

**January 25-27, 2001
San Diego, California**

**Zyprexa Physician Strategy and
Consulting Conference**



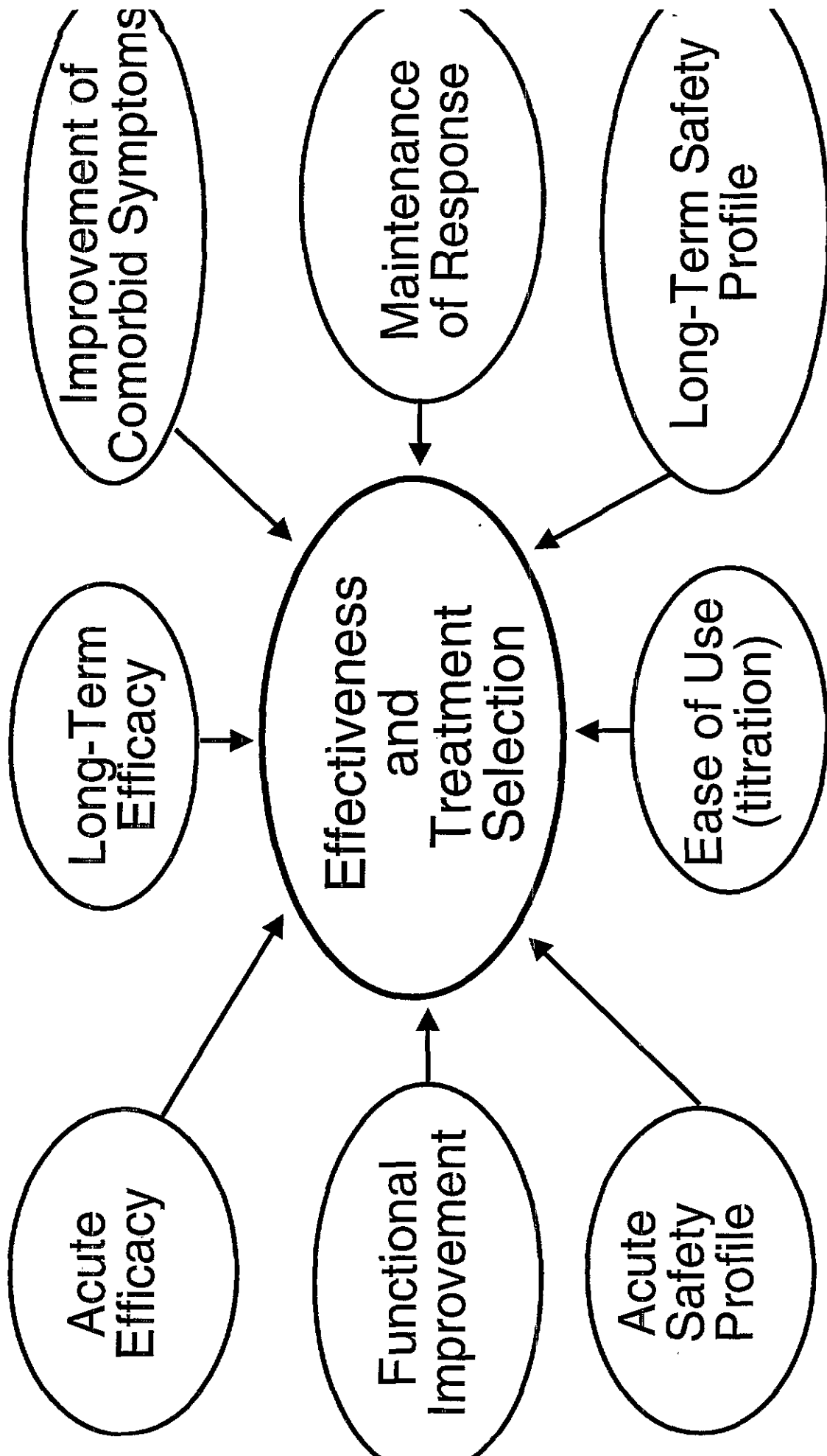
Answers That Matter.

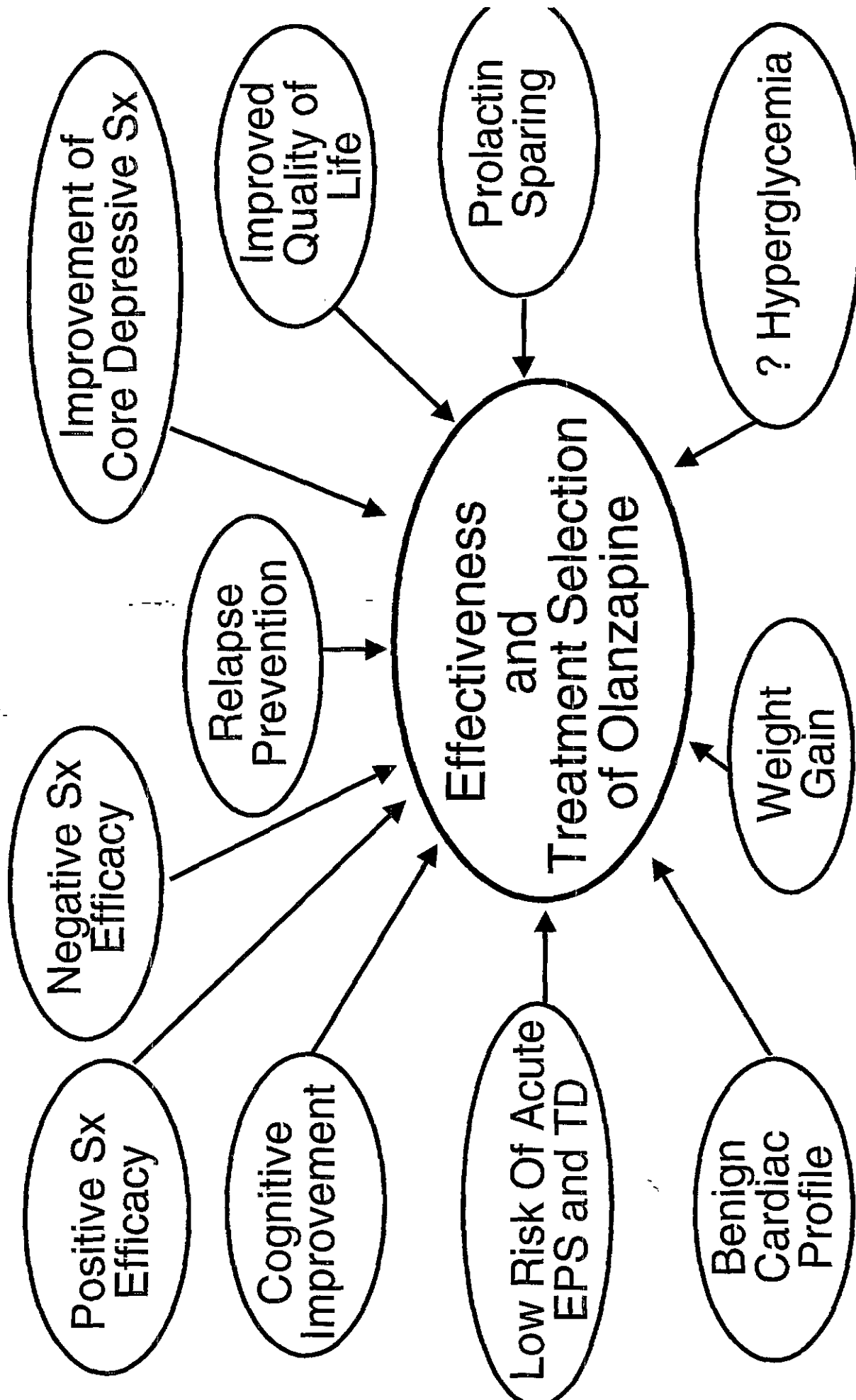
Robert W. Baker, MD
Clinical Research Physician
Eli Lilly and Company

