Pharmacologic Treatment of Schizophrenia: How Far Have We Come?

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Disclosure 2014 John M. Kane, MD				
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THE NEW YORKER

ANNALS OF MENTAL HEALTH

GOD KNOWS WHERE I AM

What should happen when patients reject their diagnosis?

BY RACHEL AVIV

MAY 30, 2011

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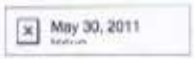


ABSTRACT: ANNALS OF MENTAL HEALTH about Linda Bishop and anosognosia. October 3, 2007, Linda Bishop was released from New Hampshire Hospital, in Concord. She had been admitted to the hospital in late October, 2006, after having been found incompetent to stand trial for a series of offenses. She refused all psychiatric medication, because she believed her diagnosis (bipolar disorder with psychosis) was a mistake. Each time she met a new psychiatrist, she declared her lack of respect for the profession. Her medical records consistently note the same traits: "extremely bright," "very pleasant," "denies completely that she has an illness." In the weeks leading up to her discharge, her doctors urged her to make arrangements for housing and follow-up care, but Linda refused, saying, "God will provide." On her fourth day out of the hospital, Linda broke into a vacant farmhouse for sale on Mountain Road, a scenic residential street. Linda had led a nomadic existence ever since she had abandoned her sleeping thirteen-year-old daughter, in 1999, leaving a note saying that she was going to meet the governor. She drifted between homeless shelters, hospitals, and jail. Describes her daily routine at the farmhouse. Throughout Linda's stay at New Hampshire Hospital, her doctors routinely noted that she lacked "insight," a term that has a troubled legacy in psychiatry. Discusses the definition and history of insight and anosognosia (used as a synonym for "poor insight") in psychiatry and the ethical imperative of getting patients to acknowledge their own disorders.

Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses

Stefan Leucht, Sandra Hierl, Werner Kissling, Markus Dold and John M. Davis

Background
The efficacy of psychopharmacological treatments has been called into question. Psychiatrists are unfamiliar with the effectiveness of common medical drugs.

Aims
To put the efficacy of psychiatric drugs into the perspective of that of major medical drugs.

Method
We searched Medline and the Cochrane Library for systematic reviews on the efficacy of drugs compared with placebo for common medical and psychiatric disorders, and systematically presented the effect sizes for primary efficacy outcomes.

Results
We included 94 meta-analyses (48 drugs in 20 medical diseases, 16 drugs in 8 psychiatric disorders). There were some general medical drugs with clearly higher effect sizes than the psychotropic agents, but the psychiatric drugs were not generally less efficacious than other drugs.

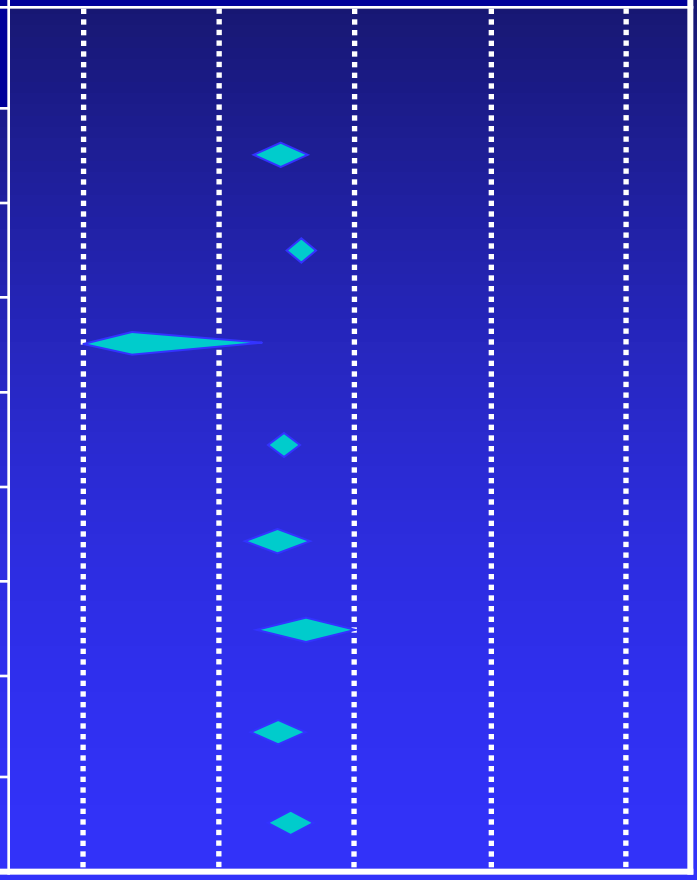
Conclusions
Any comparison of different outcomes in different diseases can only serve the purpose of a qualitative perspective. The increment of improvement by drug over placebo must be viewed in the context of the disease's seriousness, suffering induced, natural course, duration, outcomes, adverse events and societal values.

Declaration of interest
In the past 3 years S.L. has received fees for consulting and/or lectures from the following companies: Bristol-Myers Squibb, Actelion, Sanofi-Aventis, Eli Lilly, Essex Pharma, AstraZeneca, MedAvante, Alkermes, Janssen/Johnson & Johnson, Lundbeck Institute and Pfizer, and grant support from Eli Lilly. W.K. has received fees for consulting and/or lectures from Janssen-Cilag, Sanofi-Aventis, Johnson & Johnson, Pfizer, Bristol-Myers Squibb, AstraZeneca, Lundbeck, Novartis and Eli Lilly. All authors work in psychiatry.

BJP 2012, 200:97-106.

Antipsychotics vs PBO in Schizophrenia: Improved Psychopathology

Comparison	Statistics for each study					Hedges's g and 95% CI
	Hedges's g	Lower limit	Upper limit	*P*-Value	Total	
Amisulpride pooled	-0.56	-0.73	-0.39	0.0000	603	
Aripiprazole pooled	-0.41	-0.51	-0.31	0.0000	1556	
Clozapine pooled	-1.64	-2.61	-0.68	0.0009	22	
Haloperidol pooled	-0.53	-0.64	-0.43	0.0000	1540	
Olanzapine pooled	-0.59	-0.83	-0.35	0.0000	992	
Quetiapine pooled	-0.35	-0.73	0.02	0.0658	652	
Risperidone pooled	-0.59	-0.78	-0.39	0.0000	977	
Ziprasidone pooled	-0.48	-0.65	-0.32	0.0000	584	

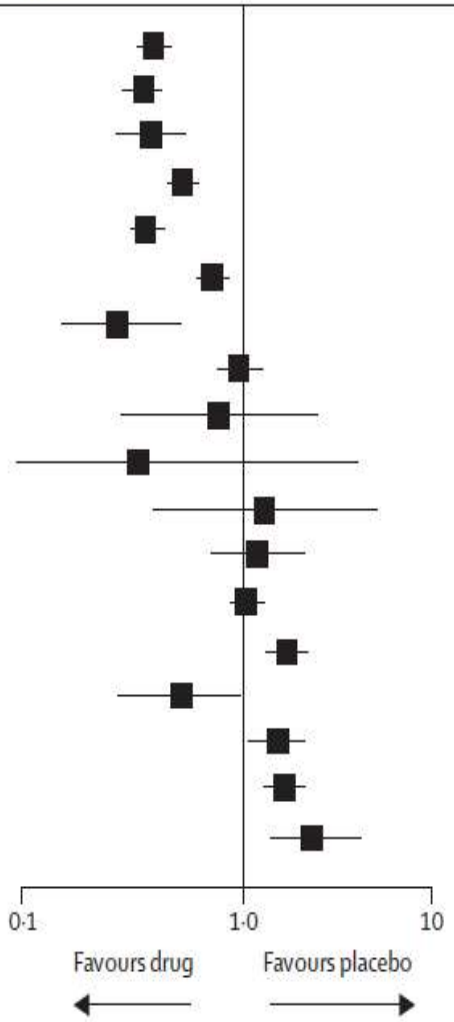


N=38, n=7723; mean ES vs PBO: -0.51; mean RD: 18% (41% vs 24%), NNT=6

Leucht S et al. *Mol Psychiatry*. 2009;14(4):429-447.

APs vs PBO for Relapse Prevention in SCZ

	Number of studies included	Drug group	Control group	Mean study duration* (months)	Risk ratio (95% CI)	Absolute difference (95% CI)	NNTB/H (95% CI)
Relapse 7–12 months	24	392/1465 (27%)	773/1204 (64%)	11	0·40 (0·33 to 0·49)	−0·39 (−0·46 to −0·32)	3 (2 to 3)
Relapse independent of duration	62	744/3395 (22%)	1718/2997 (57%)	9	0·35 (0·29 to 0·41)	−0·38 (−0·43 to −0·33)	3 (2 to 3)
Participants readmitted to hospital	16	112/1132 (10%)	245/958 (26%)	13	0·38 (0·27 to 0·55)	−0·19 (−0·27 to −0·11)	5 (4 to 9)
Dropout for any reason	57	802/2642 (30%)	1130/2076 (54%)	9	0·53 (0·46 to 0·61)	−0·24 (−0·30 to −0·17)	4 (3 to 6)
Dropout because of inefficacy	46	412/2539 (16%)	830/2007 (41%)	8	0·37 (0·31 to 0·44)	−0·27 (−0·34 to −0·19)	4 (3 to 5)
Participants unimproved/worse	14	614/880 (70%)	569/644 (88%)	5	0·73 (0·64 to 0·84)	−0·25 (0·35 to 0·14)	4 (3 to 7)
Violent/aggressive behaviour	5	9/403 (2%)	34/277 (12%)	8	0·27 (0·15 to 0·52)	−0·09 (−0·17 to −0·01)	11 (6 to 100)
Participants employed	2	63/130 (48%)	65/129 (50%)	11	0·96 (0·75 to 1·23)	−0·02 (−0·14 to 0·10)	50 (H7 to B10)†
Death (any)	14	5/1240 (<1%)	7/1116 (1%)	7	0·77 (0·28 to 2·11)	0·00 (−0·01 to 0·00)	∞
Suicide	8	0/1021	2/920 (<1%)	6	0·34 (0·04 to 3·28)	0·00 (−0·01 to 0·00)	∞
Death from natural causes	14	5/1272 (1%)	3/1129 (<1%)	7	1·24 (0·39 to 3·97)	0·00 (0·00 to 0·01)	∞
Dropout because of AE	43	129/2437 (5%)	78/1896 (4%)	8	1·16 (0·70 to 1·91)	0·00 (−0·01 to 0·02)	∞
At least one AE	10	575/1188 (48%)	450/996 (45%)	7	1·01 (0·87 to 1·18)	0·01 (−0·06 to 0·08)	100 (H17 to B13)†
At least one MD	22	304/1901 (16%)	134/1510 (9%)	7	1·55 (1·25 to 1·93)	0·06 (0·03 to 0·10)	17 (10 to 33)
Dyskinesia	13	18/1051 (2%)	37/769 (5%)	9	0·52 (0·28 to 0·97)	−0·01 (−0·02 to 0·01)	100 (H50 to B100)†
Use of antiparkinsonian medication	7	182/748 (24%)	90/569 (16%)	7	1·40 (1·03 to 1·89)	0·09 (0·02 to 0·16)	11 (6 to 50)
Sedation	10	158/1174 (13%)	85/972 (9%)	6	1·50 (1·22 to 1·84)	0·05 (0·00 to 0·10)	20 (B=∞ to H10)†
Weight gain	10	128/1231 (10%)	61/1090 (6%)	7	2·07 (2·31 to 3·25)	0·05 (0·03 to 0·07)	20 (14 to 33)



