

Comparative Effectiveness of
Antipsychotic Drugs in Patients with
Chronic Schizophrenia:
Findings to Date from the NIMH-
CATIE Schizophrenia Trial

Scott Stroup, MD, MPH

University of North Carolina at Chapel Hill



CATIE

Clinical Antipsychotic Trials of Intervention Effectiveness

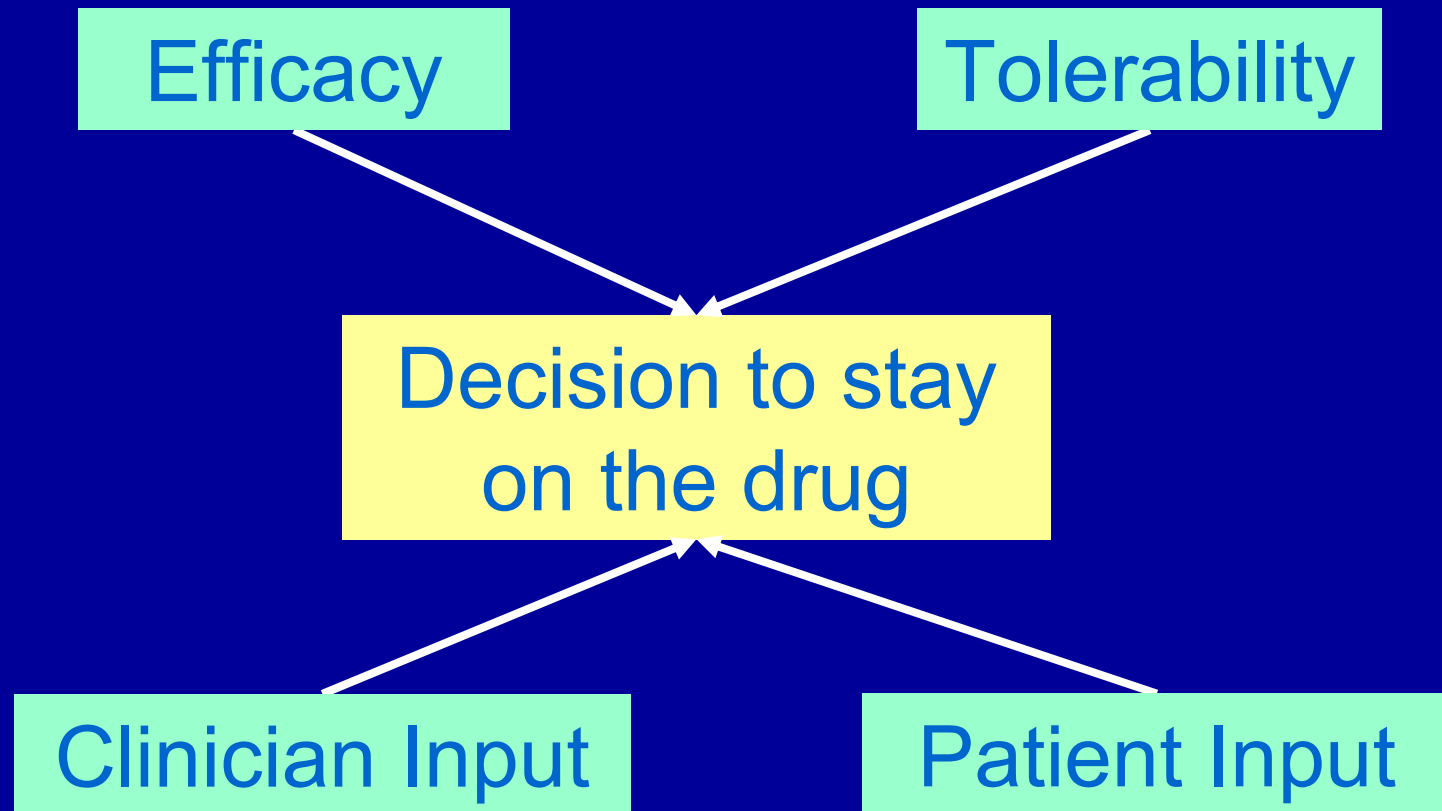
Research program to evaluate the effectiveness of antipsychotic medications for schizophrenia and Alzheimer's disease in "real-world" settings

NIMH

National Institute
of Mental Health

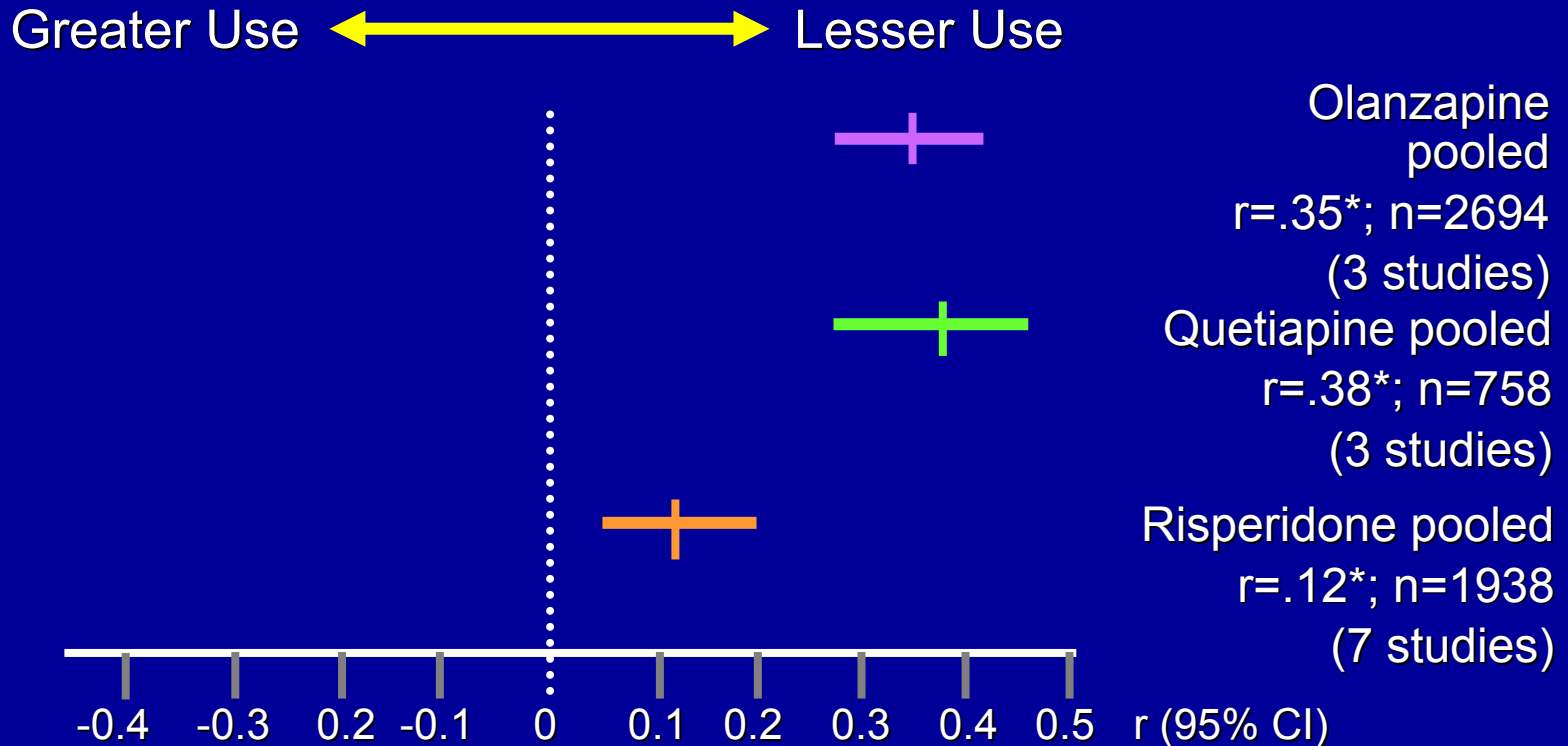
Determinants of drug effectiveness

Staying on the drug is critical



The approach to extrapyramidal side effects is a key methodologic issue in comparative studies of first- and second-generation antipsychotic drugs.