Safety Update



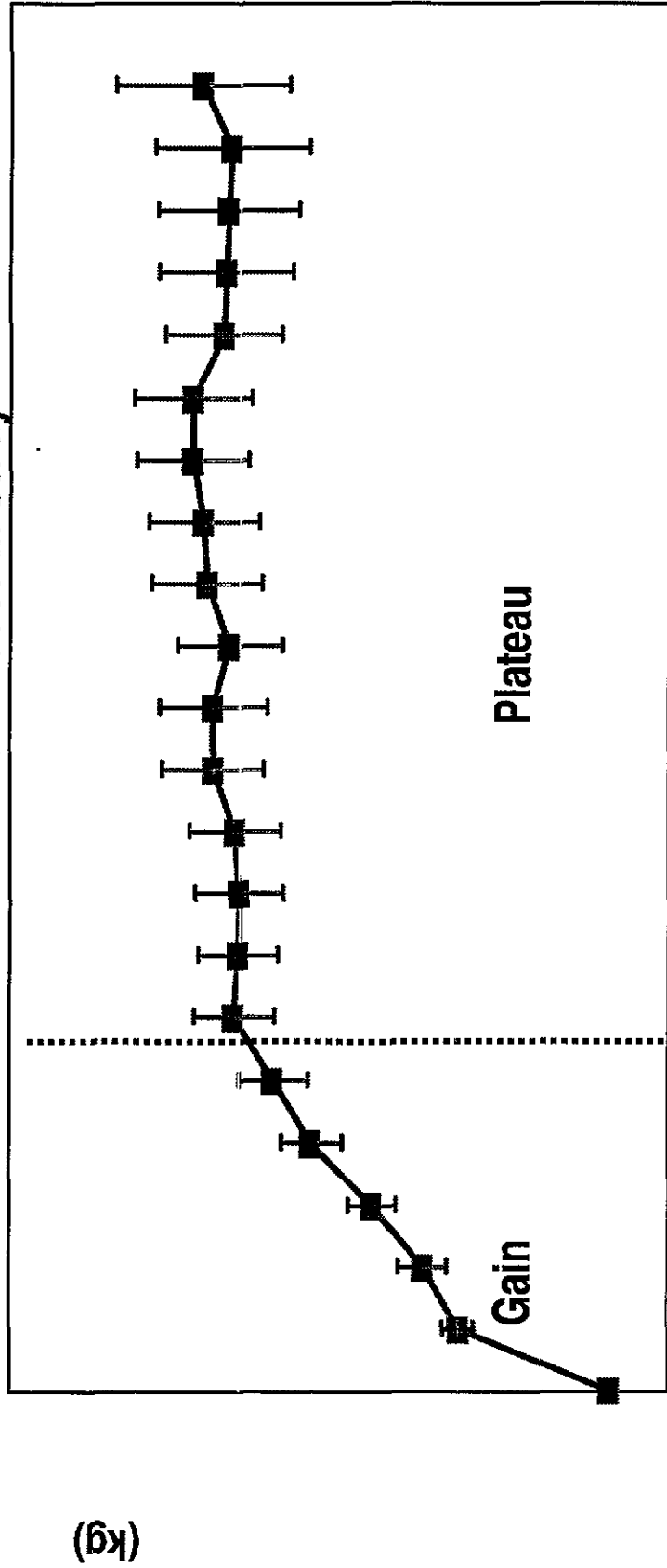
Answers That Matter.





Weight Gain/Plateau During Long-Term Olanzapine Treatment

Mean Weight Change Up to 3 Years: No Formalized Weight-Moderating Interventions Included in Study



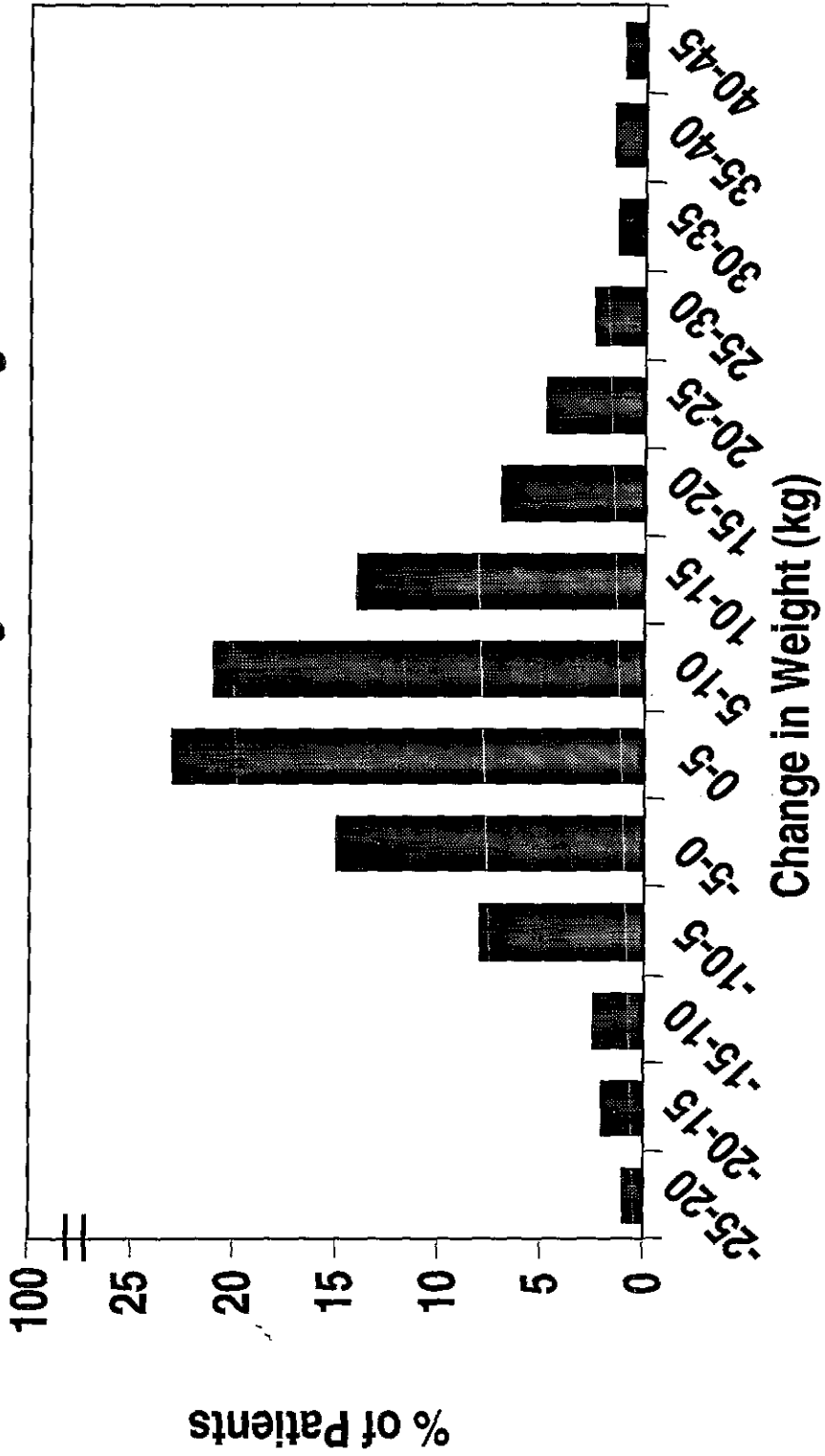
n=573

n=147

Linon BJ, et al. *J Clin Psychiatry*. In press.
Note: Double-blind and open-label olanzapine. Patients who completed at least 39 weeks of therapy.