Depot APs reduced relapse (RR 0·31, 95% CI 0·21–0·41) more than oral drugs (0·46, 0·37–0·57; p=0·03). In a meta-regression, drug-pbo advantages decreased with study length. ***Leucht S et al. Lancet. 2012;379(9831):2063-71***

Molecular Psychiatry (2011), 1–14

www.nature.com/mp

ORIGINAL ARTICLE

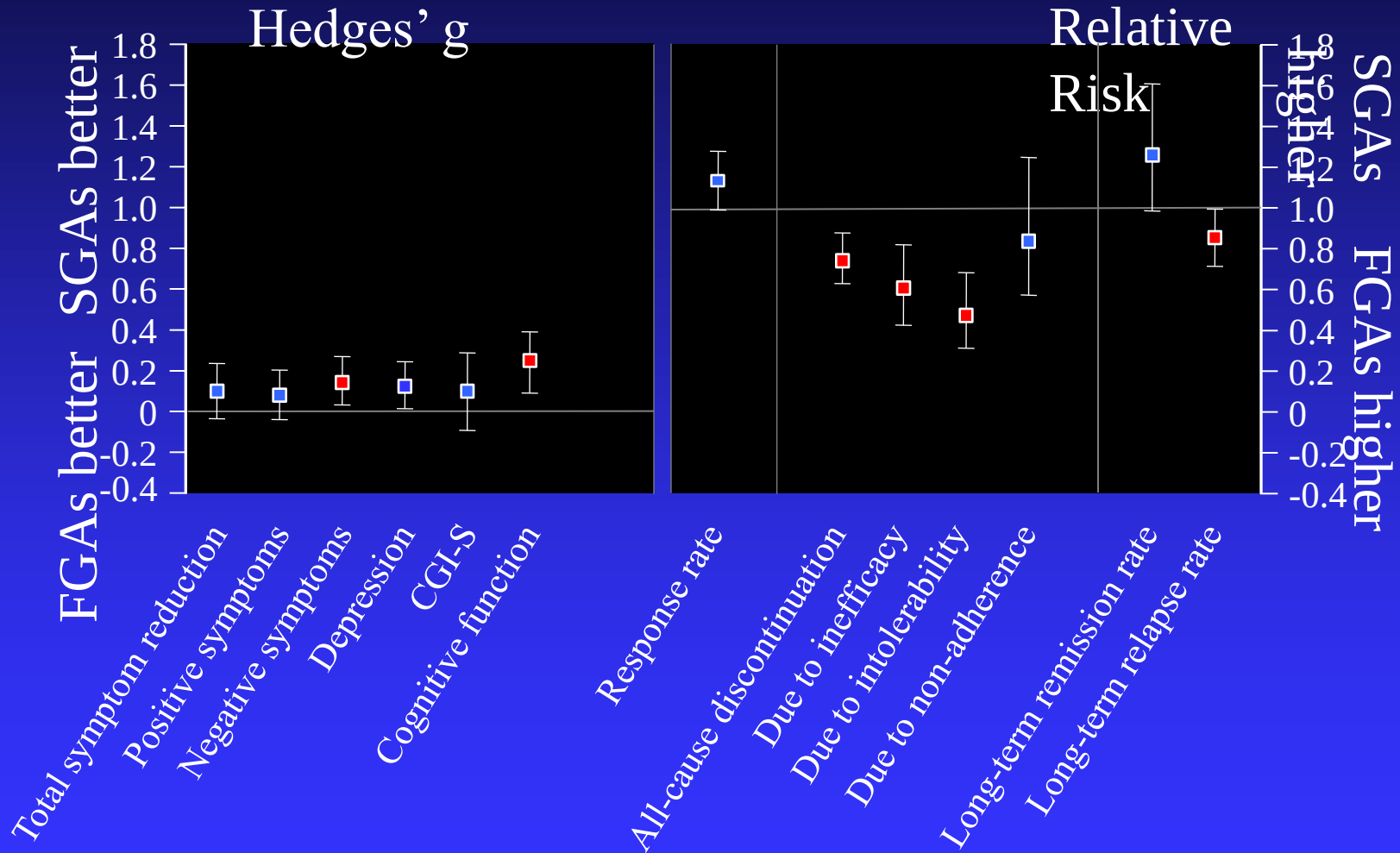
Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics

T Kishimoto[1], V Agarwal[2], T Kishi[1], S Leucht[3], JM Kane[1,4,5,6] and CU Correll[1,4,5,6]

[1]Division of Psychiatry Research, The Zucker Hillside Hospital, North Shore—Long Island Jewish Health System, Glen Oaks, NY, USA; [2]Department of Psychiatry, Albert Einstein Medical Center, Philadelphia, PA, USA; [3]Technische Universität München, Klinikum rechts der Isar, Department of Psychiatry and Psychotherapy, München, Germany; [4]Albert Einstein College of Medicine, Bronx, NY, USA; [5]The Feinstein Institute for Medical Research, Manhasset, NY, USA and [6]Hofstra North Shore LIJ School of Medicine, Hempstead, NY, USA

- N=22, n= 4206,
- Relapse Rate: SGA 29.0% < FGA 37.5%
- Relative Risk =0.80, CI 0.70-0.91
- NNT=17, CI 10-50, p=.003

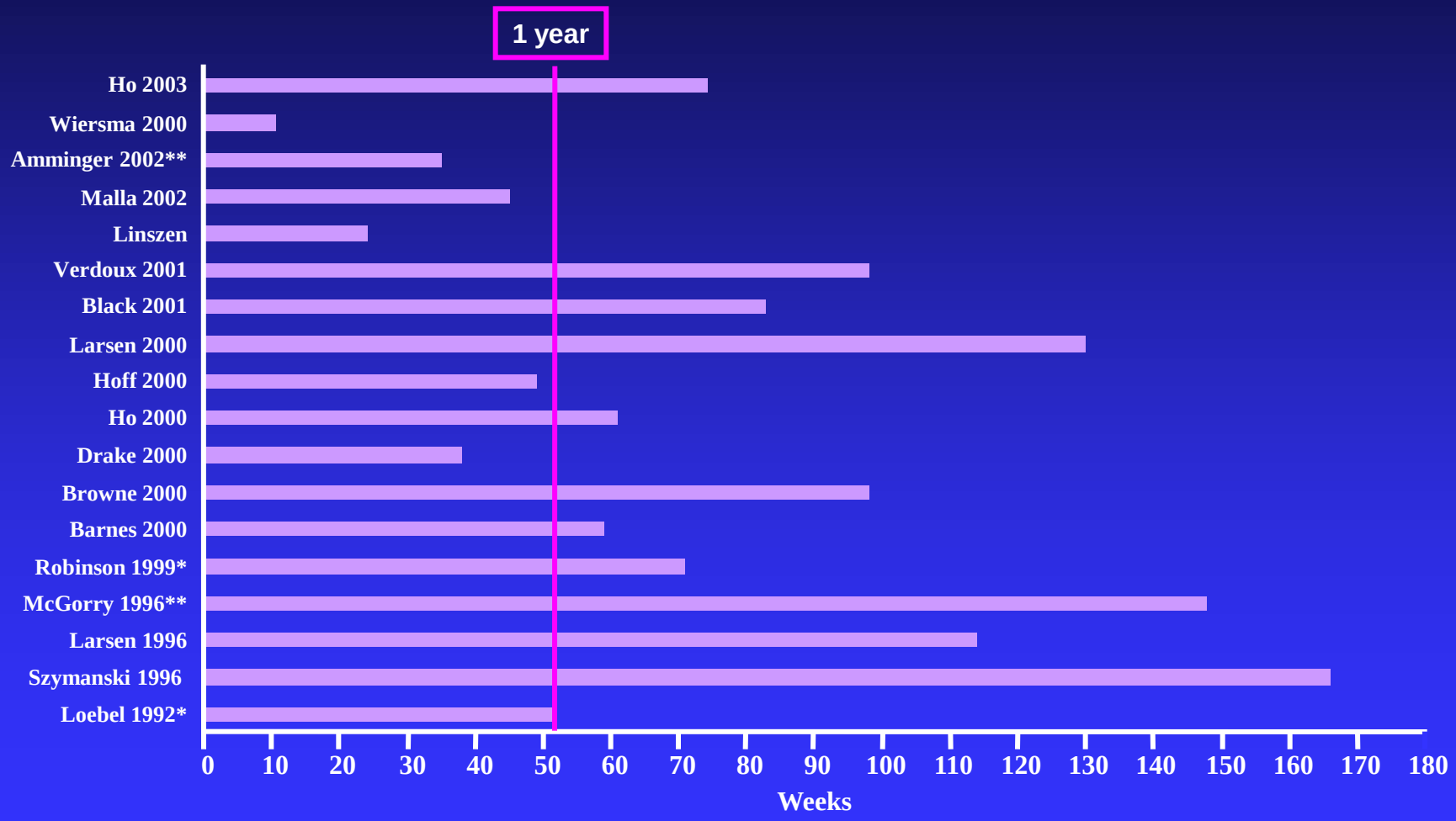
Randomized Comparison of SGAs vs FGAs in First-episode Schizophrenia