New Antipsychotics vs Haloperidol 'Pooled' Data on use of anticholinergics Use of Anticholinergic Medication



*Statistically significant.

Modified from Leucht S, et al. *Schizophr Res.* 1999;35:51-68.

Atypical antipsychotics in the treatment of schizophrenia: meta-regression analysis

(Geddes et al for the National Schizophrenia

National (UK) Schizophrenia Guideline Development Group 2000)

- Result: When the dose was <12 mg/day of haloperidol (or equivalent), atypical antipsychotics had no benefits in terms of efficacy or overall tolerability, but they still caused fewer extrapyramidal side effects.
- Conclusion: There is no clear evidence that atypicals are more effective or better tolerated than conventional antipsychotics. Therefore, conventional antipsychotics should usually be used in the initial treatment of schizophrenia

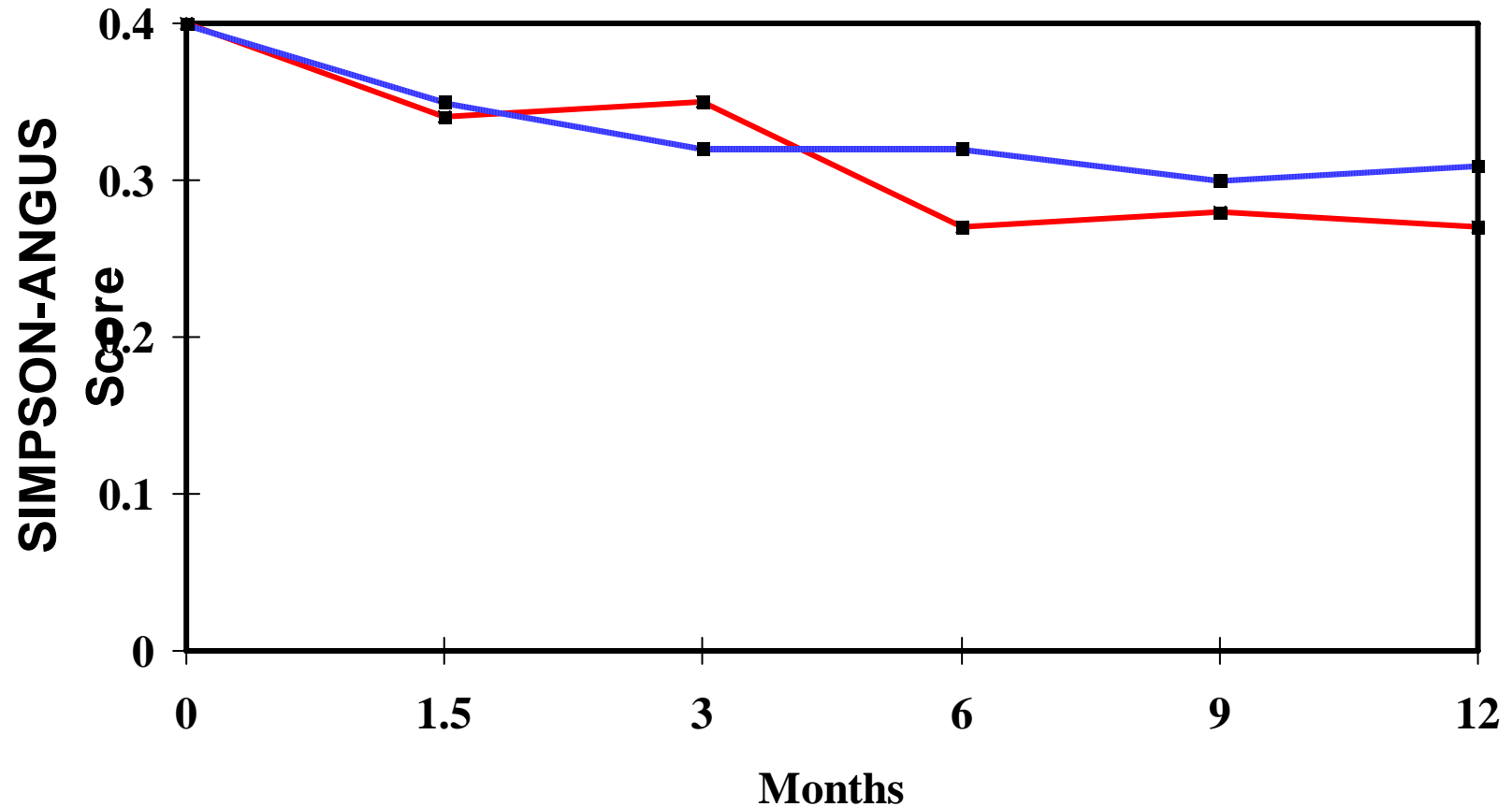
Effectiveness and cost of olanzapine and haloperidol: A randomized clinical trial

Rosenheck et al. JAMA 2003

All patients assigned haloperidol also received benztropine to minimize EPS.

Olanzapine vs. Haloperidol; Rosenheck et al, 2003

SIMPSON-ANGUS (Extra-pyramidal syndrome) - ITT



Mixed model
analysis: ns

Chronic Schizophrenia: *Key Recommendations of the Schizophrenia Patient Outcomes Research Team (PORT)*

- No clear statement of preference of SGAs over FGAs in acute or maintenance treatment
- Clozapine the treatment of choice for treatment-refractory positive symptoms; clozapine also recommended for hostility and suicidality

Rationale for CATIE

Published studies have significant limitations:

- Predominantly short-term studies designed for regulatory approval and labeling language
- Comparators are either placebo or a single active agent (usually haloperidol)
- Results have limited generalizability because they lack representative patient samples, clinical settings and treatment conditions
- Existing studies do not address critical clinical and policy questions
- Sponsored by pharmaceutical companies

Clinical experience and case reports are not an adequate substitute for data

Practical Clinical Trials

- Designed to answer questions faced by clinicians and policy makers
- Compare clinically relevant alternative interventions
- Include a representative population of study participants
- Conduct studies at representative practice settings
- Simulate actual treatment conditions
- Collect data on a broad range of health outcomes that are clinically meaningful

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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*

CATIE: *Broad Inclusion & Minimal Exclusion Criteria*

- DSM-IV schizophrenia, 18-65 years old
- Not first-episode or treatment resistant
- Concomitant medications, medical illnesses, substance use disorders allowed
- Conducted at 57 geographically, demographically and organizationally diverse sites

Primary Questions Addressed by CATIE Schizophrenia Trial

- How do the second generation antipsychotics compare with a representative first generation antipsychotic?
- What is the comparative effectiveness of the second generation antipsychotic drugs?
- Are the second generation antipsychotics cost-effective?