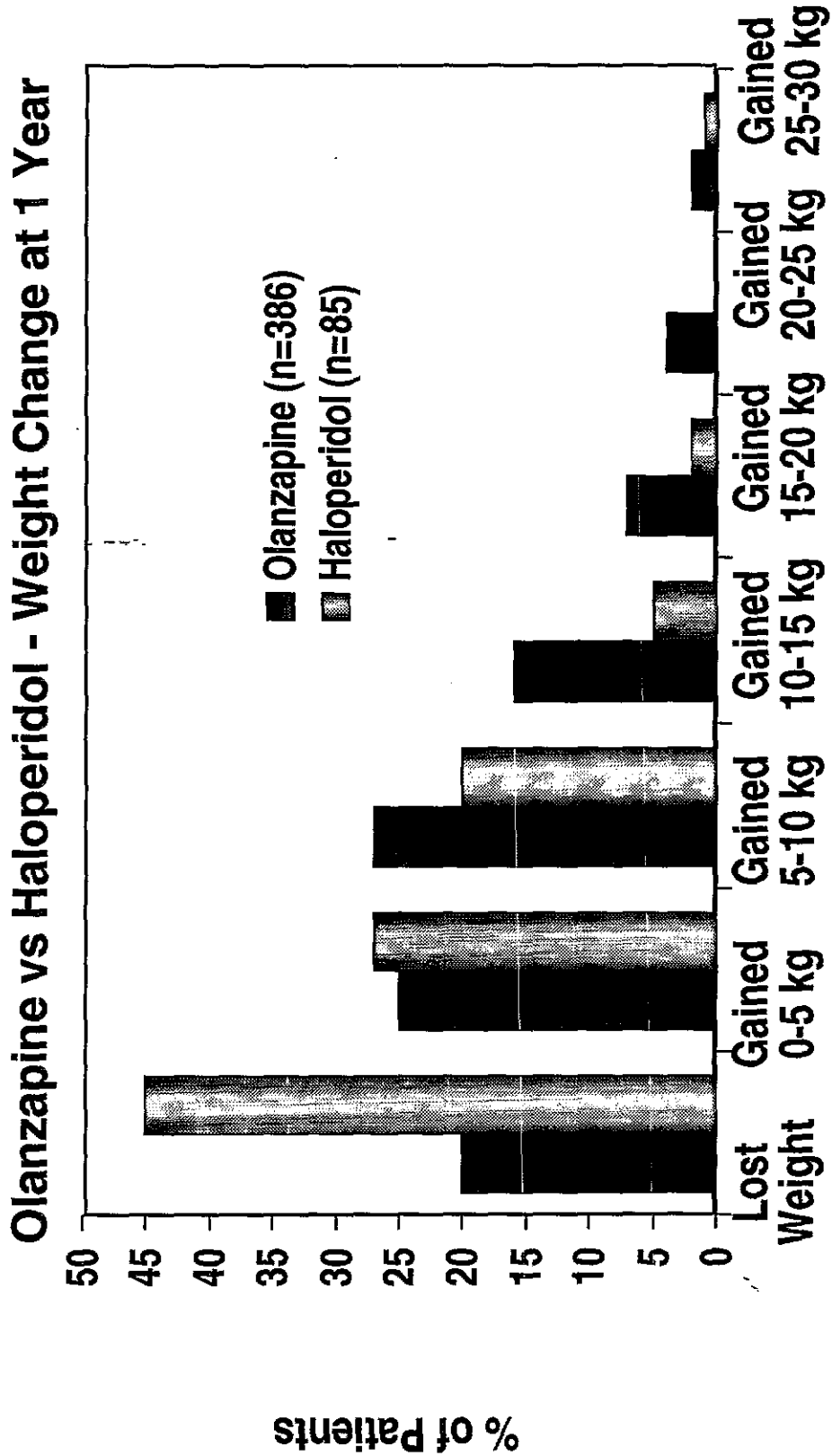
Intra-individual Variability in Weight Gain

Mean Change in Body Weight of Patients Treated With Olanzapine Up to 3 Years: No Formalized Weight-Moderating Interventions



Olanzapine n=573 at baseline, LOCF.
Kinon BJ, et al. Presented at: 38th ACNP Annual Meeting; Dec 13-17, 1999; Acapulco, Mexico.

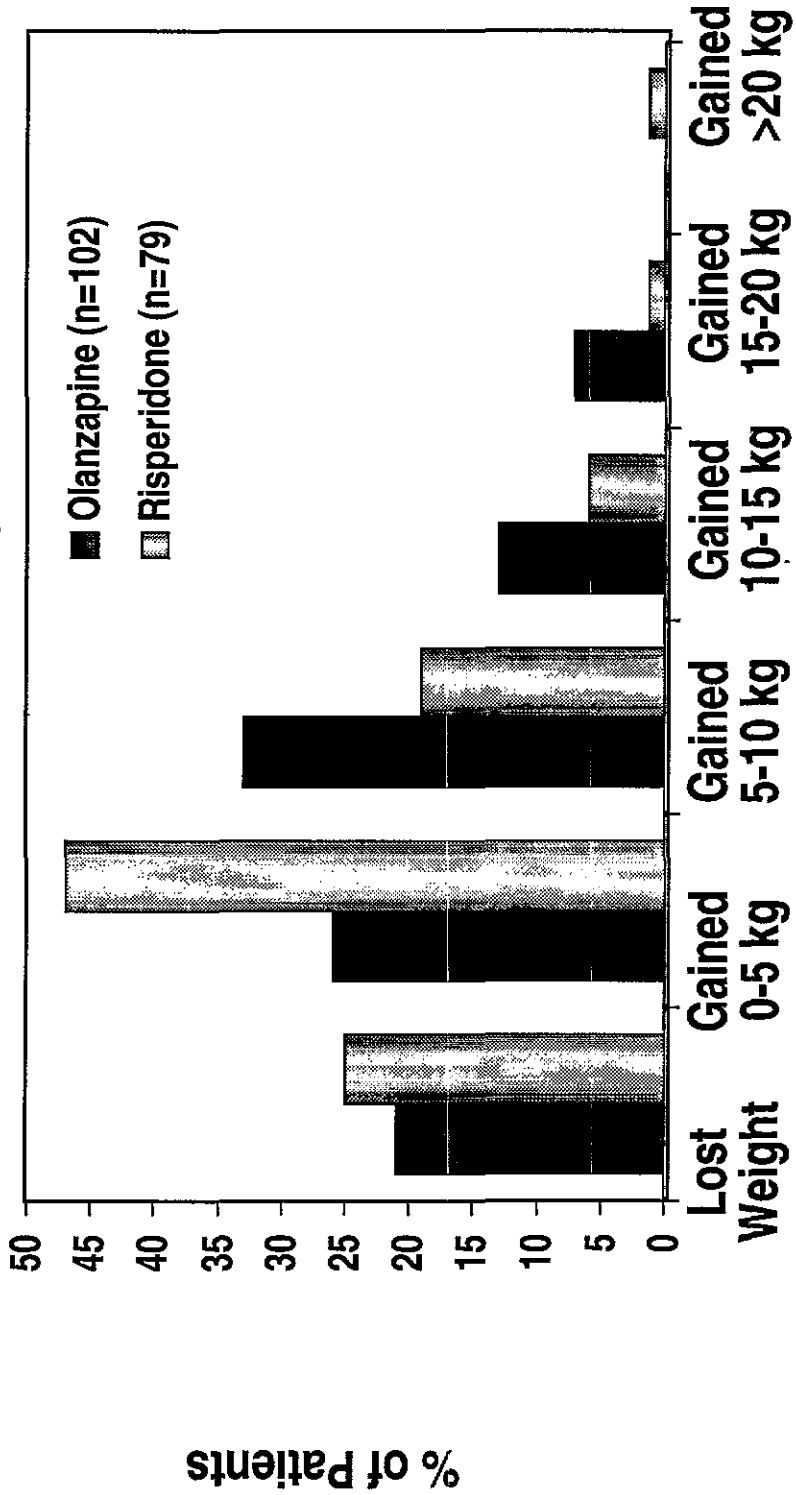
Weight Gain Variability in Haloperidol - Olanzapine Trials



Data on file, Eli Lilly and Company. 2000.