N=13, n=2519

Zhang Jet al. Int J Neuropsychopharm – in press

Reported Mean Duration of Untreated Psychosis

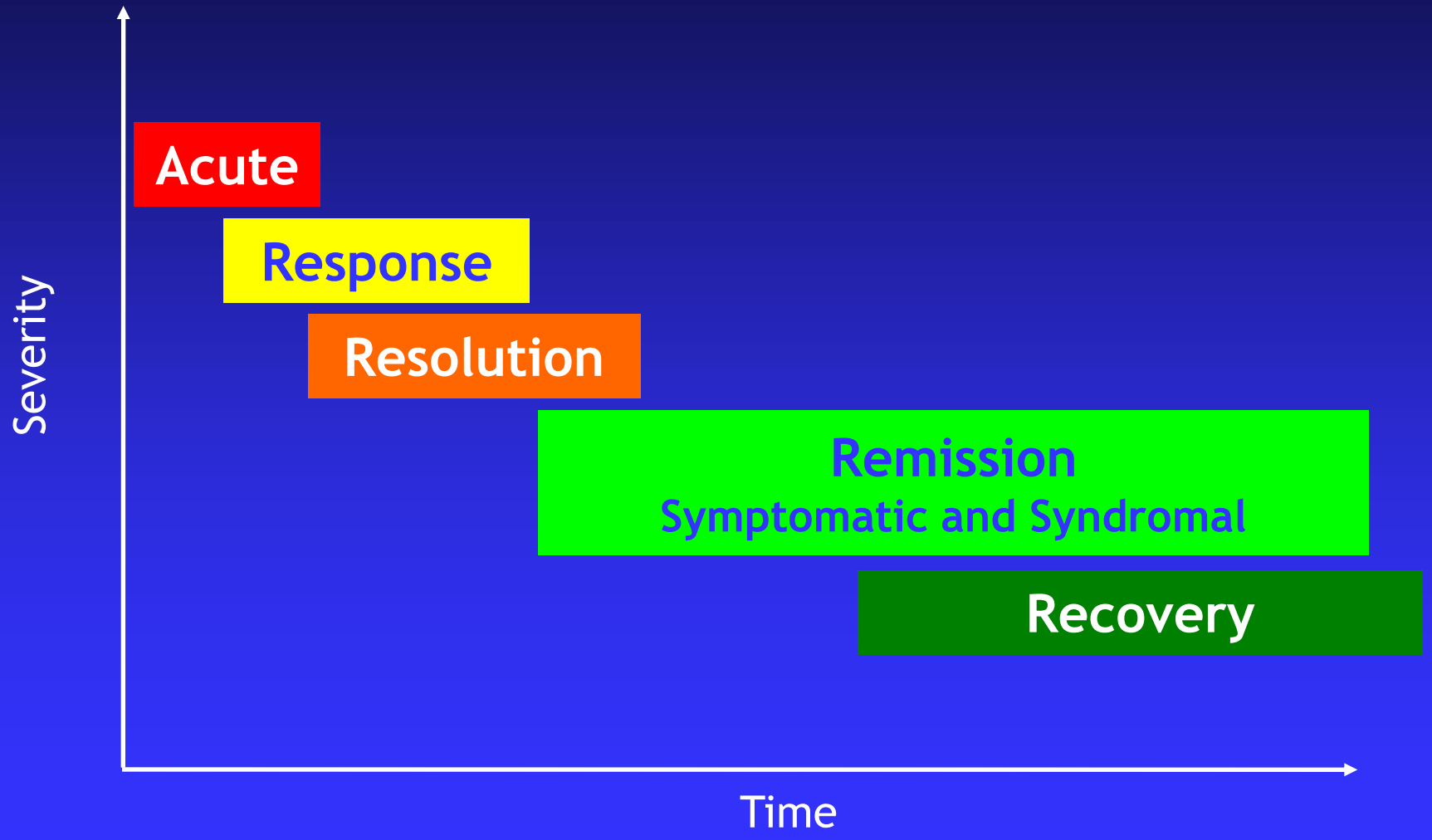


Perkins DO. *Curr Psychiatry Rep*. 2004;6:285-295. [Courtesy of Diana O. Perkins, MD, MPH. University of North Carolina at Chapel Hill.]

Implications of Delayed Treatment

- Greater decrease in functioning
- Loss of educational opportunities
- Impaired psychosocial and vocational development
- Personal suffering/family burdens
- Potential poorer response once treatment is provided
- Greater costs

Remission in Schizophrenia:Improvement Progression



How Should We Define and Measure Response?

- Change score
- Percentage improvement
- Final score
- Clinical Global Impression (CGI)

Clinical Decisions

- How much improvement is enough?
- When do we change treatments?
- When do we change them again?
- When do adverse effects determine changes in treatment?
- Can locus of care be changed?

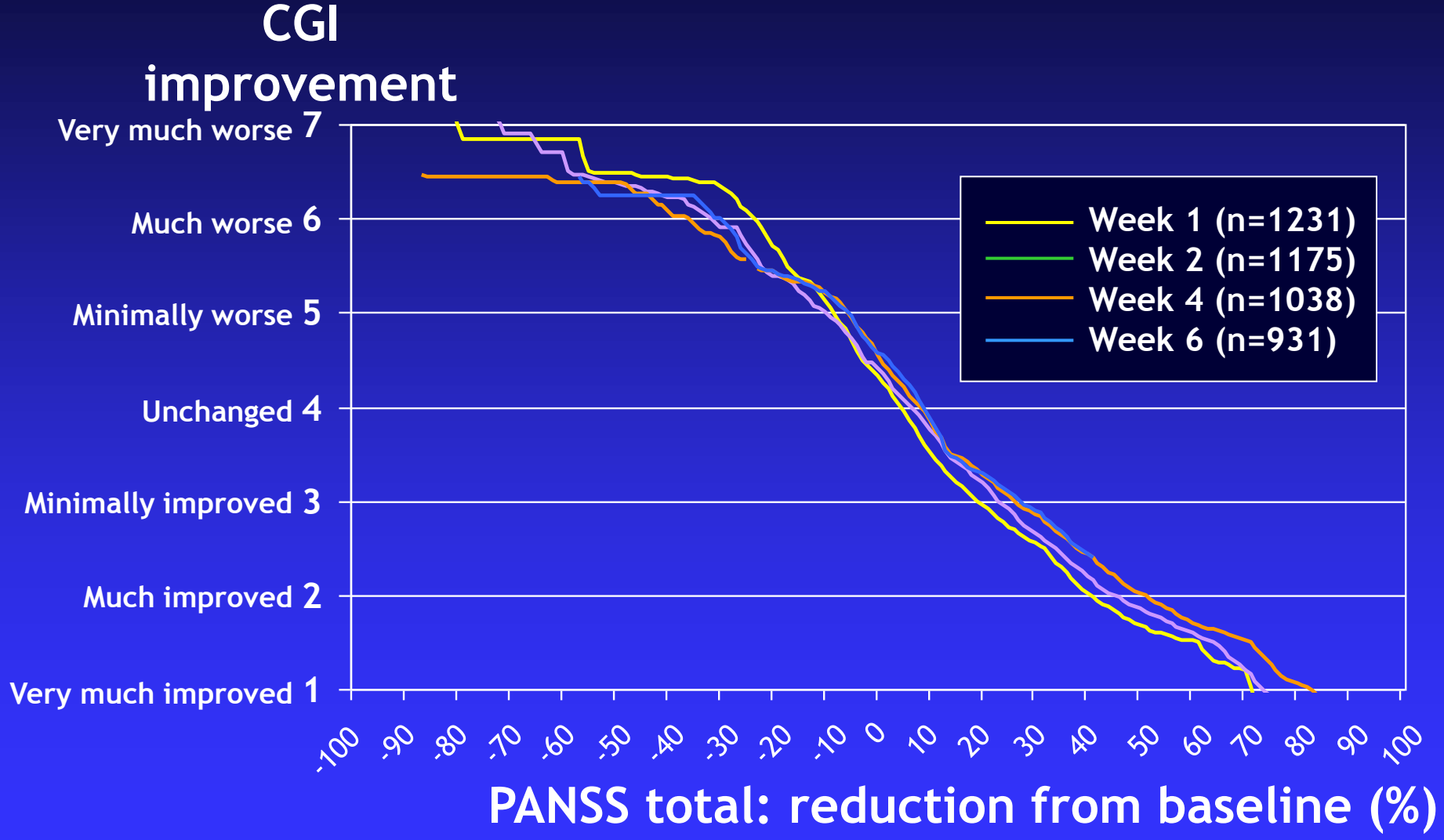
Treatment Alternatives

- Diagnostic re-evaluation/measures of adherence/adequacy (eg blood levels)
- Change in dose
- Adjunctive medication(s)
- Switching medication
- Nonpharmacologic therapies

The Value of Measurement

- Contribution to diagnostic process
- Establishing baseline severity
- Providing targets and treatment goals
- Evaluating the efficacy of treatment
- Evaluating tolerability and adverse effects
- Influencing level of care
- Medical record documentation

Linking Percentage PANSS Reduction From Baseline With CGI-Improvement Scores



Leucht S et al. *Schizophr Res.* 2005;79:231-238.

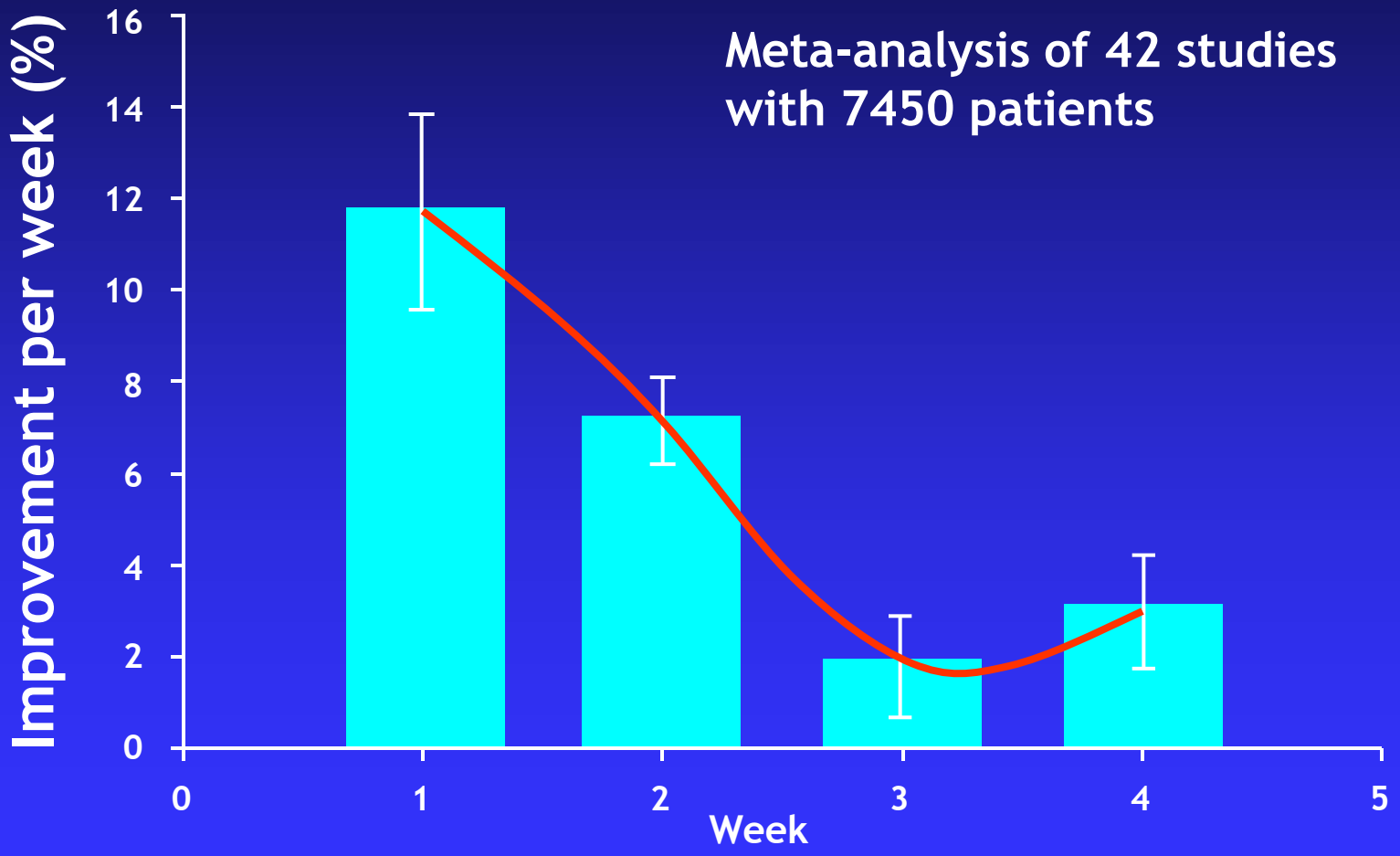
How Long Should We Wait Before Considering an Antipsychotic Ineffective?