CATIE Schizophrenia Trial: *Overview*

- Participants

1460 people with schizophrenia

- Trial duration

Subjects participate for 18 months

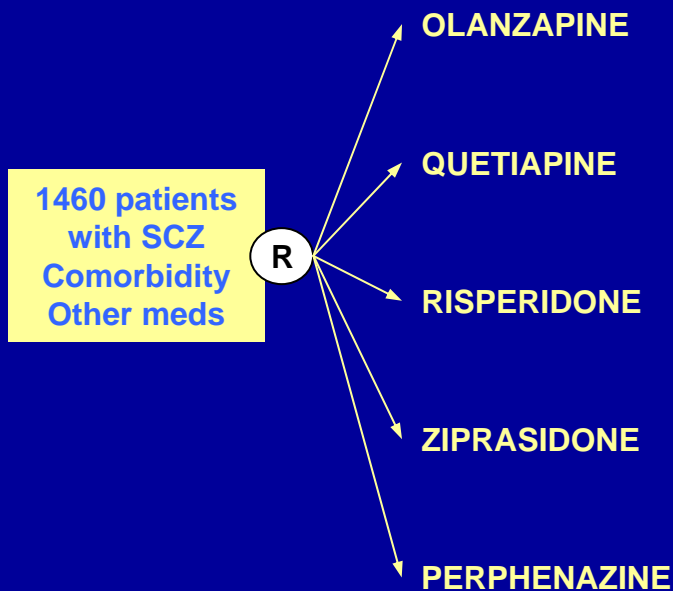
- Design

Practical trial that is a hybrid of efficacy and effectiveness trial designs

CATIE Schizophrenia Trial Design

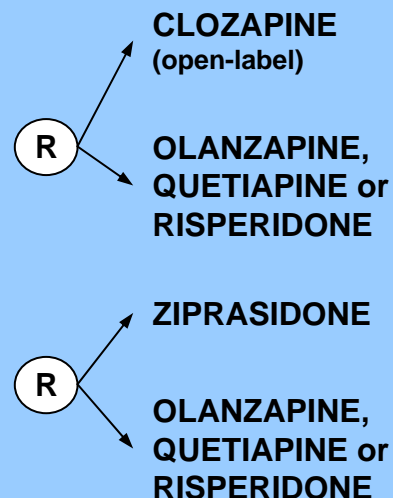
Phase 1*

Double-blind, random treatment assignment.



Phase 2

Participants who discontinue Phase 1 choose either the clozapine or the ziprasidone randomization pathways



No one assigned to same drug as in Phase 1

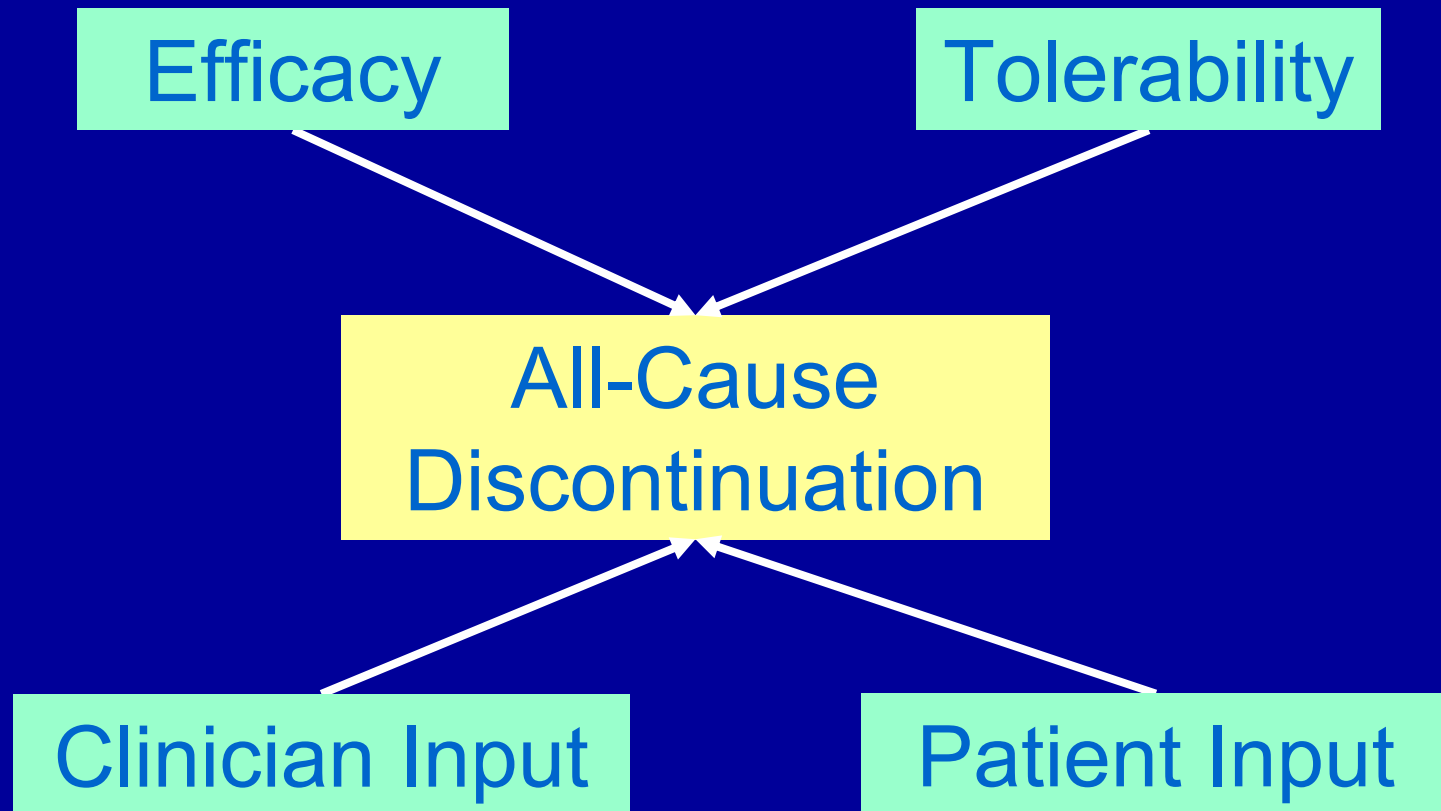
Phase 3

Participants who discontinue Phase 2 choose one of the following open-label treatments

- ARIPIPIRAZOLE
- CLOZAPINE
- FLUPHENAZINE DECANOATE
- OLANZAPINE
- PERPHENAZINE
- QUETIAPINE
- RISPERIDONE
- ZIPRASIDONE
- 2 of the antipsychotics above

*Phase 1A: participants with TD (N=231) do not get randomized to perphenazine; phase 1B: participants who fail perphenazine will be randomized to an atypical (olanzapine, quetiapine, or risperidone) before eligibility for phase 2.