Weight Gain Variability in Risperidone - Olanzapine Trials

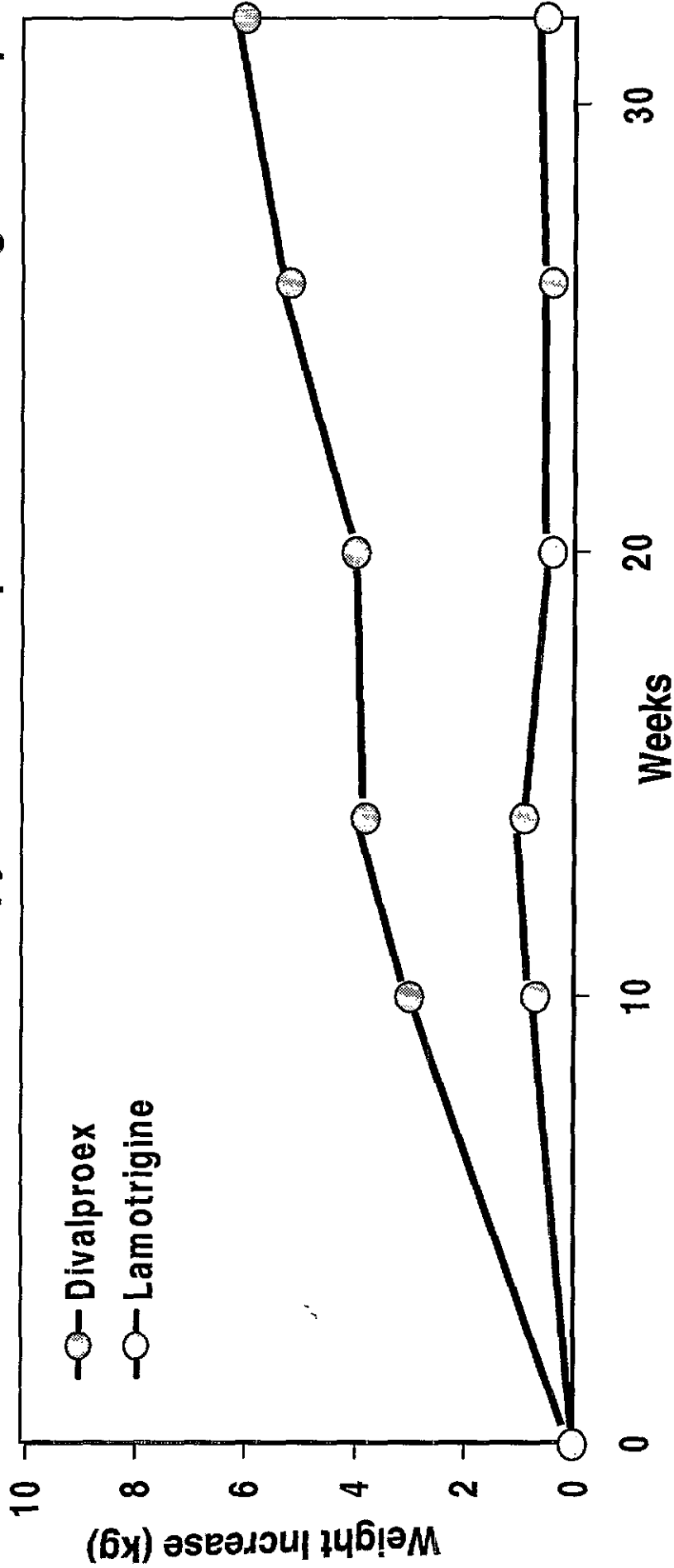
Olanzapine vs Risperidone - Weight Change at Endpoint (28 weeks)



Data on file, Eli Lilly and Company. 2000.

Divalproex-Associated Weight Gain

Double-Blind, 8-Month Monotherapy Trial of Divalproex vs Lamotrigine for Epilepsy



Biton V, et al. Eur Neuropsychopharmacol. 2000;10(suppl 3):S236.

Mean dose- divalproex =1822 mg. LTG=254 mg. Initial n- divalproex =68. LTG=65.

Note - for now, no long-term head-to-head comparison of divalproex and olanzapine is available.

Predictors of Weight Gain

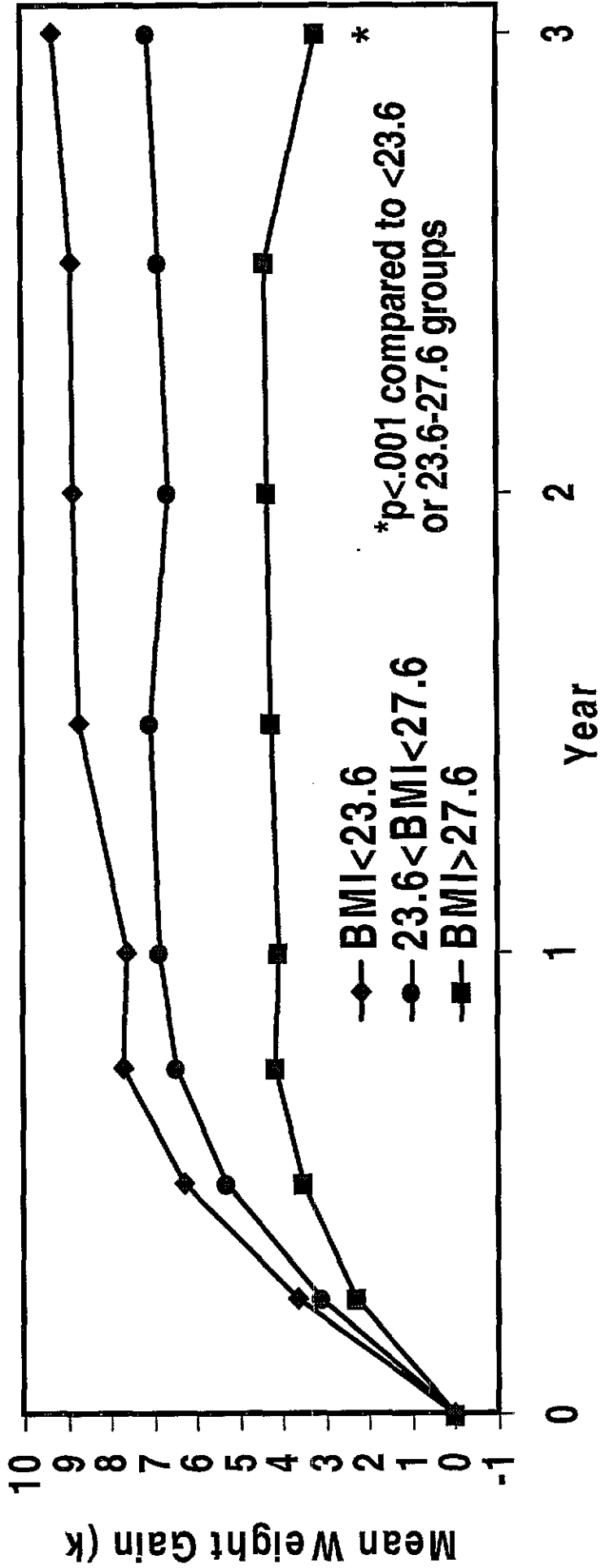
- ◆ Important predictive factors
 - Assignment to olanzapine or haloperidol
 - Positive therapeutic response
 - Low body mass index at baseline
 - Increased appetite during treatment

- ◆ Not important predictive factors
 - Assignment to olanzapine or risperidone
 - Olanzapine dose

Kinon BJ, et al. *Eur Neuropsychopharmacol.* 1998;8(suppl 2):S220.
Based on long-term comparative trials with risperidone and haloperidol (overall n=652).