Inadequate response to:	Minimum number of weeks to wait Average (SD)	Maximum number of weeks to wait Average (SD)
Initial Antipsychotic		
Little or no response	2.6 (1.3)	5.5 (2.6)
Partial response	4.4 (1.7)	9.9 (5.1)

Kane JM et al. *J Clin Psychiatry*. 2003;64(suppl 12):4-100.

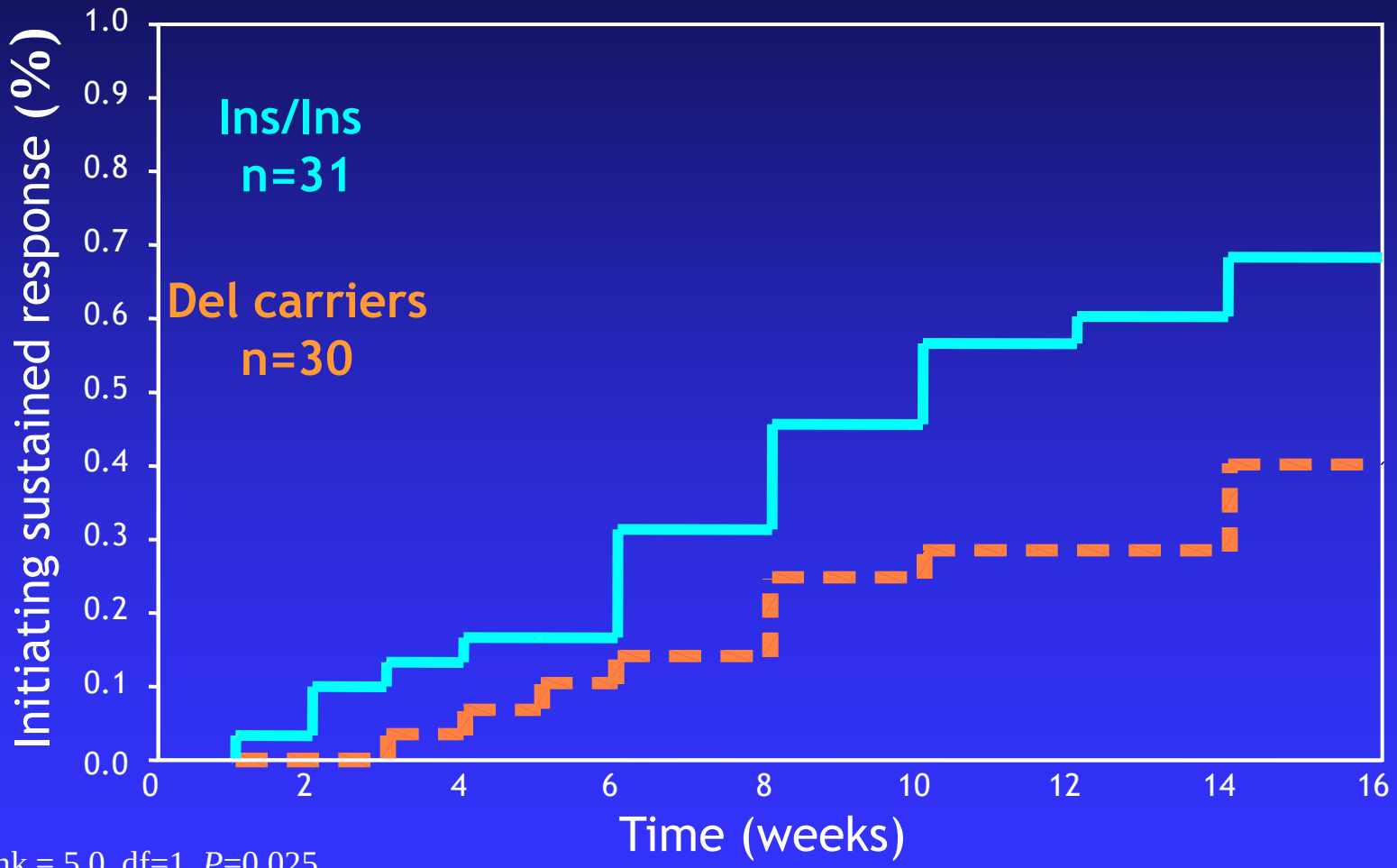
Time Course of Antipsychotic Effect

Psychotic Symptoms After Subtraction of Placebo Effect



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

DRD2 -141C Ins/Del and Response to Second-Generation Antipsychotics



Log rank = 5.0, df=1, *P*=0.025.

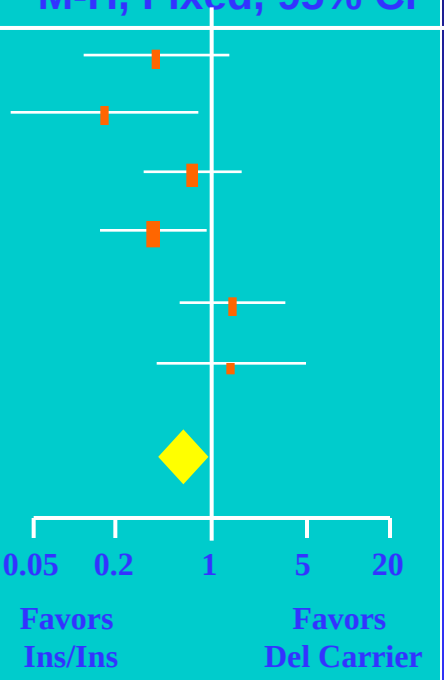
Lencz T et al. *Am J Psych.* 2006;163:529-531.

DRD2-141C Ins/Del and Antipsychotic Response: Meta–Analytic Results

Study or Subgroup	Del Carrier Events	Del Carrier Total	Ins/Ins Events	Ins/Ins Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lencz 2006	5	30	10	31	13.5%	0.42 [0.12, 1.42]
Malhotra 1999	2	21	19	51	16.5%	0.18 [0.04, 0.85]
Shen 2008	13	30	50	98	21.9%	0.73 [0.32, 1.67]
Wu 2005	8	29	53	106	27.2%	0.38 [0.16, 0.94]
Xing 2007	18	28	54	97	14.2%	1.43 [0.60, 3.42]
Yamanouchi 2003	4	41	9	125	6.6%	1.39 [0.41, 4.79]
Total (95% CI)		**179**		**508**	**100.0%**	**0.65 [0.43, 0.97]**
Total events	50		195			

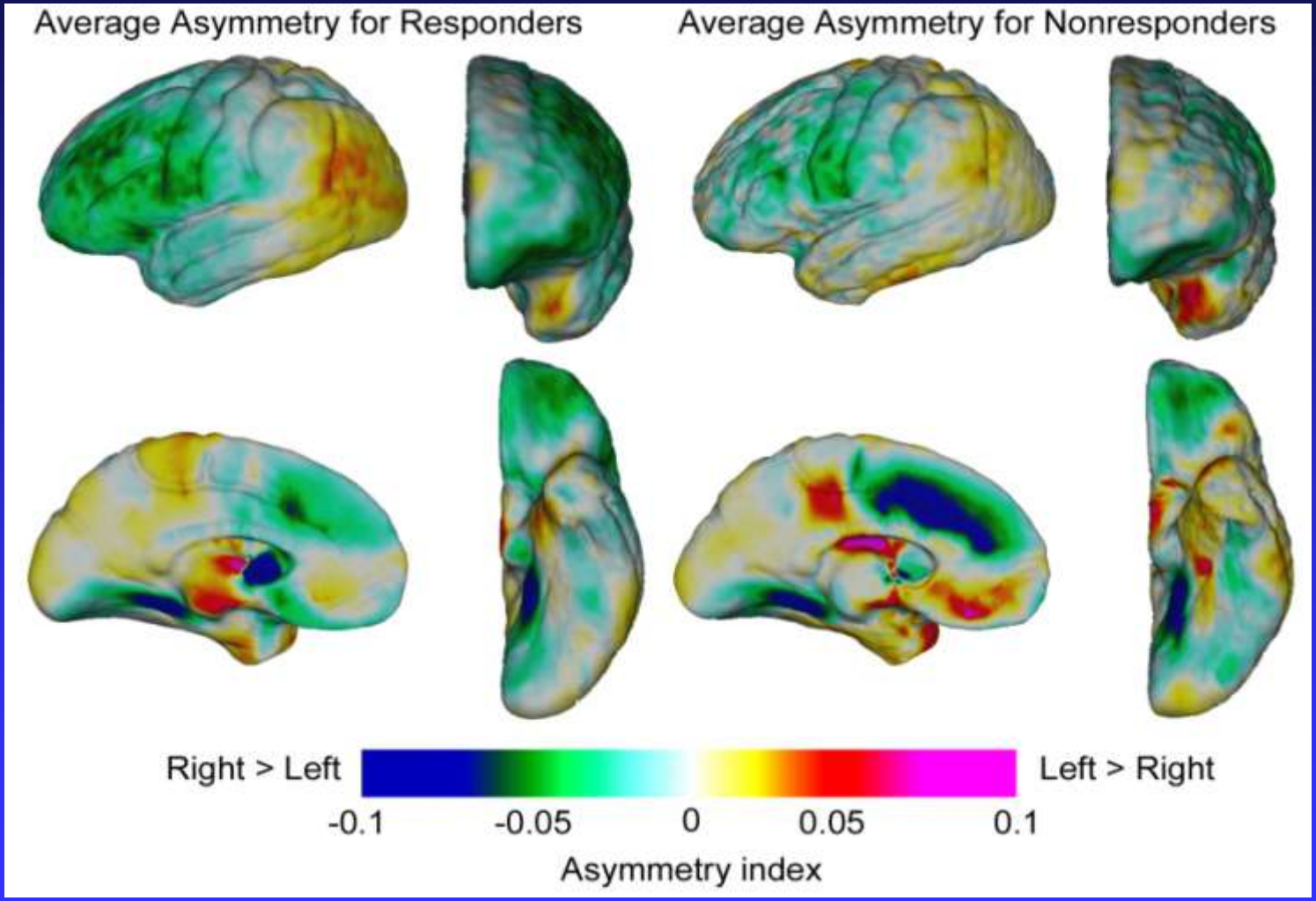
Heterogeneity: $Chi^2=9.23$, df=5 ($P=0.10$); $I^2=46\%$