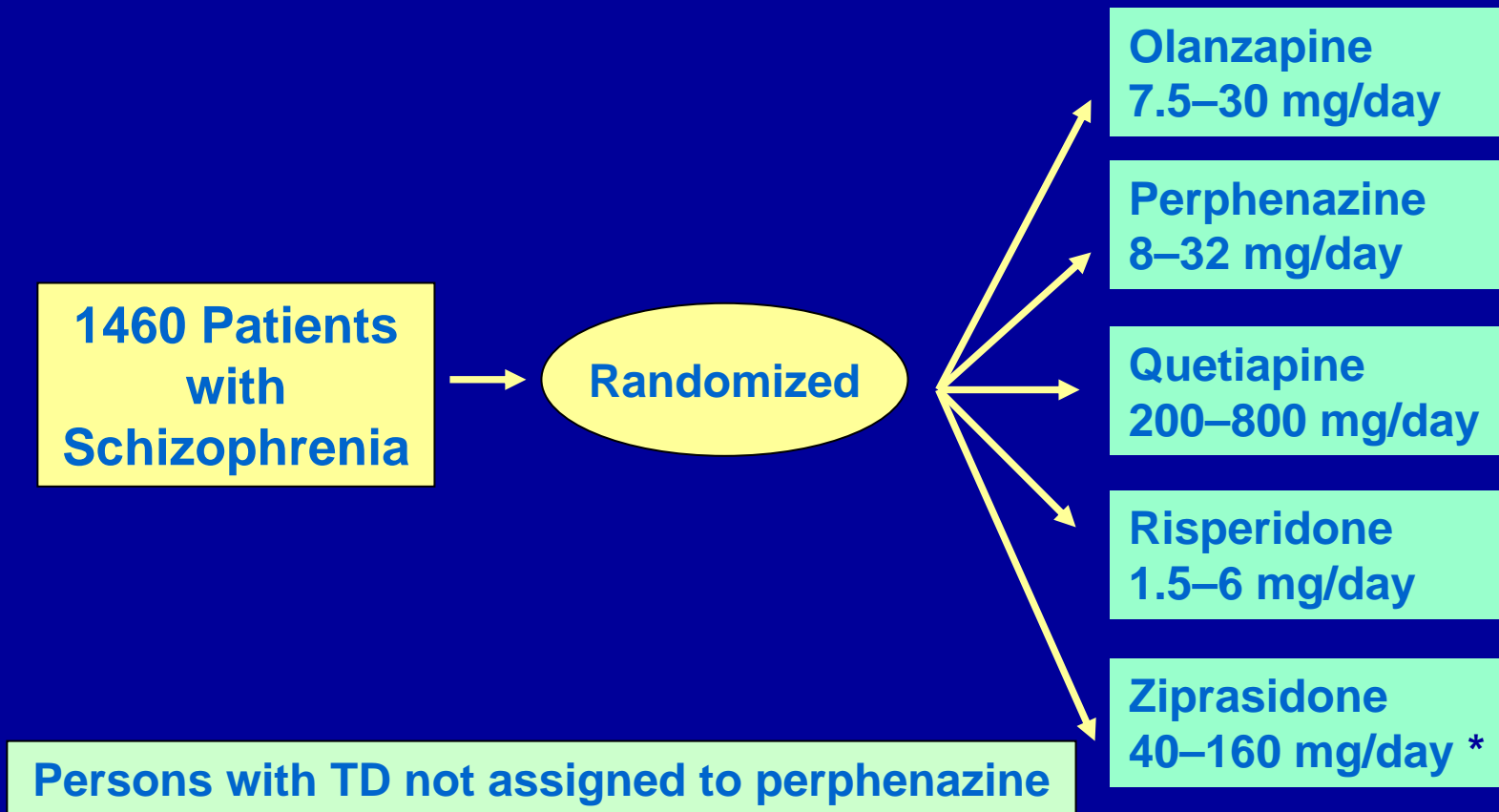
Primary Effectiveness Measure: *All-Cause Treatment Discontinuation*



Secondary Outcomes

- Symptom measures
- Safety
- Service use and costs
- Neurocognition
- Treatment adherence
- Comorbidity
- Quality of Life
- Substance use
- Violence

CATIE Phase 1: Double-Blinded and Randomized

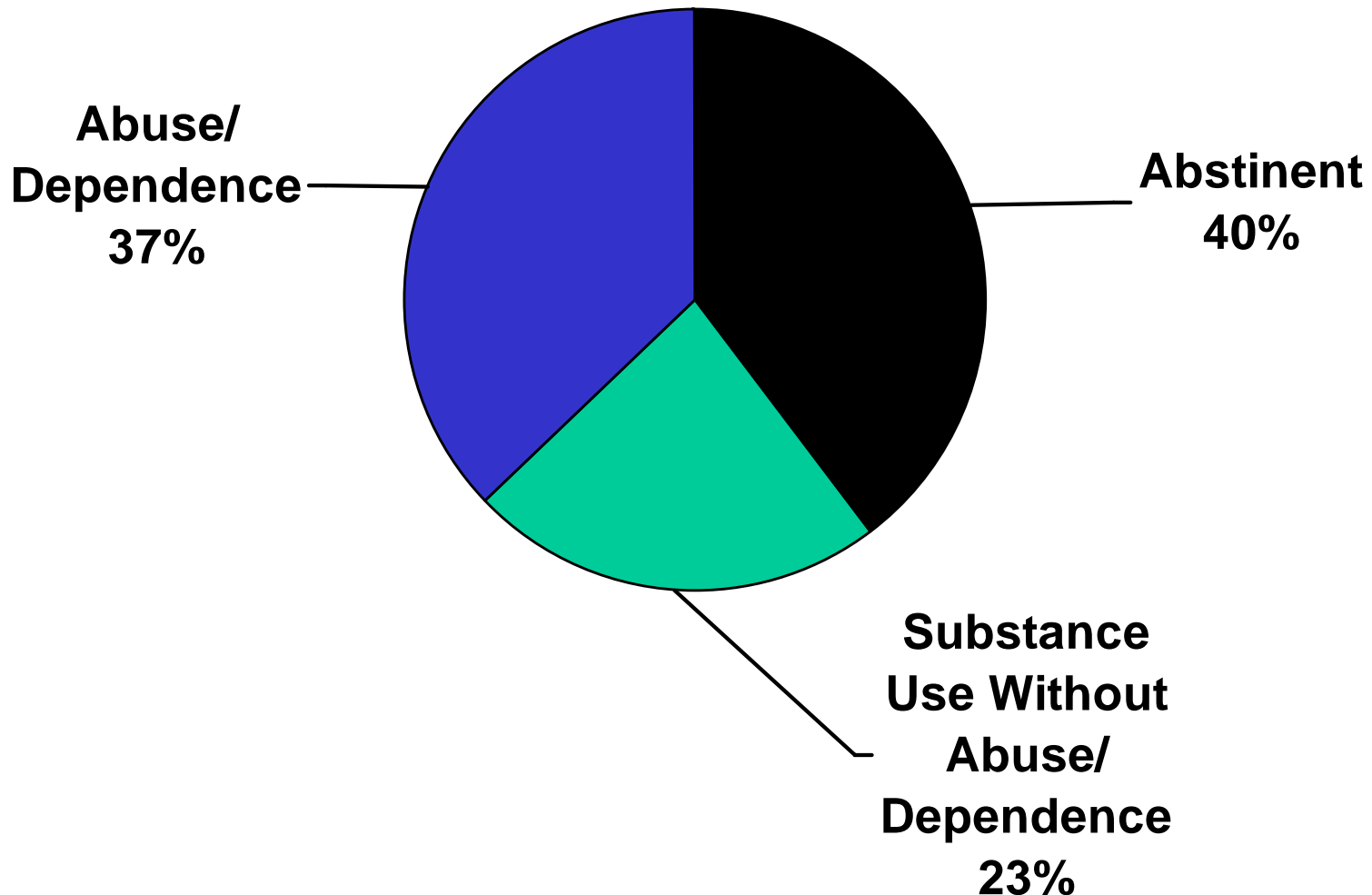


* Ziprasidone added after 40% sample enrolled

Demographic & Clinical Characteristics

Assessment	Total (n=1460)
Demographics	
Age mean (SD)	40.6 (11.1)
Gender	
Male	1080 (74%)
Race	
○ White	874 (60%)
○ Black /African-American	513 (35%)
○ All other race groups	71 (5%)
Spanish/Hispanic/ Latino ethnicity	170 (12%)
Education (years)	12.1 (2.3)
Marital Status	
○ Married	167 (11%)
○ Previously Married	425 (29%)
○ Never Married	868 (59%)
Unemployed	1217 (85%)
Exacerbation in Past 3 Months	402 (28%)
PANSS Total Score (30-210)	75.7 (17.6)
Clinician Rated CGI Severity Score (1-7) CG-S of 4 = “moderately ill”	4.0 (0.9)