Baseline BMI and Subsequent Weight Gain

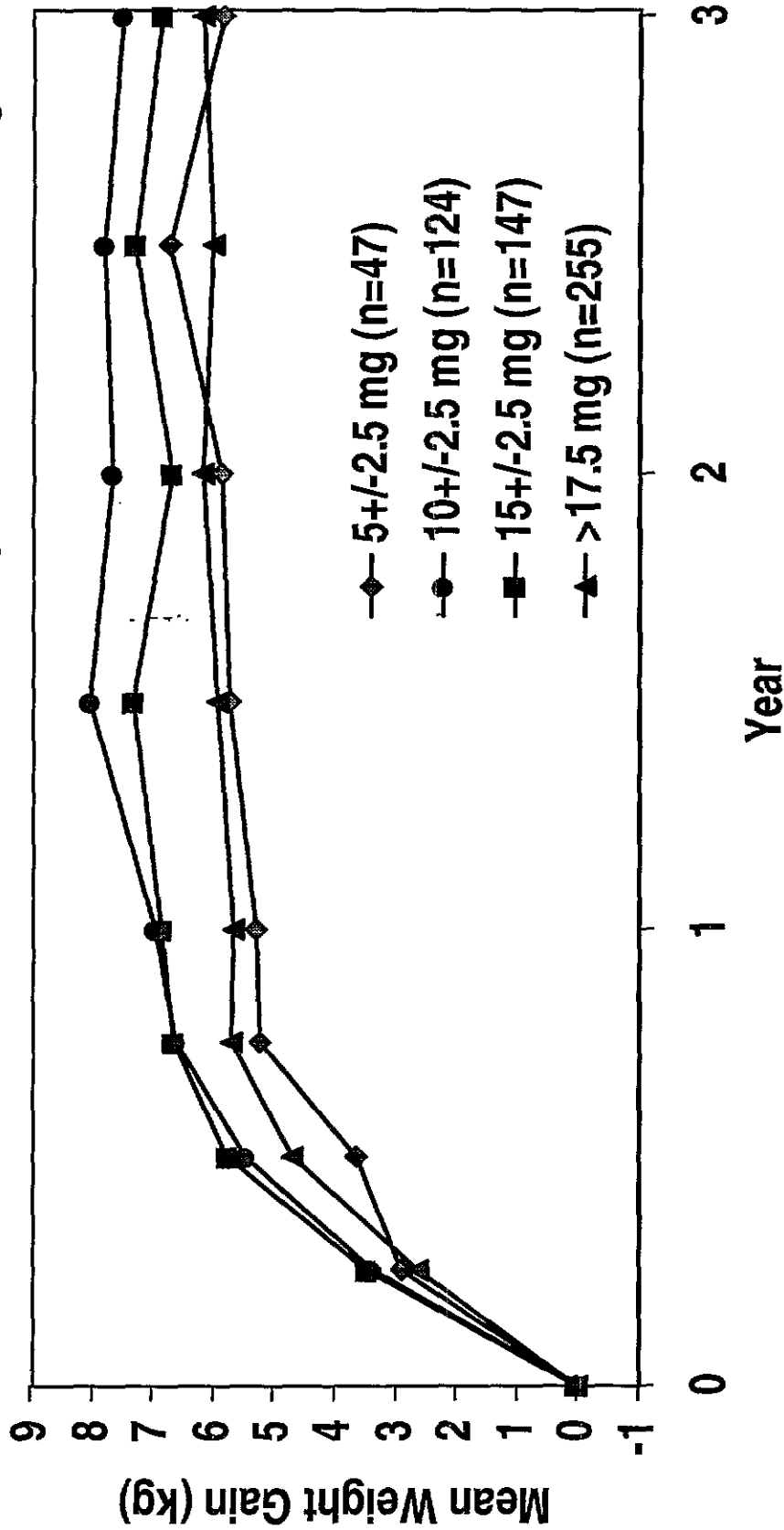
Subjects with lowest baseline BMI had the greatest mean weight gain; subjects with highest baseline BMI had the smallest mean weight gain



Kinon BJ, et al. *J Clin Psychiatry*. In press. Mean weight gain assessed by baseline BMI. Patients completing at least 39 weeks.

Weight Gain Was Not Dose Dependent

Weight Increase Was Comparable Across Groups Within the Dose Range



Kinon BJ, et al. *J Clin Psychiatry*. In press. Mean change in body weight (kg) by dose. Patients completing at least 39 weeks.

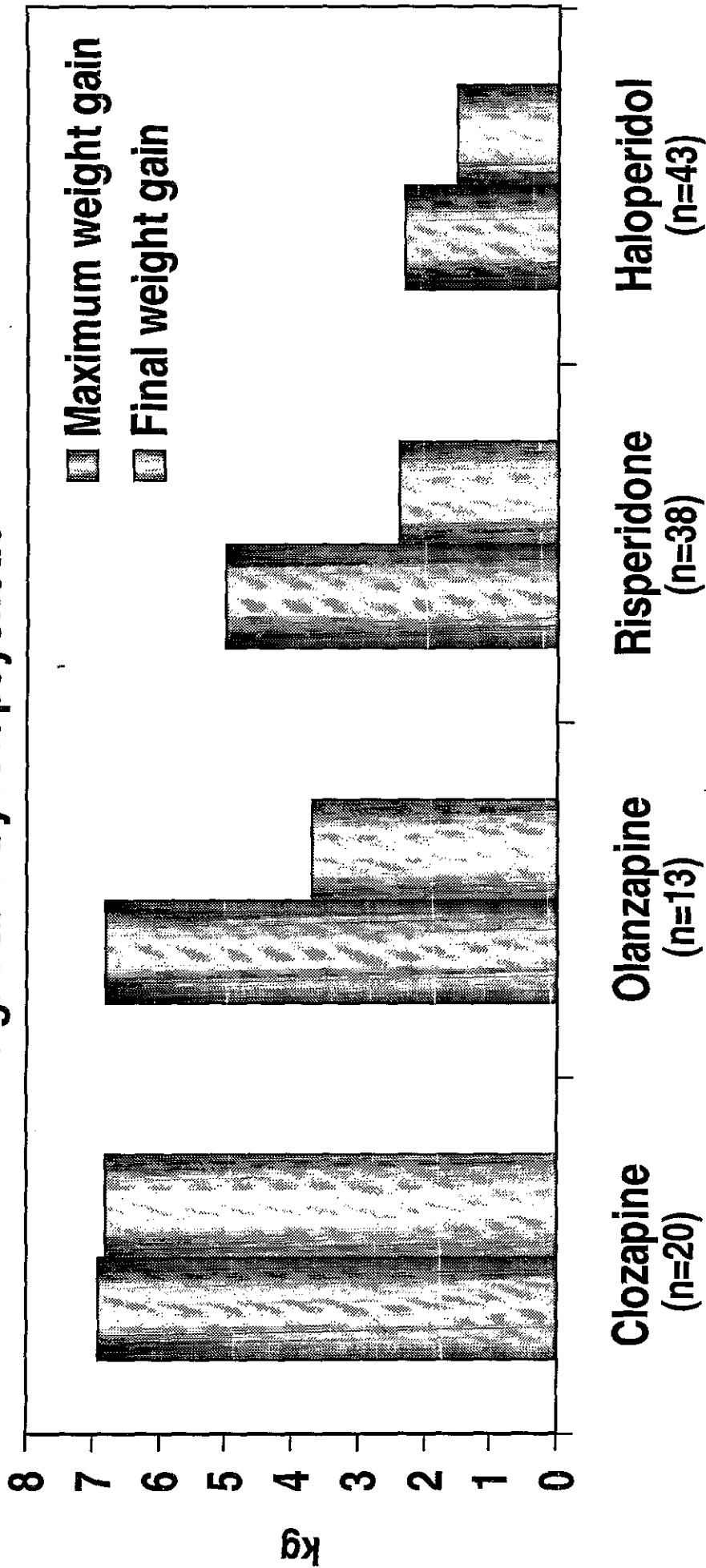
Potential Interventions for Weight

- ◆ Mechanisms
 - Being studied clinically and preclinically
 - 5HT2c and H1 receptor antagonism are possible candidates
 - Macronutrient partitioning shift?

- ◆ Nonpharmacological interventions
 - Diet and exercise

Behavioral Interventions: Led to Weight Loss in Those Who Had Put on the Most

Weight Gain by Antipsychotic



Nirshing DA, et al. *J Clin Psychiatry*. 1999;60(6):358-363.

Potential Interventions for Weight

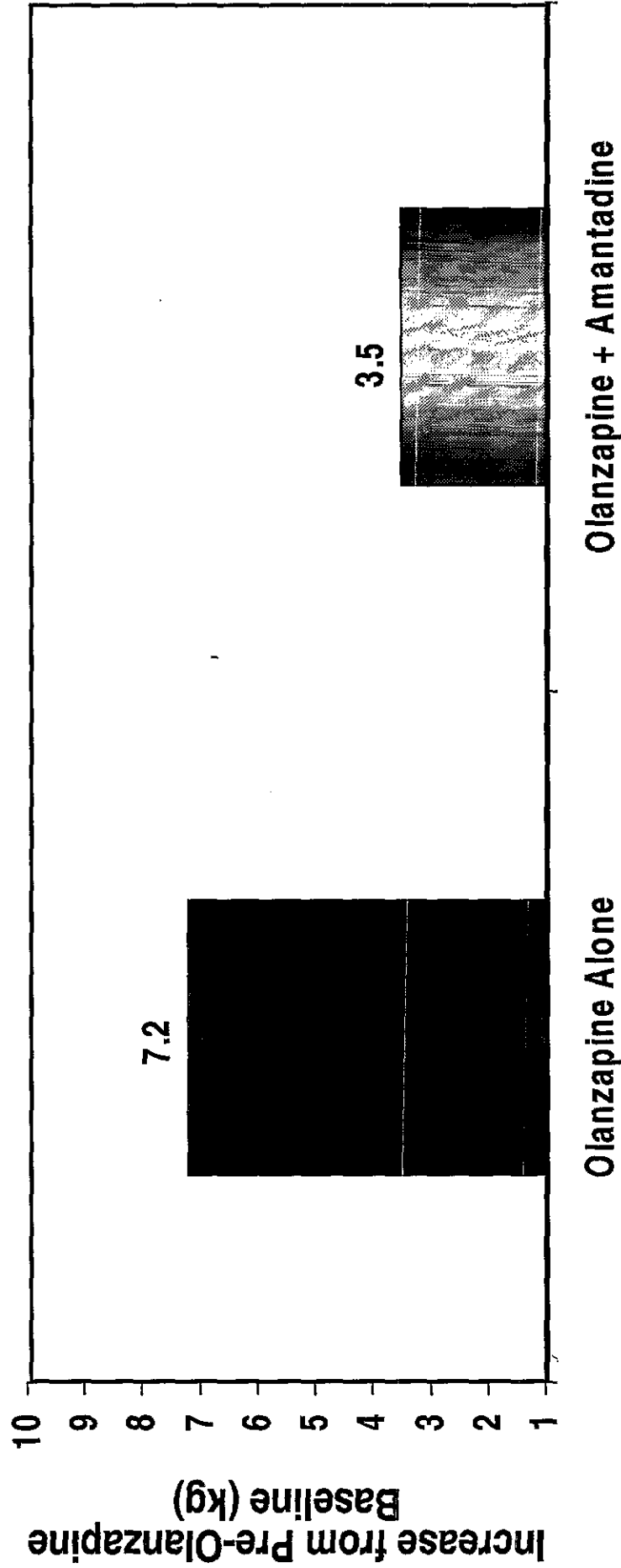
- ◆ Mechanisms
 - Being studied clinically and preclinically
 - 5HT2c and H1 receptor antagonism are possible candidates
 - Macronutrient partitioning shift?
- ◆ Nonpharmacological interventions
 - Diet and exercise
- ◆ Pharmacological interventions