Test for overall effect: $Z=2.13$ ($P=0.03$)



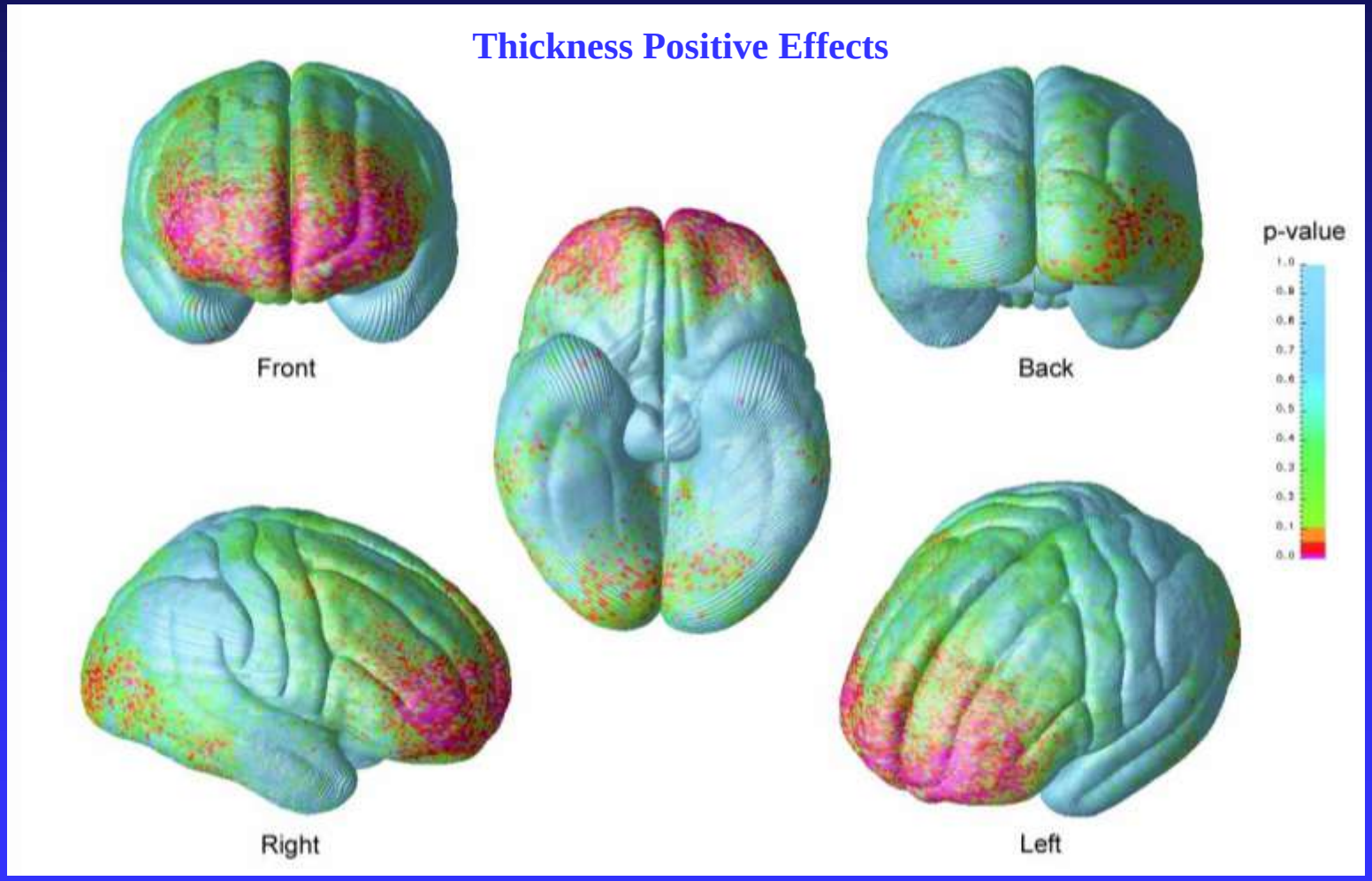
Zhang J, Am J Psychiatry – in press

MRI Scans: Average Asymmetry in Responders/Nonresponders



Szeszko PR, et al (Narr KL, Phillips OR, McCormack J, Sevy S, Gunduz-Bruce H, Kane JM, Bilder RM, Robinson DG. Magnetic resonance imaging predictors of treatment response in first-episode schizophrenia.) Schizophr Bull. 2012 May;38(3):569-78.

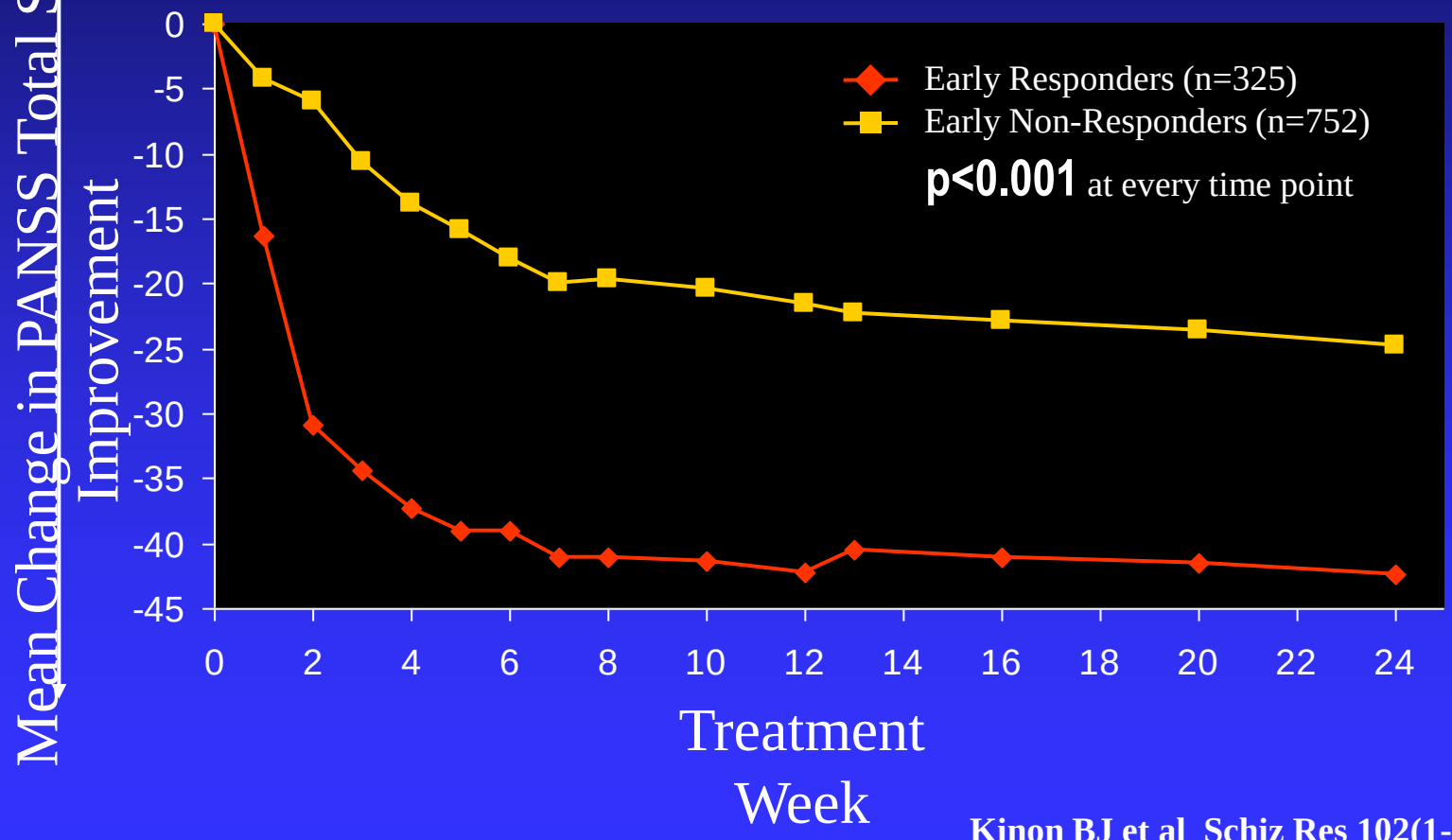
Nonresponders (N=13) to Atypical Antipsychotics Have Cortical Grey Matter Thinning, Mainly in the Frontal Lobes, Compared to Responders (N=32)



Szeszko PR, et al (Narr KL, Phillips OR, McCormack J, Sevy S, Gunduz-Bruce H, Kane JM, Bilder RM, Robinson DG. Magnetic resonance imaging predictors of treatment response in first-episode schizophrenia.) Schizophr Bull. 2012 May;38(3):569-78.