Substance Use in CATIE Subjects (Alcohol and Illicit Drugs)

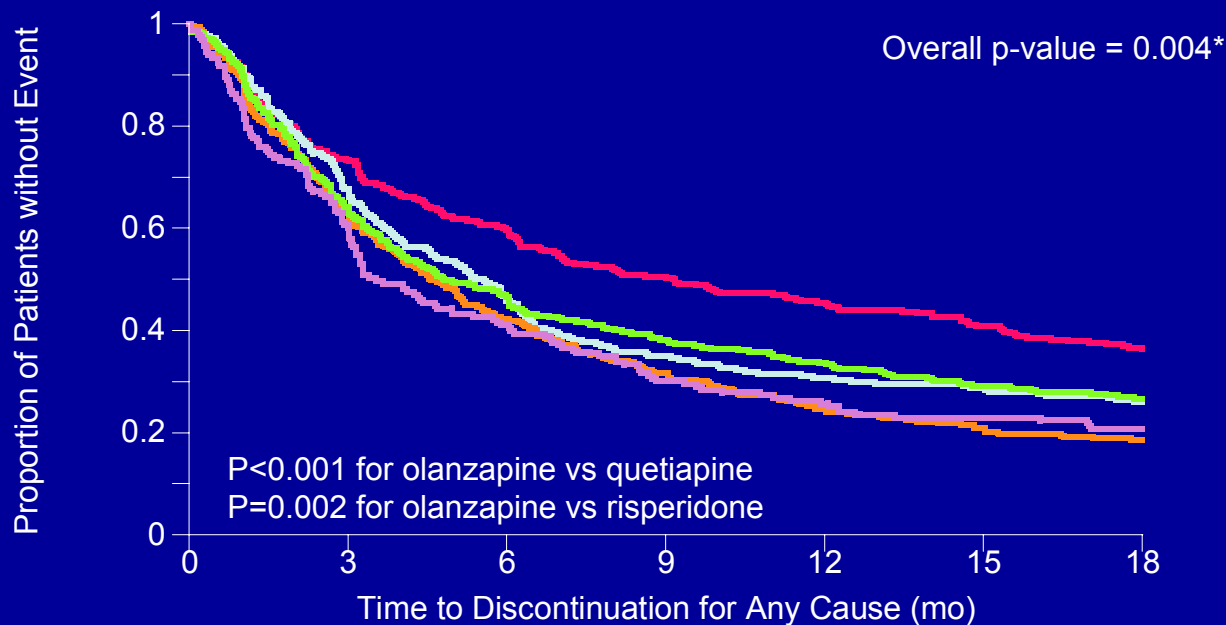


Source of data: Marvin Swartz, MD; unpublished data.

Phase I Randomization and Treatment

	OLZ (n=336)	QUET (n=337)	RISP (n=341)	PER (n=261)	ZPR (n=185)	p-value
Intent-to-treat patients	330	329	333	257	183	-
Average modal dose (mg)	20.1	543.4	3.9	20.8	112.8	-
Patients reaching maximal dose	40%	44%	40%	40%	48%	<0.001