Medications that Potentially Counteract Weight Gain

- ◆ Topiramate
- ◆ Sibutramine
- ◆ Amantadine
- ◆ Nizatidine
- ◆ Others

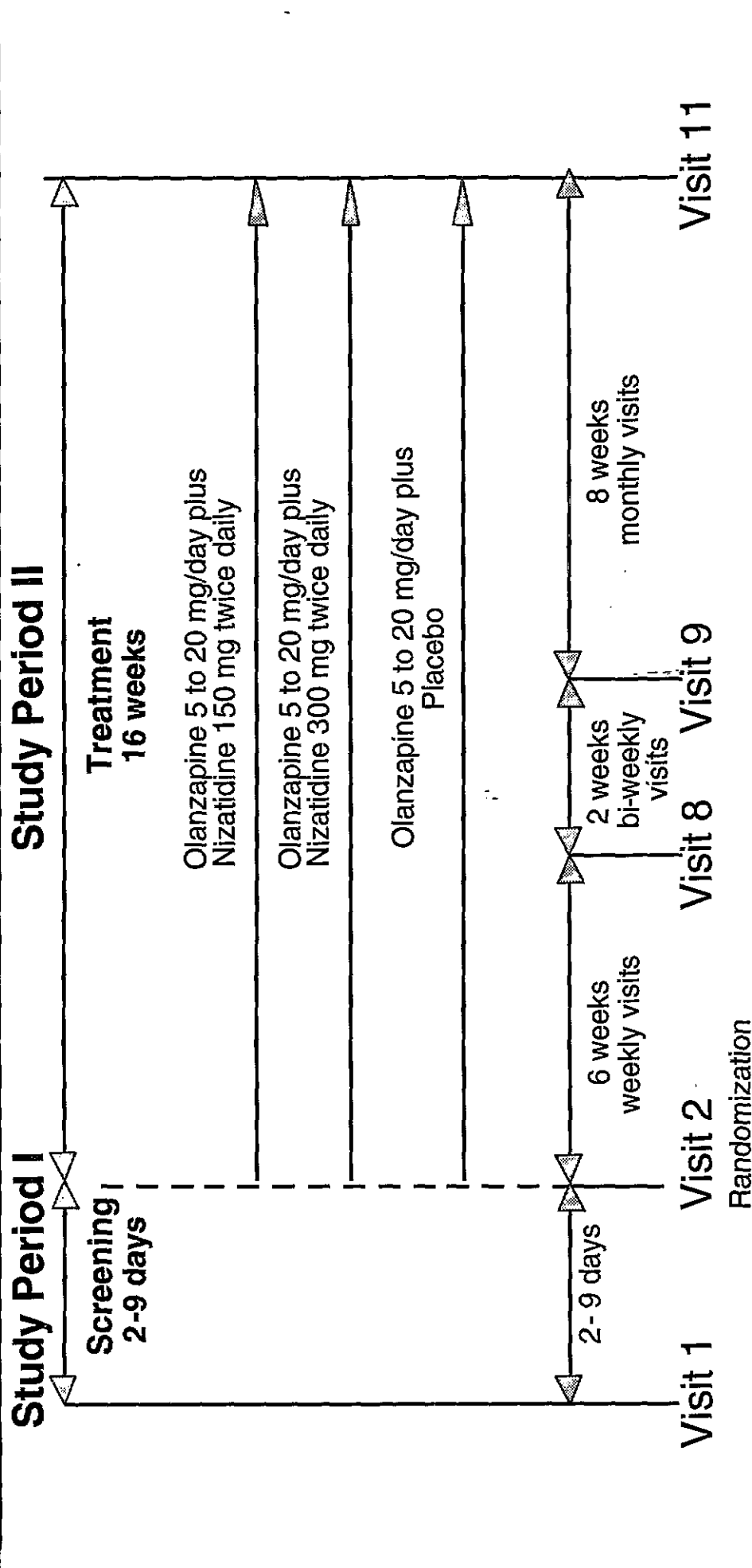
None has been studied adequately to date.

Adjunctive Amantadine Attenuates Olanzapine-Associated Weight Gain



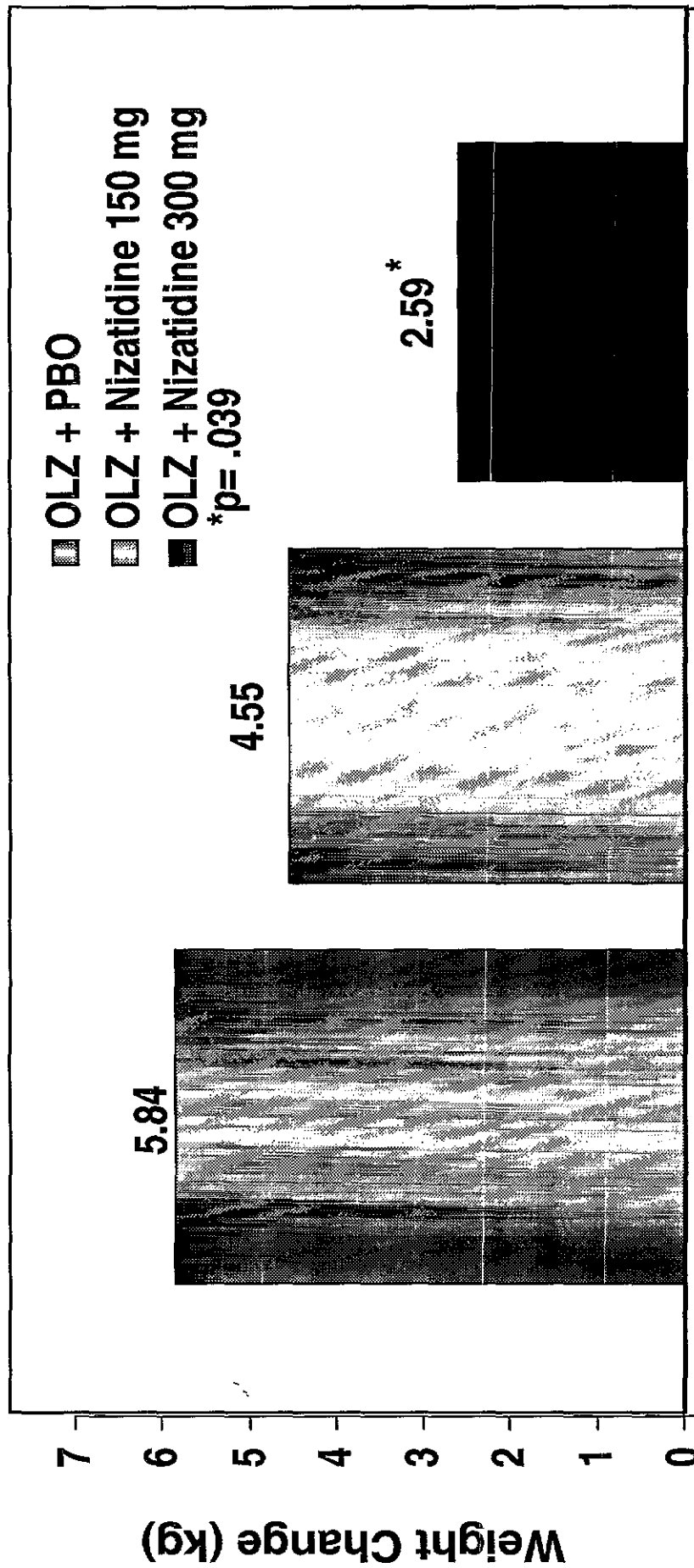
Case Series: Floris and Lejeune, 2000. Mean olanzapine dose=8.3 mg. Mean amantadine dose=175 mg. Amantadine added after 13± 13 weeks on olanzapine. Overall olanzapine treatment equals 34 ± 7 weeks.

