CATIE Phase I: Double-Blind and Randomized



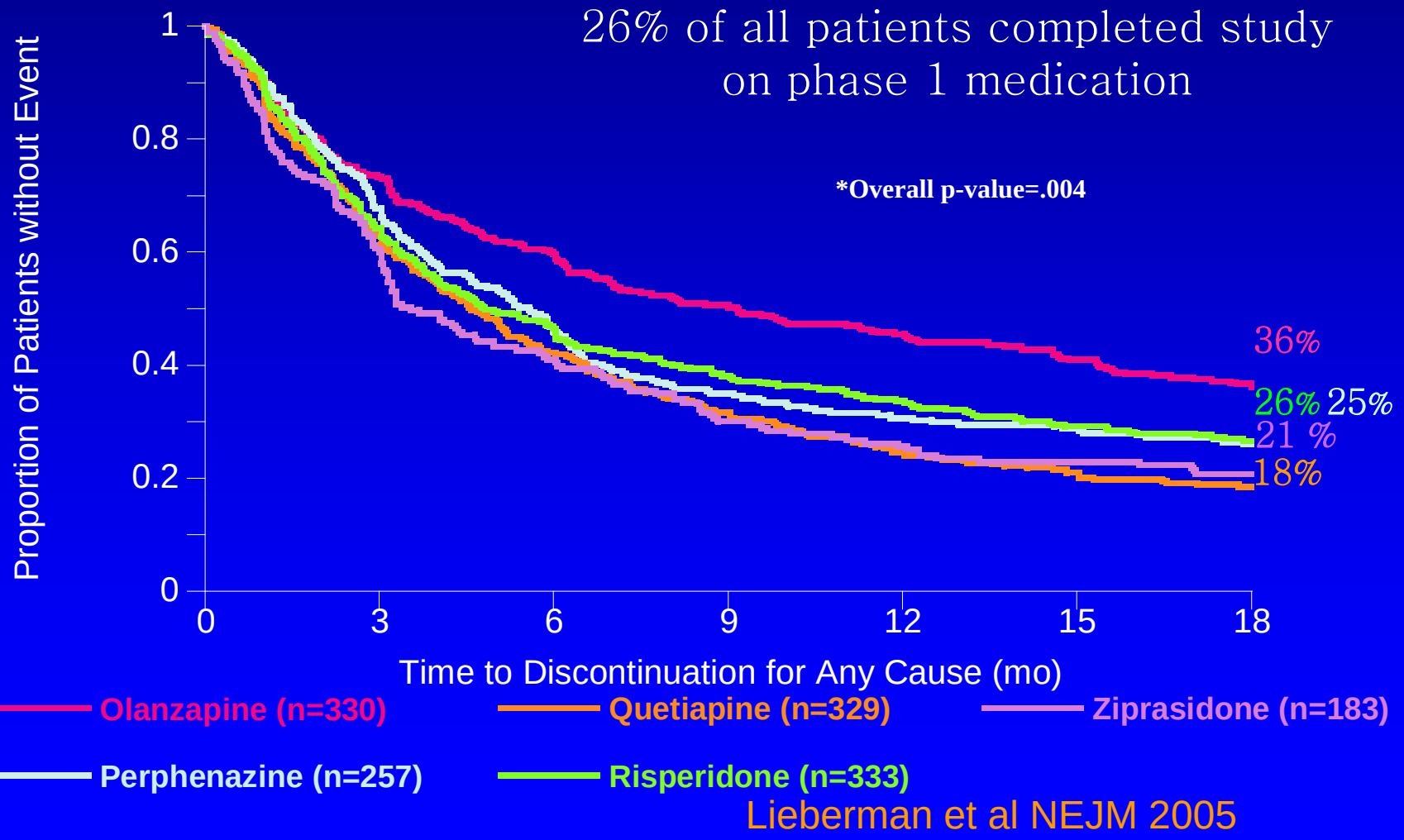
*Ziprasidone added after 40% sample enrolled.
Stroup et al. *Schizophr Bull*. 2003, Lieberman et al NEJM 2005
This information includes a dose that has not been approved by the US FDA.

Primary Effectiveness Measure: All-Cause Treatment Discontinuation



Stroup TS, et al. *Schizophr Bull.* 2003;29(1):15-31.

PHASE 1: Time to Discontinuation for Any Reason



Lieberman et al NEJM 2005

Balancing Scientific Rigor, Clinical Relevance, and Ethical Conduct of Research

- *What is the optimal combination of PC and AC trials and other aspects of trial design including outcome measures, to evaluate clinically relevant efficacy and safety for regulatory approval of a NCE?*

- Long term PC outpatient trials do not meet minimum ethical threshold of Declaration of Helsinki (October, 2008) and inpatient PC trials beyond short term pose ethical questions and are impractical

- With AC trials, possibility of erroneously concluding efficacy based on non-inferiority (Type 1 error) in active controlled trials poses public health risk. Thus, regulatory approval solely with AC trials is problematic

Recommended Design of Phase 2 Trial for Antipsychotic Drugs in Schizophrenia
Efficacy Unknown; Dose Unknown

- Optimal trial is Randomized, DB, PC with multiple fixed dose arms of NCE and AC group for assay sensitivity
- Acute exacerbation; not first episode; not treatment resistant
- Trial Duration: 2 to 4 weeks (longer if NCE requires titration)
- Mandatory inpatient for duration of trial to minimize risk
- Rigorous safety assessments
- Primary outcome is change from baseline in the PANSS Positive Sx subscale and PANSS –Excited Component
- Frequent assessment to characterize time course of response
- Ideally 2 trials – goal is to establish acute antipsychotic efficacy and identify preliminary dose relationships of efficacy and tolerability.

If phase 2 placebo comparisons are positive, proceed to large phase 3 active-control trial

- Large, high quality, AC, non-inferiority design
- DB, randomized, flexible dose; acute exacerbation
- Not first episode; not treatment resistant
- Duration 6 weeks, with option for responders to continue in DB treatment
- Start as inpatient but hospitalization duration is clinically determined
- Primary outcome for acute phase - mean change from baseline in PANSS total score at 6 weeks (LOCF) to define cumulative therapeutic effect over this time frame
- Establish narrow margin for non-inferiority

DB Extension of Phase 3 Active-control Trial: Maintenance/Long-term Safety

- DB long-term extension of AC trials provides maintenance treatment data for safety/efficacy
- Rigorous safety assessments (safety outcomes are the primary outcome measure of long-term DB extension phase)
- Measures of effectiveness in long term treatment such as treatment retention, symptom exacerbation, re-hospitalization are secondary outcome measures
- Systematically collect data on other factors that influence outcome in long term treatment e.g., adherence, substance abuse
- Long term outpatient placebo-controlled trials and drug withdrawal trials cannot be ethically justified simply to prove long term efficacy; long term efficacy and relapse prevention effectiveness is evident from historical literature. No drug which has been effective in treatment of acute psychosis has NOT been effective (or lost effectiveness) in long term treatment.

Negative Symptoms and Cognitive Enhancement Trials: Largely Adjunctive Treatments

- TURNS model
- Stable patients on stable doses of antipsychotics
- Placebo-controlled, randomized, add-on design
- Low risk
- Generally longer duration (although not always)

Thank you for your attention !