Early Treatment Responders Demonstrated Better Symptom Improvement Than Early Non-Responders

Early Responders Showed Significantly More Improvement on PANSS Total Score Than Early Non-Responders at All Time Points from Week 1 to Week 24

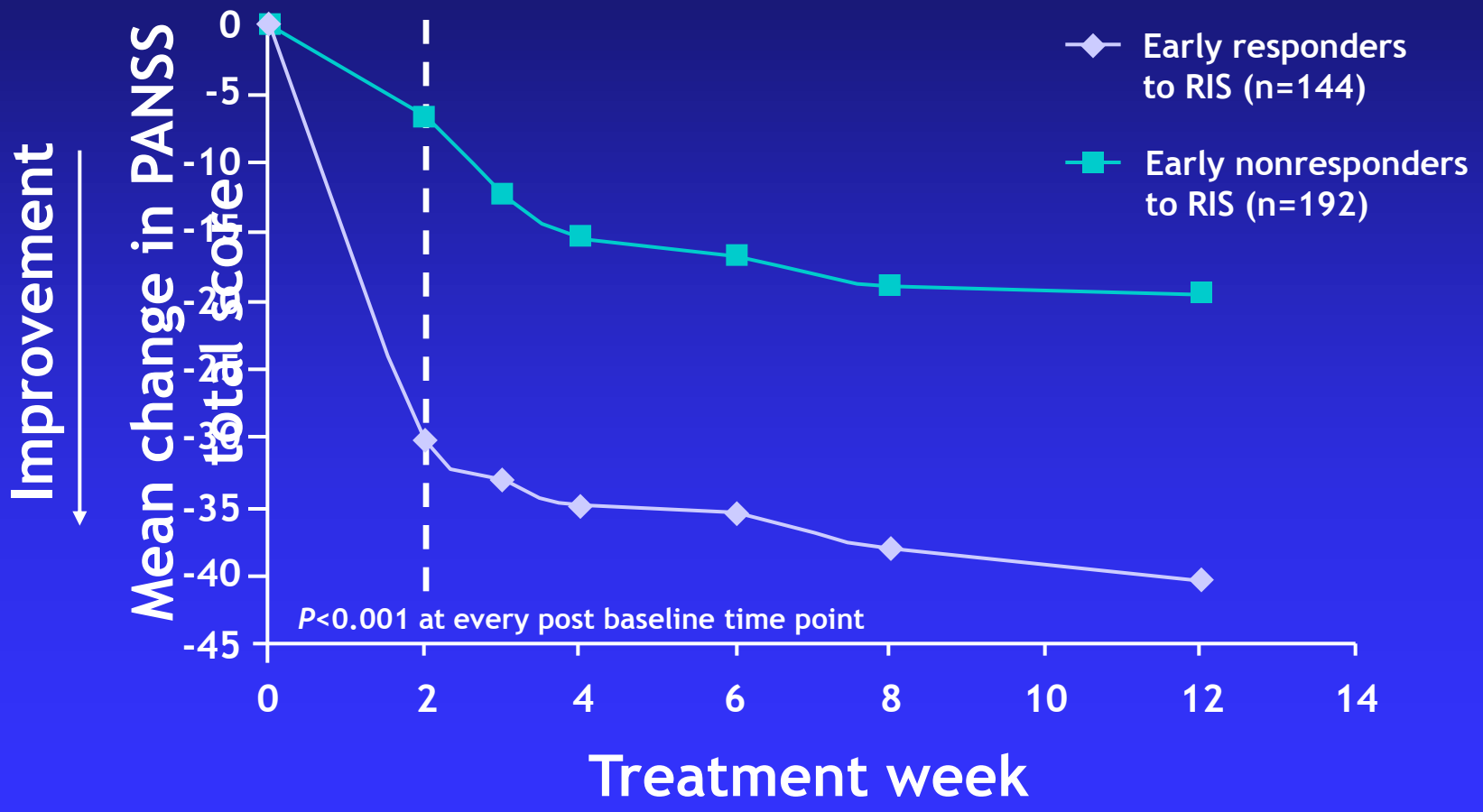


Response was defined as ≥ 20% improvement in PANSS Total Score at 2 weeks

Kinon BJ et al Schiz Res 102(1-3):230-40, 2008

Results – Primary Outcome

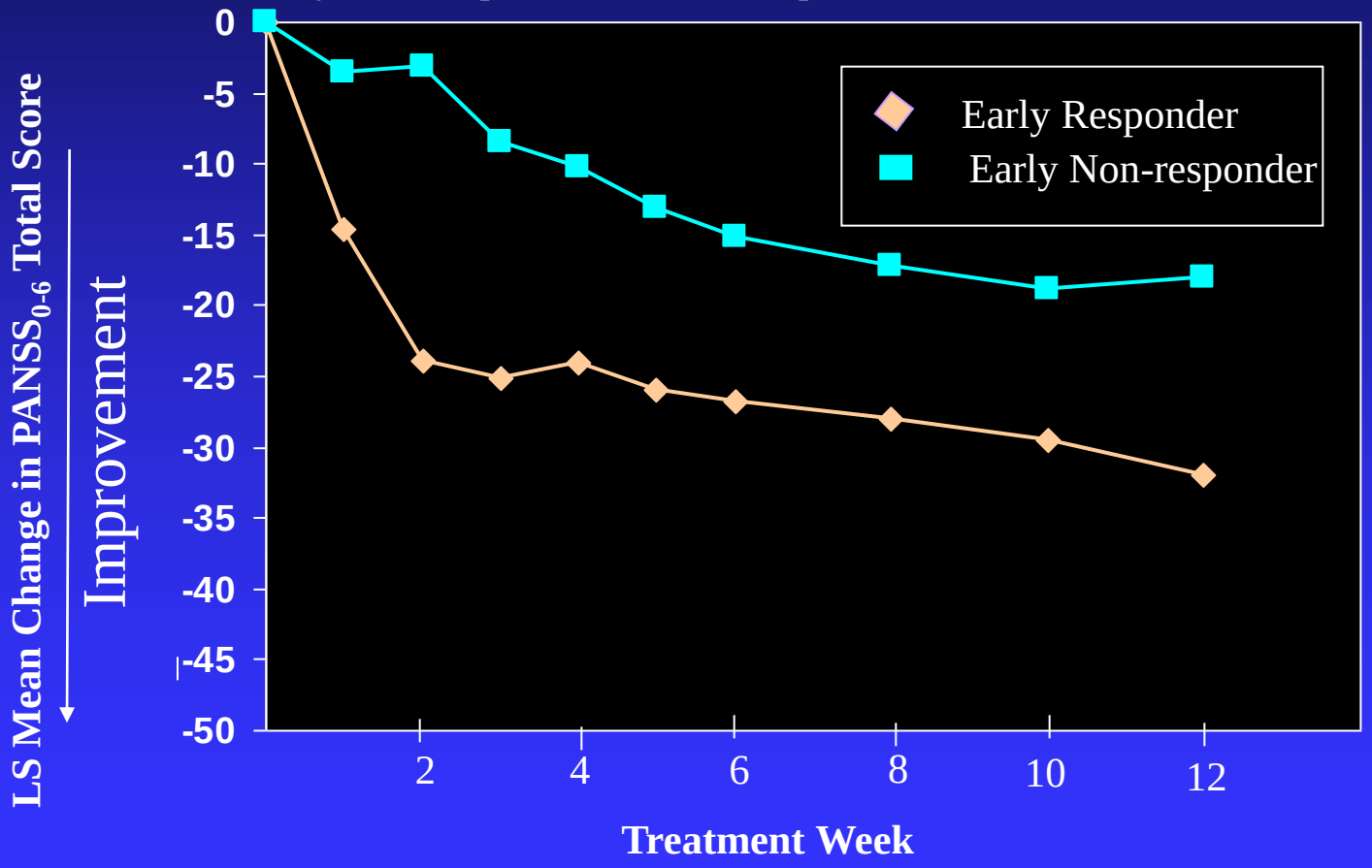
Mean Change From Baseline in PANSS Total Score (*RIS Only Patients*)



Kinon B et al. Presented at the 1st Schizophrenia International Research Society Meeting. Venice, Italy; June 21-25, 2008.

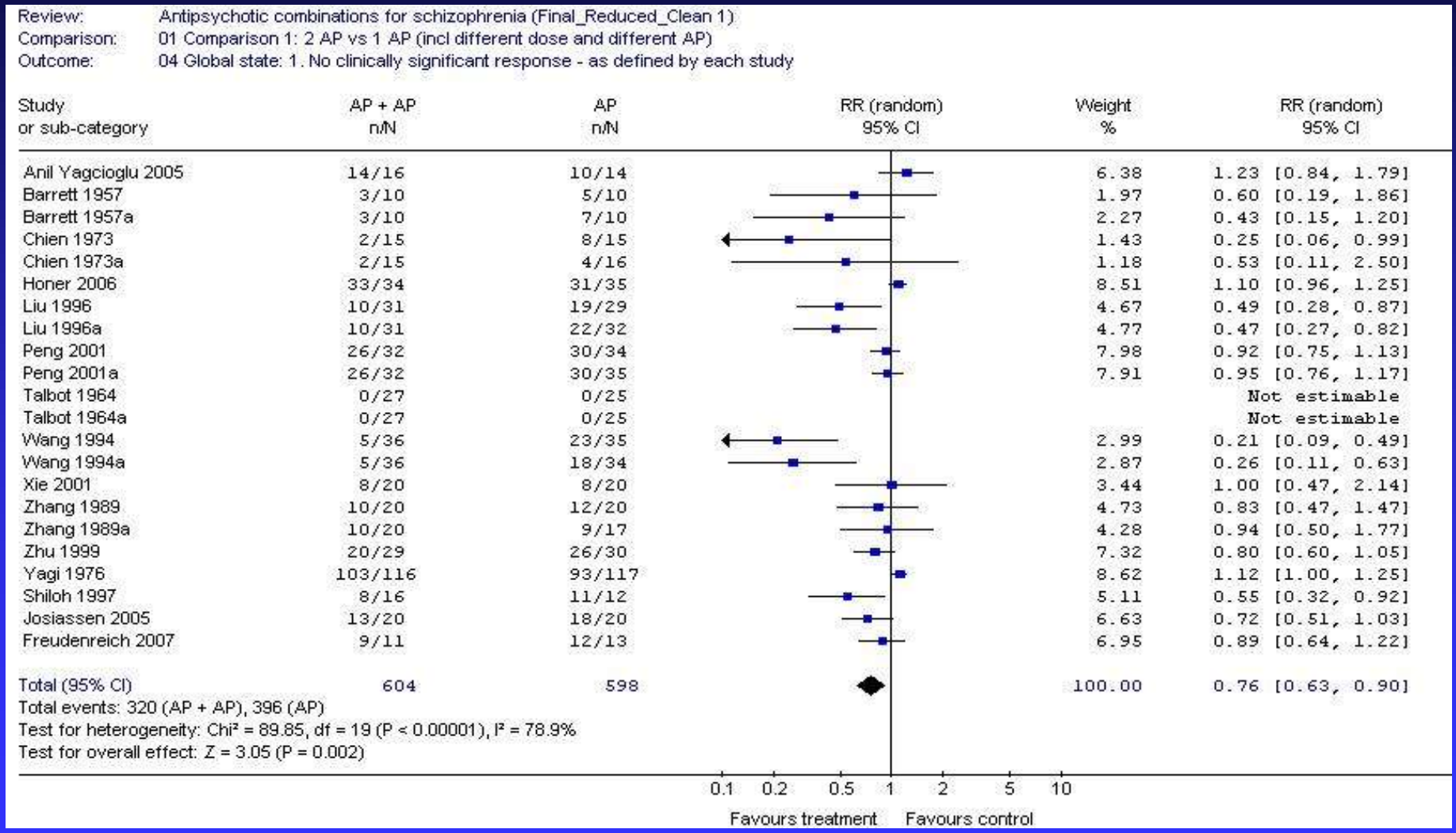
Symptom Improvement in Early Responders[a] and Early Non-Responders in First Episode Schizophrenia: $PANSS_{0-6}$ Total Score

Early Responders showed significantly more improvement ($p<.001$) in $PANSS_{0-6}$ Total score than Early Non-responders at all time points from Week 1 to Week 12.