Nizatidine for the Prevention of Olanzapine-Associated Weight Gain



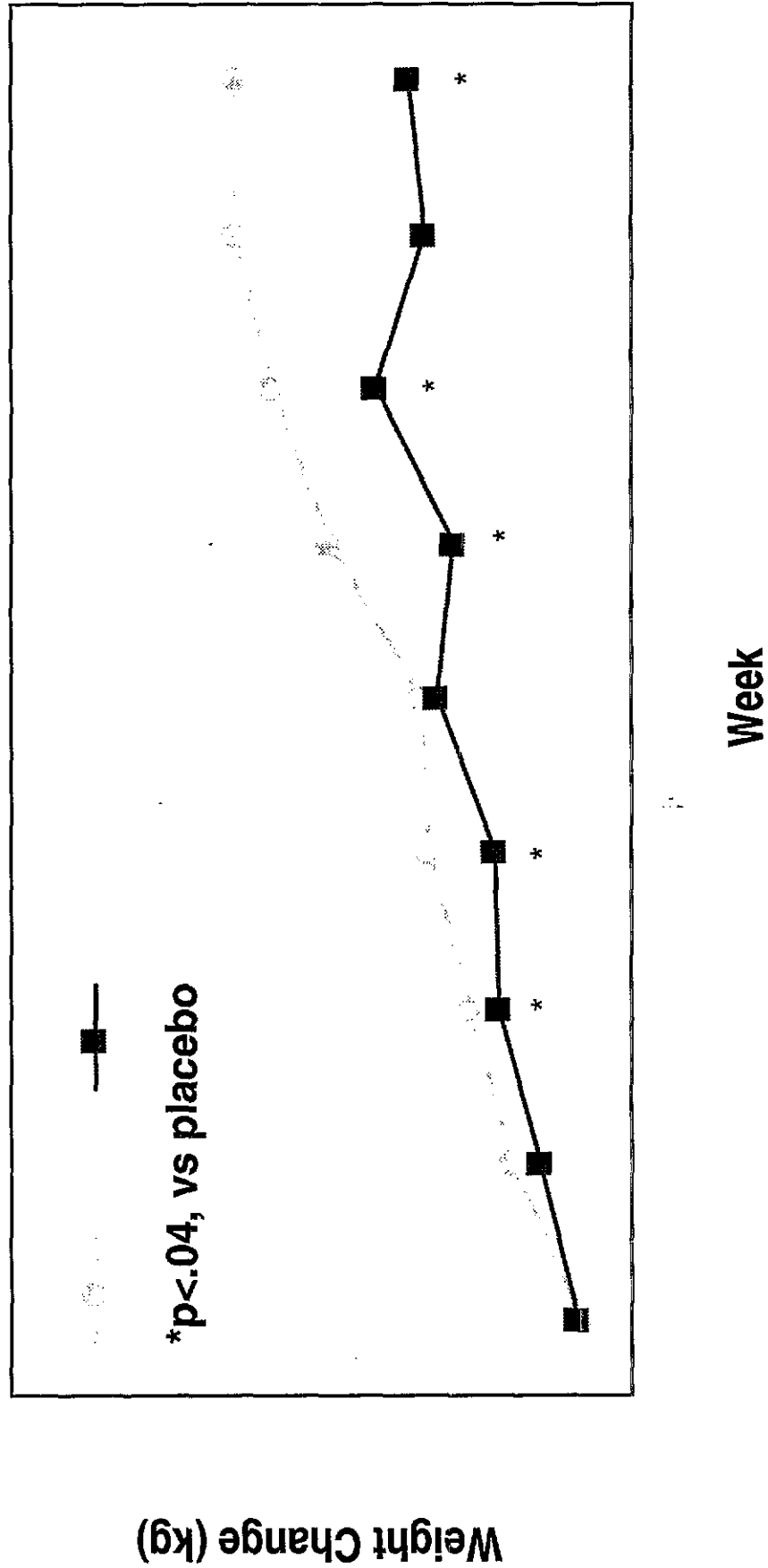
Data on file, Eli Lilly and Company. 2000
The combination use of olanzapine and nizatidine has not received FDA approval.

The Effects of Nizatidine on Olanzapine-related Weight Gain (N=74)



Data on file, Eli Lilly and Company. 2000
Nizatidine 300 mg vs placebo
The combination use of olanzapine and nizatidine has not received FDA approval.

The Effects of Nizatidine on Olanzapine-related Weight Gain (N=74)



Data on file, Eli Lilly and Company. 2000
The combination use of olanzapine and nizatidine has not received FDA approval.

Recommendations: Weight Gain on Olanzapine

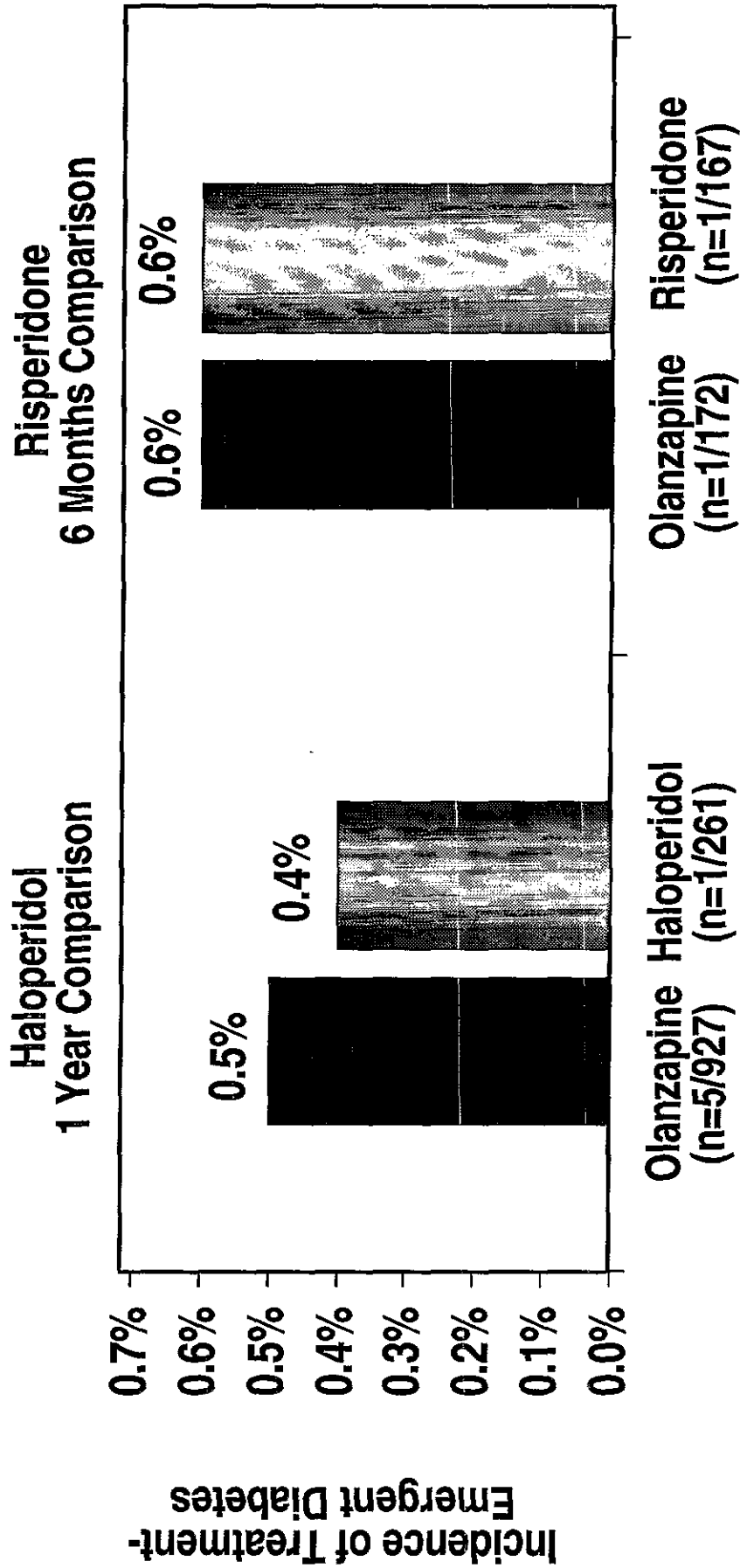
- ◆ Do not rule out olanzapine trial solely because of baseline obesity
- ◆ Reduce likelihood of weight gain through upfront counseling and education
- ◆ Expect substantial intra-individual variation
- ◆ Consider early intervention for patients developing ravenous appetite or rapid initial gain
- ◆ Expect weight to plateau after 9 months
- ◆ Dose to therapeutic effect as reducing dose is not likely to remediate weight gain
- ◆ Consider behavioral and/or pharmacological measures as they are likely to remediate weight gain for some patients