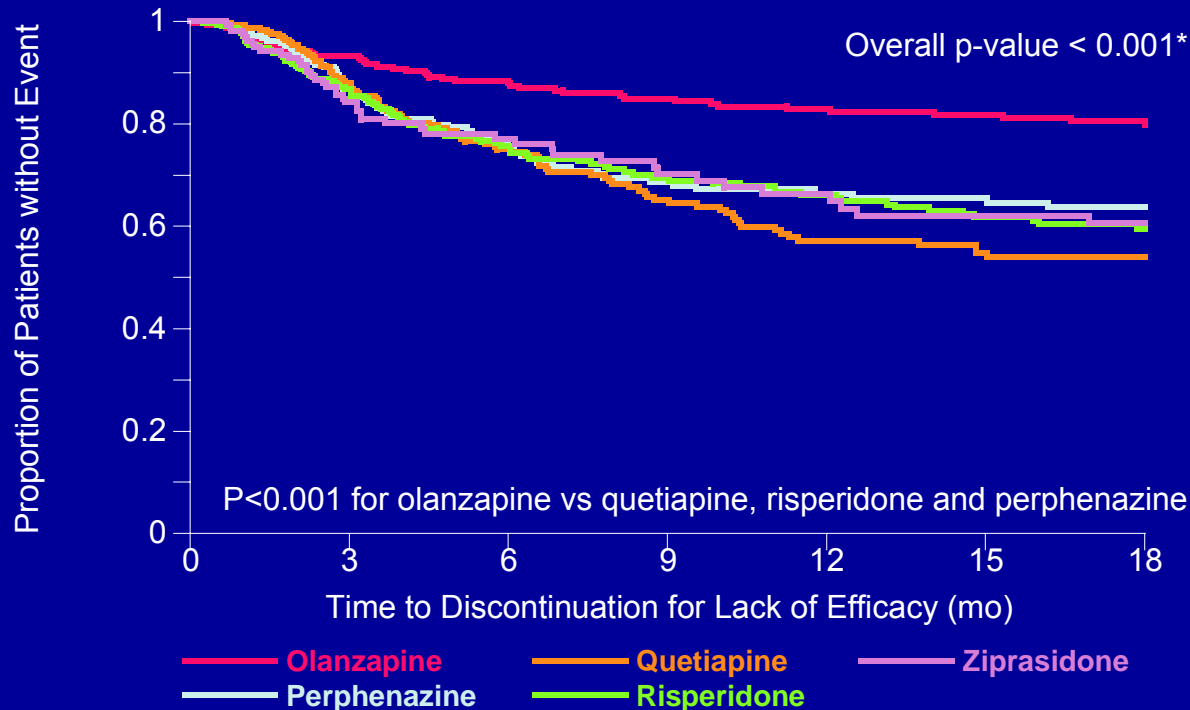
Time to Discontinuation for Any Reason



— Olanzapine — Quetiapine — Ziprasidone
— Perphenazine — Risperidone

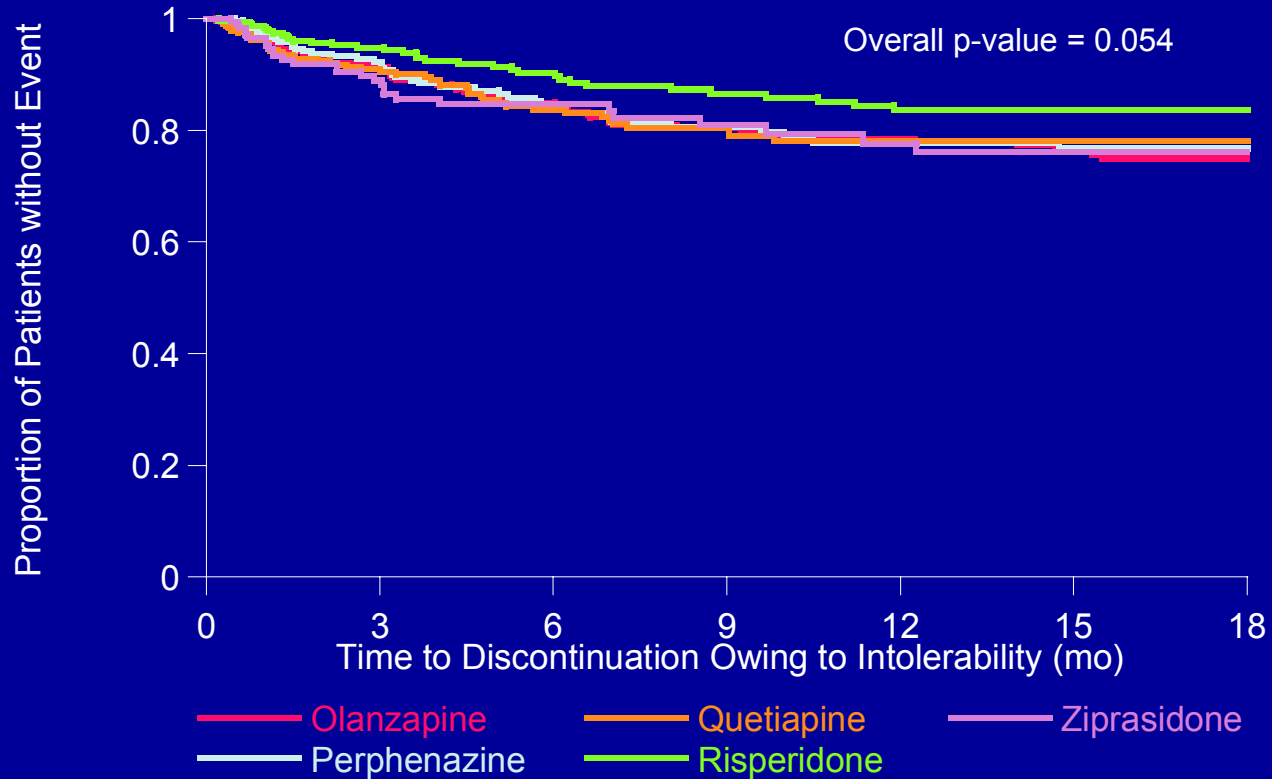
	OLZ (n=330)	QUET (n=329)	RISP (n=333)	PER (n=257)	ZPR (n=183)
Discontinued	210 (64%)	269 (82%)	245 (74%)	192 (75%)	145 (79%)
Kaplan-Meier Median (mos) [95%CI]	9.2 [6.9, 12.1]	4.6 [3.9, 5.5]	4.8 [4.0, 6.1]	5.6 [4.5, 6.3]	3.5 [3.1, 5.4]
Hazard ratios for Olanzapine	---	0.63 < 0.001*	0.75 0.002*	0.78 0.021	0.76 0.028

Time to Discontinuation for Lack of Efficacy



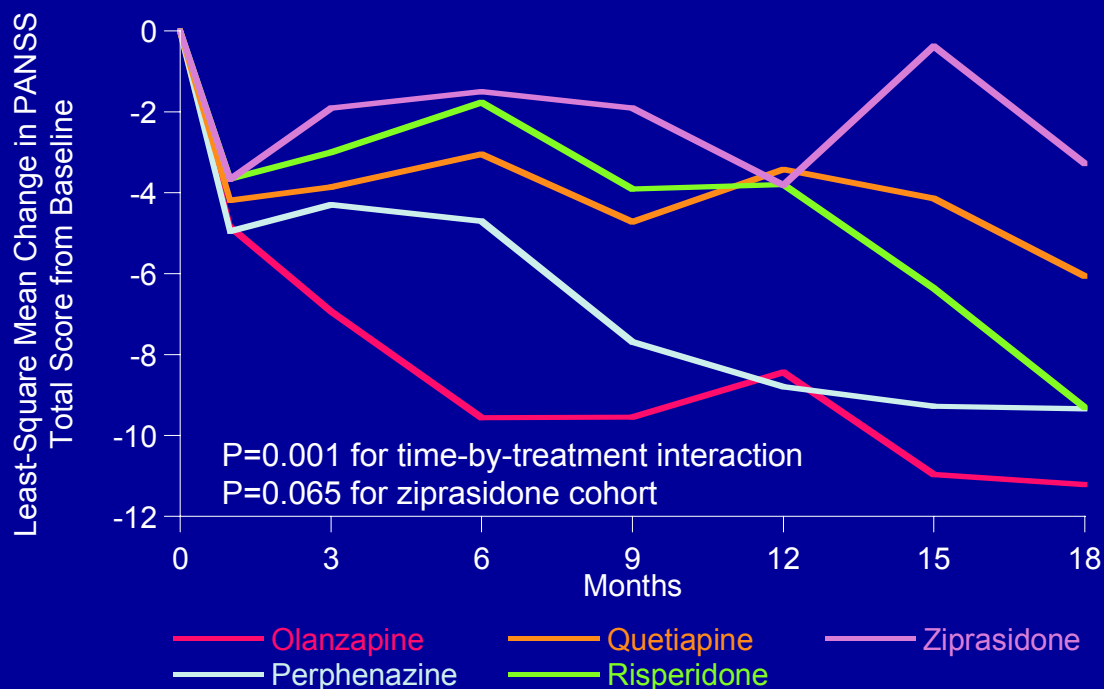
	OLZ (n=330)	QUET (n=329)	RISP (n=333)	PER (n=257)	ZPR (n=183)
Discontinued	48 (15%)	92 (28%)	91 (27%)	65 (25%)	44 (24%)
Kaplan-Meier 25th %tile (mos) [95%CI]	- [18.0, -]	6.0 [4.5, 8.0]	6.0 [4.4, 9.0]	6.1 [4.5, 9.1]	6.9 [3.2, 12.1]
Hazard ratios for Olanzapine	---	0.41 < 0.001*	0.45 < 0.001*	0.47 < 0.001*	0.59 0.026

Time to Discontinuation for Intolerability



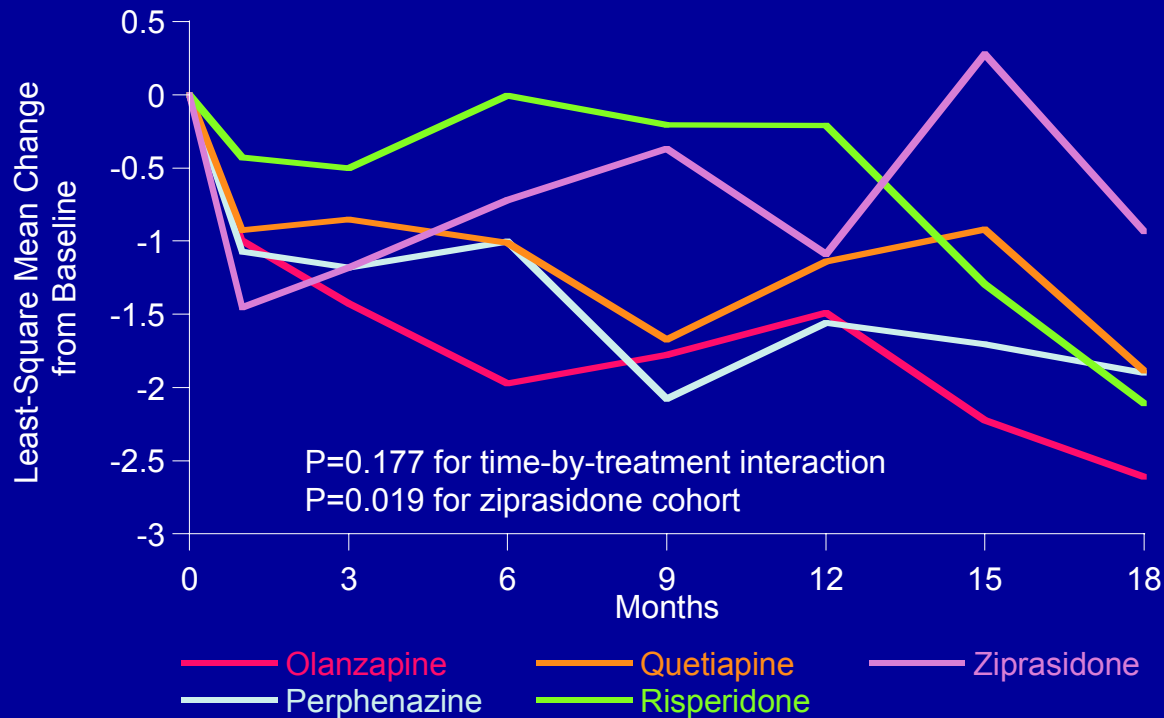
	OLZ (n=330)	QUET (n=329)	RISP (n=333)	PER (n=257)	ZPR (n=183)
Discontinued	62 (19%)	49 (15%)	34 (10%)	40 (16%)	28 (15%)
Hazard ratios for Risperidone	0.62 0.027	0.65 0.051	---	0.60 0.043	0.79 0.41