* Response was defined as ≥26.2% improvement in $PANSS_{0-6}$ Total score at Week 2

Meta-Analysis of 19 RCTs of Antipsychotic Combinations: Inefficacy As Defined By Study



N=22, n=1202, RR: 0.76, 95% CI: 0.63-0.90, p=0.002, NNT: 7, CI: 4-17, p=0.0008

Correll CU et al. Schizophr Bull. 2009 Mar;35(2):443-57.

Clozapine for the Treatment-Resistant Schizophrenic

A Double-blind Comparison With Chlorpromazine

John Kane, MD; Gilbert Honigfeld, PhD; Jack Singer, MD; Herbert Meltzer, MD; and the Clozaril Collaborative Study Group

• **The treatment of schizophrenic patients who fail to respond to adequate trials of neuroleptics is a major challenge. Clozapine, an atypical antipsychotic drug, has long been of scientific interest, but its clinical development has been delayed because of an associated risk of agranulocytosis. This report describes a multicenter clinical trial to assess clozapine's efficacy in the treatment of patients who are refractory to neuroleptics. *DSM-III* schizophrenics who had failed to respond to at least three different neuroleptics underwent a prospective, single-blind trial of haloperidol (mean dosage, 61 ± 14 mg/d) for six weeks. Patients whose condition remained unimproved were then randomly assigned, in a double-blind manner, to clozapine (up to 900 mg/d) or chlorpromazine (up to 1800 mg/d) for six weeks. Two hundred sixty-eight patients were entered in the double-blind comparison. When a priori criteria were used, 30% of the clozapine-treated patients were categorized as responders compared with 4% of chlorpromazine-treated patients. Clozapine produced significantly greater improvement on the Brief Psychiatric Rating Scale, Clinical Global Impression Scale, and Nurses' Observation Scale for Inpatient Evaluation; this improvement included "negative" as well as positive symptom areas. Although no cases of agranulocytosis occurred during this relatively brief study, in our view, the apparently increased comparative risk requires that the use of clozapine be limited to selected treatment-resistant patients.**

(*Arch Gen Psychiatry* 1988;45:789-796)

refractory subgroup remains a major public health problem—these individuals require more intensive care and are subject to the persistent disabilities associated with chronic schizophrenia. In addition, the continued presence of psychotic signs and symptoms makes these patients less available to psychosocial and vocational rehabilitation.

It is estimated that about 1 million Americans suffer from schizophrenia. While there are no definitive data available on how many do not respond to neuroleptics, extrapolations from clinical trial data suggest that there may be 100 000 to 200 000 such patients.

Data from maintenance medication trials indicate that even among patients initially responsive to antipsychotic drugs, 20% to 30% may relapse during the first year or two of maintenance drug treatment.[3] A proportion of these patients contributes to the number in the subgroup of patients refractory to treatment. Since many of these patients remain ill, there is a cumulative increase in the number of people in the treatment-refractory category.

See also p 865.

The recognition that some patients do not benefit from typical neuroleptics has resulted in research along two fronts: (1) to identify phenomenologic, demographic, and/or biologic factors that may be associated with poor treatment response and (2) to explore alternative treatment strategies that might be beneficial to this subgroup

ORIGINAL ARTICLE

Clozapine and Haloperidol in Moderately Refractory Schizophrenia

A 6-Month Randomized and Double-blind Comparison

John M. Kane, MD; Stephen R. Marder, MD; Nina R. Schooler, PhD; William C. Wirshing, MD; Daniel Umbricht, MD; Robert W. Baker, MD; Donna A. Wirshing, MD; Allan Safferman, MD; Rohan Ganguli, MD; Marjorie McMeniman, PhD; Michael Borenstein, PhD

Background: Despite the demonstrated efficacy of clozapine in severely refractory schizophrenia, questions remain regarding its efficacy for primary negative symptoms, comparison with a moderate dose of a first-generation antipsychotic, and adverse effects during a longer-term trial. This study examined its efficacy in partially responsive, community-based patients, compared clozapine with moderate-dose haloperidol, and extended treatment to 6 months.

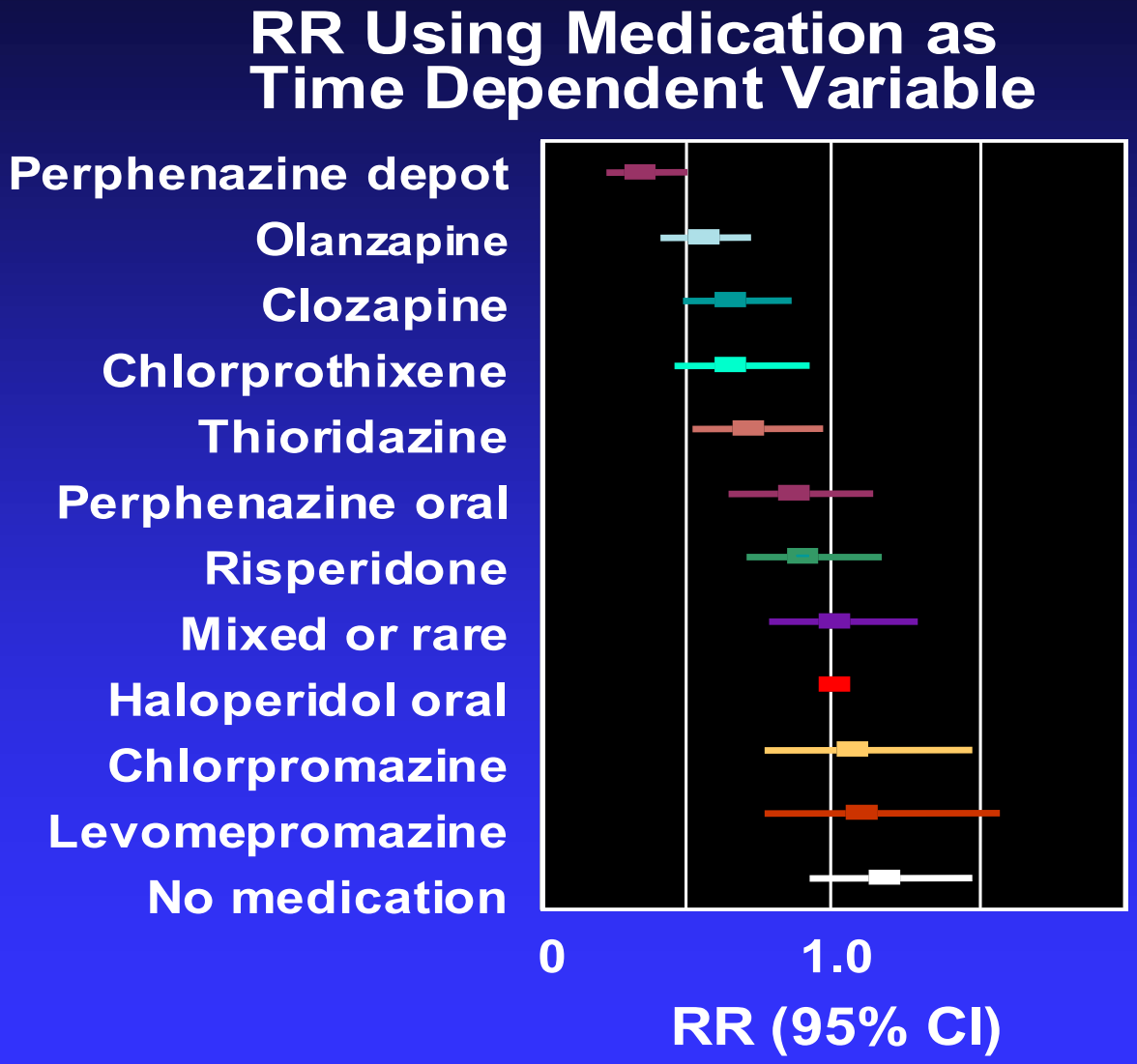
Methods: Randomized, double-blind, 20-week trial comparing clozapine (n=37) with haloperidol (n=34). Subjects with schizophrenia who were being treated in community settings at 3 collaborating clinical facilities were enrolled.

Results: Subjects treated with haloperidol were significantly more likely to discontinue treatment for lack of efficacy (51%) than were those treated with clozapine (12%). A higher proportion of clozapine-treated subjects met an a priori criterion of improvement (57%) compared with haloperidol-treated subjects (23%). Significantly greater improvement was seen in symptoms of psychosis, hostile-suspiciousness, anxiety-depression, thought disturbance, and total score measured on the Brief Psychiatric Rating Scale. No differences were detected in negative symptoms using the Brief Psychiatric Rating Scale or the Schedule for Assessment of Negative Symptoms. Subjects treated with clozapine experienced more excess salivation, dizziness, and sweating and less dry mouth and decreased appetite than those treated with haloperidol.

Conclusions: Compared with a first-generation antipsychotic given in a moderate dose, clozapine offers substantial clinical benefits to treatment-refractory subjects who can be treated in the community. Advantages are seen in a broad range of symptoms but do not extend to negative symptoms.