Glucose Elevation

Lilly

Answers That Matter.

Incidence of Treatment-Emergent Diabetes of Diabetes: Longer Term Comparisons from Olanzapine Schizophrenia Registration Trials



Data on file, Eli Lilly and Company.

Glycemic Effects of Treatment With Olanzapine and Other Psychotropic Medications

Olanzapine Clinical Trial Database:

Advantages: **Size**

Parallel group controls

Random treatment assignment

Limitation:

Not primarily glycemia studies:
random glucose

Analyses Included:

Mean glucose change from baseline in all patients

Rates of individuals with treatment-emergent elevation

Change in Mean Random Glucose During Head-to-Head Schizophrenia Trials

STUDY	TRT	Δ GLUCOSE	p
vs risperidone	OLZ	2.6 mg/dl	NS
	RIS	1.9 mg/dl	
vs haloperidol	OLZ	3.8 mg/dl	<.0001
	HAL	-0.1 mg/dl	
vs clozapine	OLZ	3.0 mg/dl	.0002
	CLZ	14.3 mg/dl	
vs placebo	OLZ	1.4 mg/dl	<.01
	PBO	-1.6 mg/dl	

Change from baseline in least square mean of random glucose across controlled trials.

Glucose Thresholds

Glucose (mg/dL)	Interpretation
110	Fasting plasma glucose upper limit of normal
126	Fasting plasma glucose suggests diabetes
140	Random capillary glucose (fingertstick) suggests need for further evaluation
160	Random plasma glucose suggests need for further evaluation
200	Random plasma glucose suggests diabetes

American Diabetes Association. *Diabetes Care*. 2000;23(suppl 1):S1-116.

Analysis of Likelihood of Random Glucose Elevation Over Specific Thresholds

- ◆ Olanzapine-treated patients not significantly different than haloperidol or risperidone controls at any examined threshold (126, 140, 160, 200 mg/dL)
- ◆ Olanzapine-treated patients significantly less likely than clozapine controls to cross 126 mg/dL or 140 mg/dL threshold

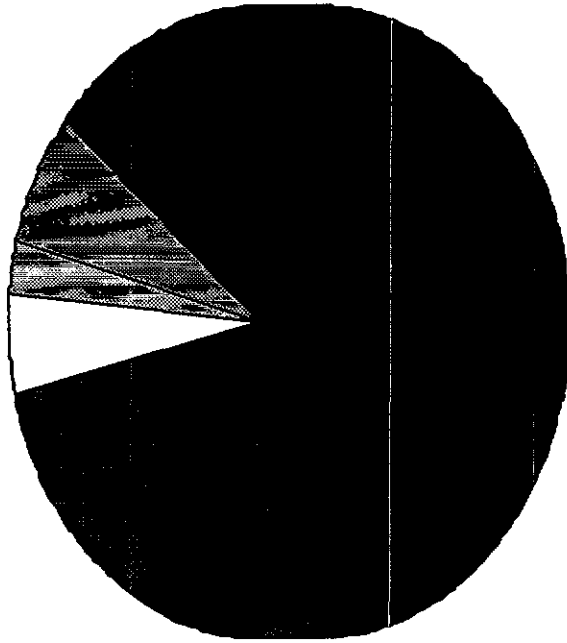
**Hazard (risk) ratio estimated by Cox regression.
Data on file, Eli Lilly and Company.**

Diabetes and Hyperglycemia

- ◆ **Common in the general US population**
- ◆ **More common in psychiatric patients**

Hyperglycemia Is Prevalent in the General US Population

- Normoglycemic
- Diagnosed
- ▨ Undiagnosed diabetes
- ▩ Borderline diabetes



Estimated prevalence rates for the period 1988-1994,
US adults:

- Diagnosed diabetes = 5.1%
- Undiagnosed diabetes = 2.7%
- Abnormally high but sub-threshold fasting glucose = 6.9%

Prevalence of Diabetes and Impaired Glucose Tolerance Are Relatively High in Schizophrenia and Bipolar Disorder

- ◆ Rates of Type II diabetes mellitus in schizophrenia reportedly are 2-4 times the general population¹⁻⁴
- ◆ Rate in hospitalized bipolar patients reported 2-3 times the general population⁵
- ◆ Several psychotropics have been associated with high insulin levels and possible insulin resistance (e.g., chlorpromazine⁶, divalproex⁷), yet diabetes may be just as common in untreated patients⁴
- ◆ Elevated rates of glycemic abnormalities were described in psychiatric patients even before the introduction of antipsychotics or mood stabilizers⁸⁻¹¹

1. Keskiner A, et al. *Psychosomatics*. 1973;14(3):176-181. 2. McKee HA, et al. *J Clin Hosp Pharm*. 1986;1(4):297-299. 3. Mukherjee, Schizoph Res. 1995. 4. Mukherjee S, et al. *Compr Psychiatry*. 1996;37(1):68-73. 5. Cassidy F, et al. *Am J Psychiatry*. 1999;156(9):1417-1420. 6. Erle G, et al. *Eur J Clin Pharmacol*. 1977;11(1):15-18. 7. Isojarvi JI, et al. *Ann Neurol*. 1996;39(5):579-584. 8. Braceland et al, *Am J Psychiatry* 1945.

9. Freeman, *Arch Neurol Psychiatry*, 1946. 10. Langfeldt *Acta Psychiatr Scand*, 1952. 11. Lorenz *Arch Neurol Psychiatry*, 1922.

Conclusions

- ◆ Likelihood of diabetes or elevation of random glucose above threshold was similar on olanzapine to risperidone and haloperidol controls
- ◆ Diabetes is common in the US generally, and probably much more so in the seriously mentally ill
- ◆ Further research is underway

James A Harper
02/13/01 08:39 AM

To: Alan Breier/AM/LLY@Lilly, Roland Powell/AM/LLY@Lilly, William J
Robinson/AM/LLY@Lilly, Gino Santini/AM/LLY@Lilly, Gary D
Tollefson/AM/LLY@Lilly, Albertus VanDenBergh/EMA/LLY@Lilly
cc: Jacqueline S Coy/AM/LLY@Lilly, Alice L Finch/AM/LLY@Lilly, Stacey L
Fout/AM/LLY@Lilly, Suzanne Myers/AM/LLY@Lilly, Lee
OMara/AM/LLY@Lilly, Barbara L Whitaker/AM/LLY@Lilly
Subject: Re: ****IMPORTANT**** Pre-Read for 2/14/01 Policy Committee Meeting

Attached is the "pre-read" for the Zyprexa update scheduled for the Policy Committee on Wednesday, February 14. An executive summary for your convenience, has been provided; however, detailed information has also been included should you desire more extensive background.

 
Zyprexa Executive Summary 2-12-01 frm Harper Ziprasidone Zyprexa 2-14-01.p

JAH

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