PANSS Total Score



Interaction of time \times treatment indicates significant variation in treatment effects over time. Improvement was initially greatest with olanzapine but its advantage diminished over time. The number of patients declines over assessment times. Least -square mean estimates are from a mixed model, which assumes that data are missing at random. Values at later time points are based on the observed data for continuing patients as well as estimated data for discontinued patients.

PANSS Negative Score



The number of patients declines over assessment times. Least -square mean estimates are from a mixed model, which assumes that data are missing at random. Values at later time points are based on the observed data for continuing patients as well as estimated data for discontinued patients.

Hospitalizations for Exacerbation of Schizophrenia

Assessment	OLZ (n=336)	QUET (n=337)	RISP (n=341)	PER (n=261)	ZPR (n=185)	P-value
No of patients hospitalized	38 (11%)	68 (20%)	51 (15%)	41 (16%)	33 (18%)	<0.001
Hospitalizations per person-years of exposure (risk ratio)	81/280 (0.29)	131/199 (0.66)	103/229 (0.45)	89/175 (0.51)	62/109 (0.57)	-

Treatment-Emergent Adverse Events

Assessment	OLZ (n=336)	QUET (n=337)	RISP (n=341)	PER (n=261)	ZPR (n=185)	P-value
Any Serious AE	10%	9%	10%	11%	10%	0.47
Suicide attempt	1%	1%	<1%	<1%	<1%	0.99
Suicide ideation	<1%	<1%	1%	1%	1%	0.49
Any Moderate or Severe AE by Systematic Inquiry	70%	65%	68%	65%	64%	0.14
Insomnia	16%	18%	24%	25%	30%	<0.001
Hypersomnia / Sleepiness	31%	31%	28%	28%	24%	0.18
Urinary Hesitancy / Dry Mouth / Constipation	24%	31%	25%	22%	20%	<0.001
Sex Drive/ Sexual Arousal/ Sexual Orgasm	27%	20%	27%	25%	19%	0.59
Gynecomastia / Galactorrhea	2%	2%	4%	2%	3%	0.15
Menstrual Irregularities	12%	6%	18%	11%	14%	0.17
Incontinence / Nocturia	5%	4%	7%	2%	5%	0.04
Sialorrhea	4%	4%	7%	5%	6%	0.20
Orthostatic Faintness	9%	11%	11%	11%	13%	0.08
Skin Rash	7%	6%	6%	3%	5%	0.18
Any Moderate or Severe Spontaneously Reported AE	36%	34%	36%	30%	35%	0.10

Treatment-Emergent Neurologic Effects

Assessment	OLZ (n=336)	QUET (n=337)	RISP (n=341)	PER (n=261)	ZPR (n=185)	P-value
AIMS Severity Index ≥ 2 (2=mild incapacitation)	14%	13%	16%	17%	14%	0.23
Barnes: Global Clinical Assessment ≥ 3						
Including TD patients	5%	5%	7%	7%	9%	0.24
Excluding TD patients	5%	5%	6%	7%	10%	0.19
(3=moderate Akathisia)						
Simpson-Angus: EPS Mean Scale Score ≥ 1						
Including TD patients	8%	4%	8%	6%	4%	0.47
Excluding TD patients	7%	4%	8%	6%	5%	0.50
(1=mild or slight symptoms)						
Anticholinergic Agents added	8%	3%	9%	10%	8%	0.01

Weight change from Baseline to Last Observation

Assessment	Statistic	OLZ (n=336)	QUET (n=337)	RISP (n=341)	PER (n=261)	ZPR (n=185)	P-value
Weight Gain > 7%	(%)	30%	16%	14%	12%	7%	<0.001
Weight: Change (lbs)	Mean (S.E.)	9.4 (0.9)	1.1 (0.9)	0.8 (0.9)	-2.0 (1.1)	-1.6 (1.1)	<0.001
	Median	7	1	0	-1	-2	
	Range	-14, 42	-25, 25	-24, 24	-29, 22	-24, 18	
Weight Change / Treatment Duration (lbs/month)	Mean (S.E.)	2.0 (0.3)	0.5 (0.2)	0.4 (0.3)	-0.2 (0.2)	-0.3 (0.3)	<0.001
	Median	0.8	0.1	0.0	-0.1	-0.3	
	Range	-1.4, 9.5	-4.4, 6.3	-4.6, 5.7	-4.9, 4.0	-5.3, 5.9	

Laboratory Chemistry: Change from Baseline to Average of Two Highest Values

Assessment	Statistic	OLZ (n=336)	QUET (n=337)	RISP (n=341)	PER (n=261)	ZPR (n=185)	P-value
Blood glucose (mg/dL)	Mean (S.E.)	15.0 (2.8)	6.8 (2.5)	6.7 (2.0)	5.2 (2.0)	2.3 (3.9)	0.59
	Median	7.0	4.3	5.5	1.5	2.5	
	Exposure-adjusted. Mean (S.E.)	13.7 (2.5)	7.5 (2.5)	6.6 (2.5)	5.4 (2.8)	2.9 (3.4)	
Hemoglobin A1C (%)	Mean (S.E.)	0.41 (0.09)	0.05 (0.05)	0.08 (0.04)	0.10 (0.06)	-0.10 (0.14)	0.01
	Median	0.20	0.10	0.05	0.05	0.10	
	Exposure-adjusted. Mean (S.E.)	0.40 (0.07)	0.04 (0.08)	0.07 (0.08)	0.09 (0.09)	0.11(0.09)	
Cholesterol (mg/dL)	Mean (S.E.)	9.7 (2.1)	5.3 (2.1)	-2.1 (1.9)	0.5 (2.3)	-9.2 (5.2)	<0.001
	Median	8.5	3.5	-3.0	0.5	-1.0	
	Exposure-adjusted. Mean (S.E.)	9.4 (2.4)	6.6 (2.4)	-1.3 (2.4)	1.5 (2.7)	-8.2 (3.2)	
Triglycerides (mg/dL)	Mean (S.E.)	42.9 (8.4)	19.2 (10.6)	-2.6 (6.3)	8.3 (11.5)	-18.1 (9.4)	<0.001
	Median	33.5	17.5	3.0	2.0	-7.0	
	Exposure-adjusted. Mean (S.E.)	40.5 (8.9)	21.2 (9.2)	-2.4 (9.1)	9.2 (10.1)	-16.5 (12.2)	
Prolactin (ng/mL)	Mean (S.E.)	-6.1 (1.2)	-9.3 (1.4)	15.4 (1.5)	0.4 (1.7)	-4.5 (1.6)	<0.001
	Median	-0.9	-2.7	9.2	1.4	-2.4	
	Exposure-adjusted. Mean (S.E.)	-8.1 (1.4)	-10.6 (1.4)	13.8 (1.4)	-1.2 (1.6)	-5.6 (1.9)	

Reasons for Discontinuation Due to Intolerability

All Randomized Patients

Assessment	Statistic	OLZ (n=336)	QUET (n=337)	RISP (n=341)	PER (n=261)	ZPR (n=185)	P-value
Discontinued for Intolerability							
Discontinued for Intolerability	n (%)	62 (18%)	49 (15%)	34 (10%)	40 (15%)	28 (15%)	0.04
Tolerability Discontinuations: Most Problematic Side Effect							
Weight/Metabolic	n (%)	31(9%)	12(4%)	6 (2%)	3 (1%)	6 (3%)	<0.001
Extrapyramidal	n (%)	8 (2%)	10(3%)	11(3%)	22(8%)	7 (4%)	0.002
Sedation	n (%)	7 (2%)	9 (3%)	3 (1%)	7 (3%)	0	0.10
Other	n (%)	16(5%)	18(5%)	14(4%)	8 (3%)	15(8%)	0.16

Key Messages

- CATIE provides important new information on antipsychotic drugs that should greatly assist doctors and patients in making individualized treatment choices.
- Overall, all the medications were comparably effective but were associated with high rates of discontinuation due to intolerable side effects, failure to adequately control symptoms, or other reasons.

Key Messages

- Olanzapine was somewhat more efficacious than the other drugs but also was associated with significant weight gain and metabolic changes.
- The older medication perphenazine generally performed as well as the newer medications. The older medication was as well tolerated as the newer drugs and was as effective as three of the newer medications. Contrary to expectations, EPS was not seen more frequently with perphenazine than with the newer drugs.

Key Messages

- Treatments for persons with schizophrenia must be individualized. Doctors and patients must carefully evaluate the tradeoffs between efficacy and side effects in choosing an appropriate medication. What works for one person may not work for another.

Some early reactions

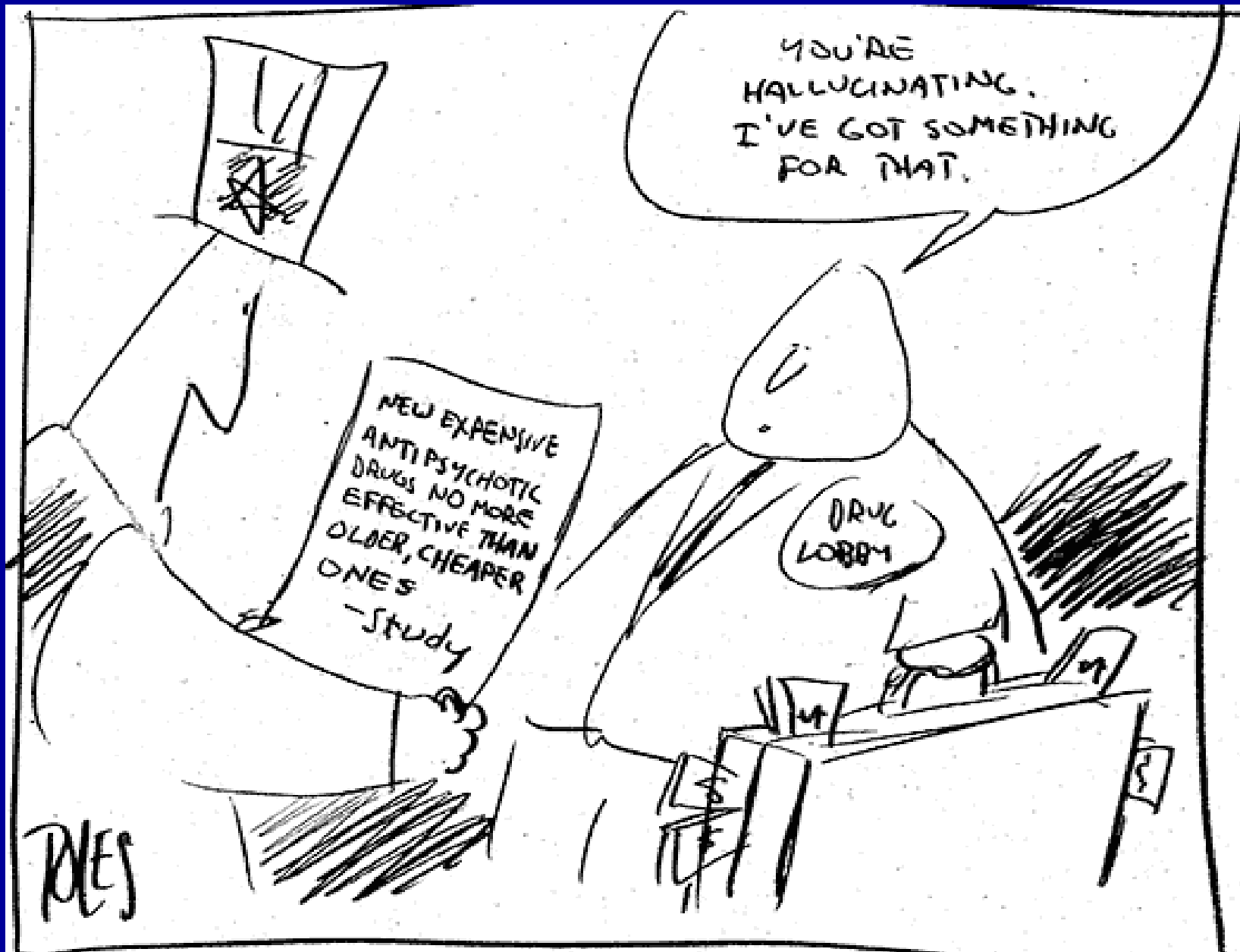
- Washington Post
New Antipsychotic Drugs Criticized
Federal Study Finds No Benefit Over
Older, Cheaper Drug
September 20, 2005; A01
- New York Times
Study Finds Little Advantage in New
Schizophrenia Drugs
September 20, 2005 F-1
- The Wall Street Journal
Generic Fares Well in Big Psychiatry
Study: Newer Costlier Drugs Have Little
Advantage for Schizophrenia
September 20, 2005 D-1

“Psychiatry hasn’t advanced in thirty years!”

Schizophrenia Anonymous-Durham is going
retro to celebrate Halloween

On 9/20, the researchers got their treat: the
psychiatric patients got the trick.

...while saving Medicaid money and
adjusting to those vintage neuroleptics,
here’s some music to get you in the mood:
“Let’s twist again”



FAQs

- Are the newer medications better than the older ones?
- Are the newer drugs all the same?
- Are the older drugs all the same? Do the results with perphenazine apply to the others?

FAQs

- Why were the discontinuation rates so high?
- Were the doses comparable?
- Was the study long enough to make comparisons regarding tardive dyskinesia?

FAQs

- Should everyone be switched to a cheaper drug?
- Should we keep everything on the formulary?
- Why not start with the cheapest drugs?

FAQs

- Do we know what to do when someone doesn't do well on one medication?

CATIE results still to come

- Cost-effectiveness evaluation
- Phase 2 studies:
 - Efficacy pathway: clozapine vs. a second atypical
 - Tolerability pathway: ziprasidone vs. a second
- Neurocognition
- Substance use, violence

Thank you.