Arch Gen Psychiatry. 2001;58:965-972

Relative Risk (RR) of Rehospitalisation



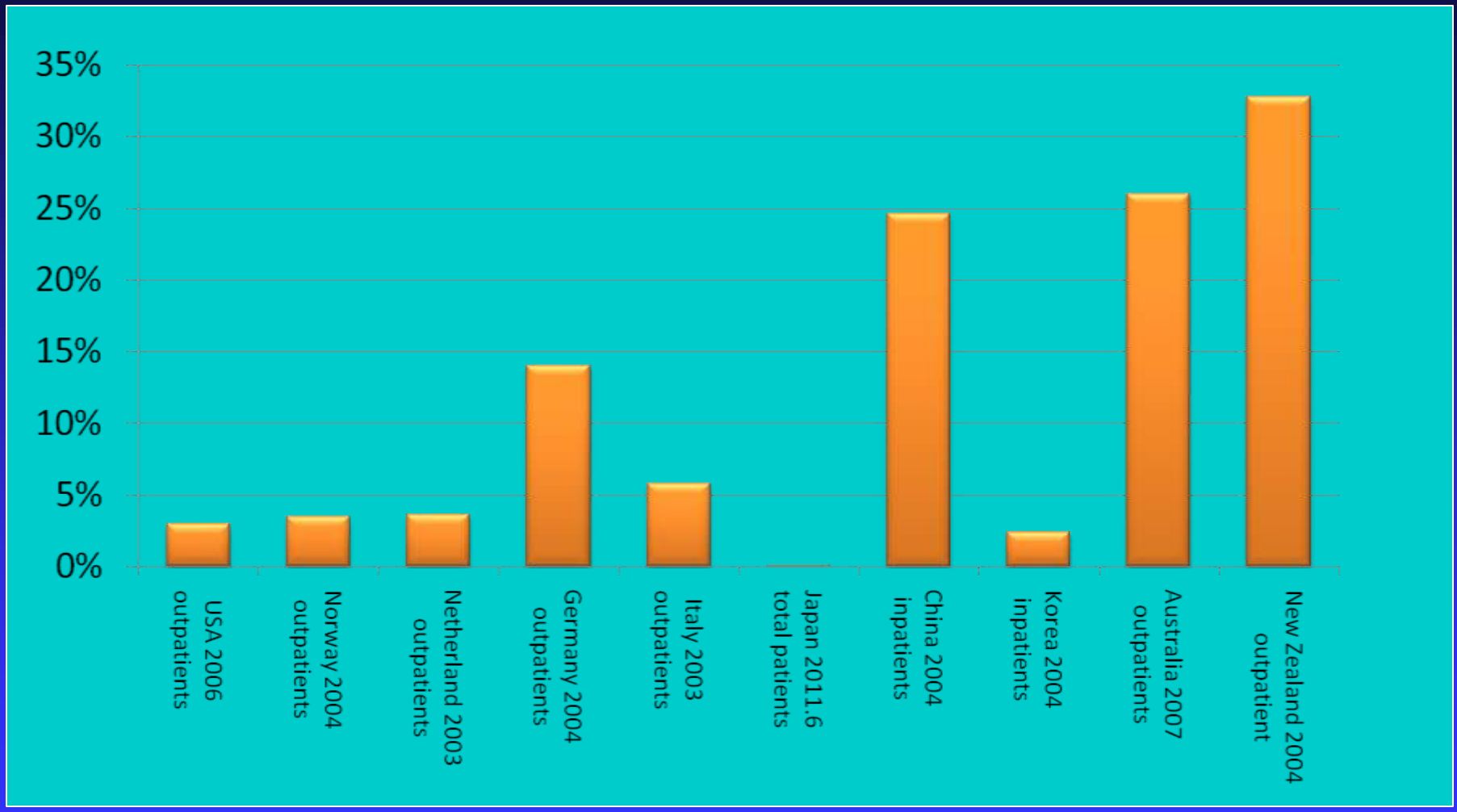
Tiihonen J, et al. *BMJ.* 2006;333(7561):224-229.

Guidelines Regarding Clozapine

Guidelines	Basic Use	Specific Clinical Features
American Psychiatry Association (APA)	• Persistent psychotic Sx after 2 AP trials – *"should be given strong consideration"*	• Persistent hostility, aggressive behavior • Persistent SI • TD
Schizophrenia Patient Outcomes Research Team (PORT)	• Persistent and clinically significant positive Sx after ≥2 AP trials (including ≥1 SGA) –*"should be used"*	• Persistent hostility/ violent behaviors – *"should be used"* • Marked and persistent SI/ behaviors – *"should be offered"* • NMS, persistent dystonia/severe or very distressing TD – *"should be offered"*
Texas Medication Algorithm Project (TMAP)	• No-response or partial response to 2 AP trials (including ≥1SGA)	• History of recurrent suicidality, violence or comorbid substance abuse –*"consider earlier trial"* • Persistent positive Sx >2 years –*"warrants"* • Persistent positive Sx >5 years –*"requires"* clozapine trial independent of # of AP trials
Canadian Psychiatric Association	•No-response to AP trials from 2 classes	• Persistent SI/ behaviors –*"should be considered"* • Persistent aggressivity –*"may be helped by"*
National Institute for Health and Clinical Excellence (NICE)	• Sequential use of ≥2 APs (including ≥1 SGA)	

AP=antipsychotic, NMS=neuroleptic malignant syndrome, SI=suicidal ideation, Sx=symptoms, TD=tardive dyskinesia

Clozapine Prescription Rate for Schizophrenia
-International Comparison-



Data were obtained from several studies and the settings can vary from study to study.

Kishimoto et al. In preparation

Monshat K et al. Australas Psychiatry. 2010 Jun; 18(3) : 238-41.
Shinfuku N et al. Int Rev Psychiatry. 2008 Oct; 20(5): 460-8.
Weinbrenner S et al. Pharmacosychiatry. 2009 Mar; 42(2): 66-71. Epub 2009 Mar 23.
Gherden P et al. Eur J Clin Pharmacol. 2010 Sep; 66(9): 911-7. Epub 2010 Jun 3.
Haro JM et al. Acta Psychiatr Scand Suppl. 2003; (416) : 7-15.
Wheeler AJ. Ann Pharmacother. 2008 Jun; 42(6): 852-60. Epub 2008 May13.

HLA-DQB1 Genotype and Clozapine-induced Agranulocytosis

	Marker Positive[a]		Marker Negative[a]				
	Cases	Controls	Cases	Controls	OR	Sens	Spec
Cohort I	8	1	24	52	17.33	25.0%	98.1%
Cohort II	9	1	38	71	16.82	19.1%	98.6%
Combined	17	2	62	123	16.86	21.5%	98.4%

[a] "REC 21G" is *HLA-DQB1* 6672G>C, Marker Positive is nonGG (GC or CC),Marker Negative is GG

Athanasiou et al. J Clin Psychiatry 2011;72(4):458-463

Mortality Associated With Mental Disorders: Mean Years of Potential Life Lost

Year	AZ	MO	OK	RI	TX	UT
1997		26.3	25.1		28.5	
1998		27.3	25.1		28.8	29.3
1999	32.2	26.8	26.3		29.3	26.9
2000	31.8	27.9		24.9		

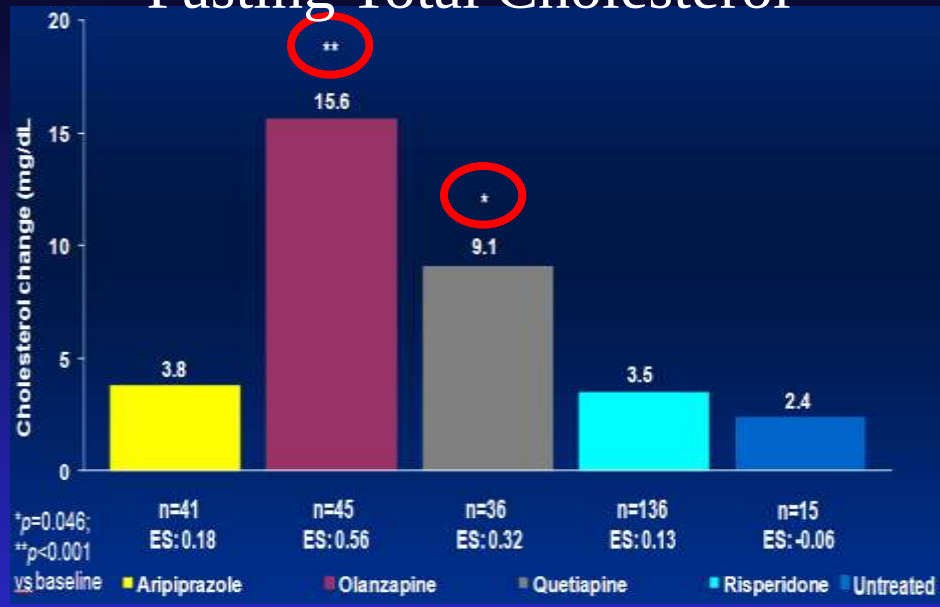
Compared with the general population, persons with major mental illness lose 25-30 years of normal life span

Colton CW, Manderscheid RW. Prev Chronic Dis [serial online] 2006 Apr [date cited]. Available at: URL:http://www.cdc.gov/pcd/issues/2006/apr/05_0180.htm

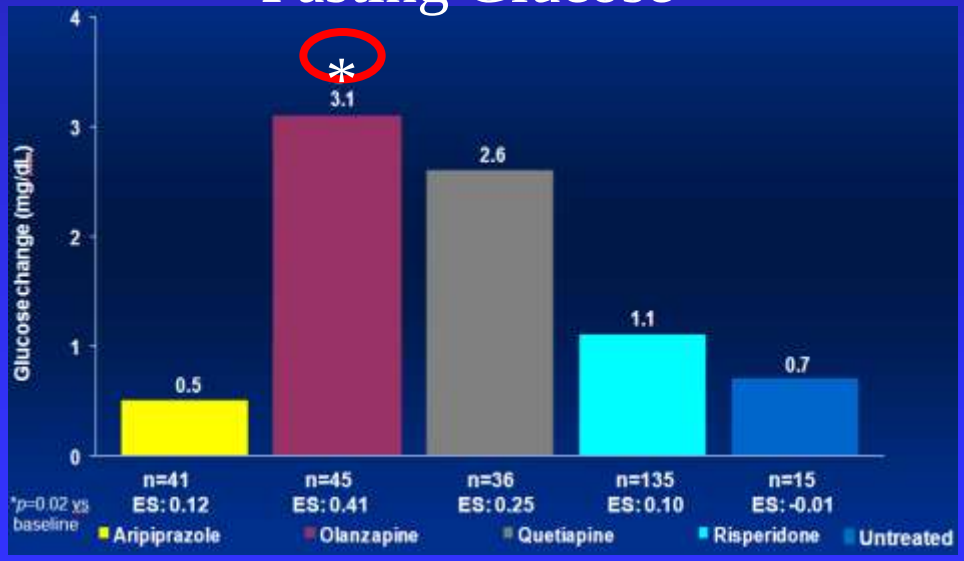
12-week Cardiometabolic Effects of SGAs in AP-Naïve Youth

Body Weight

Fasting Total Cholesterol



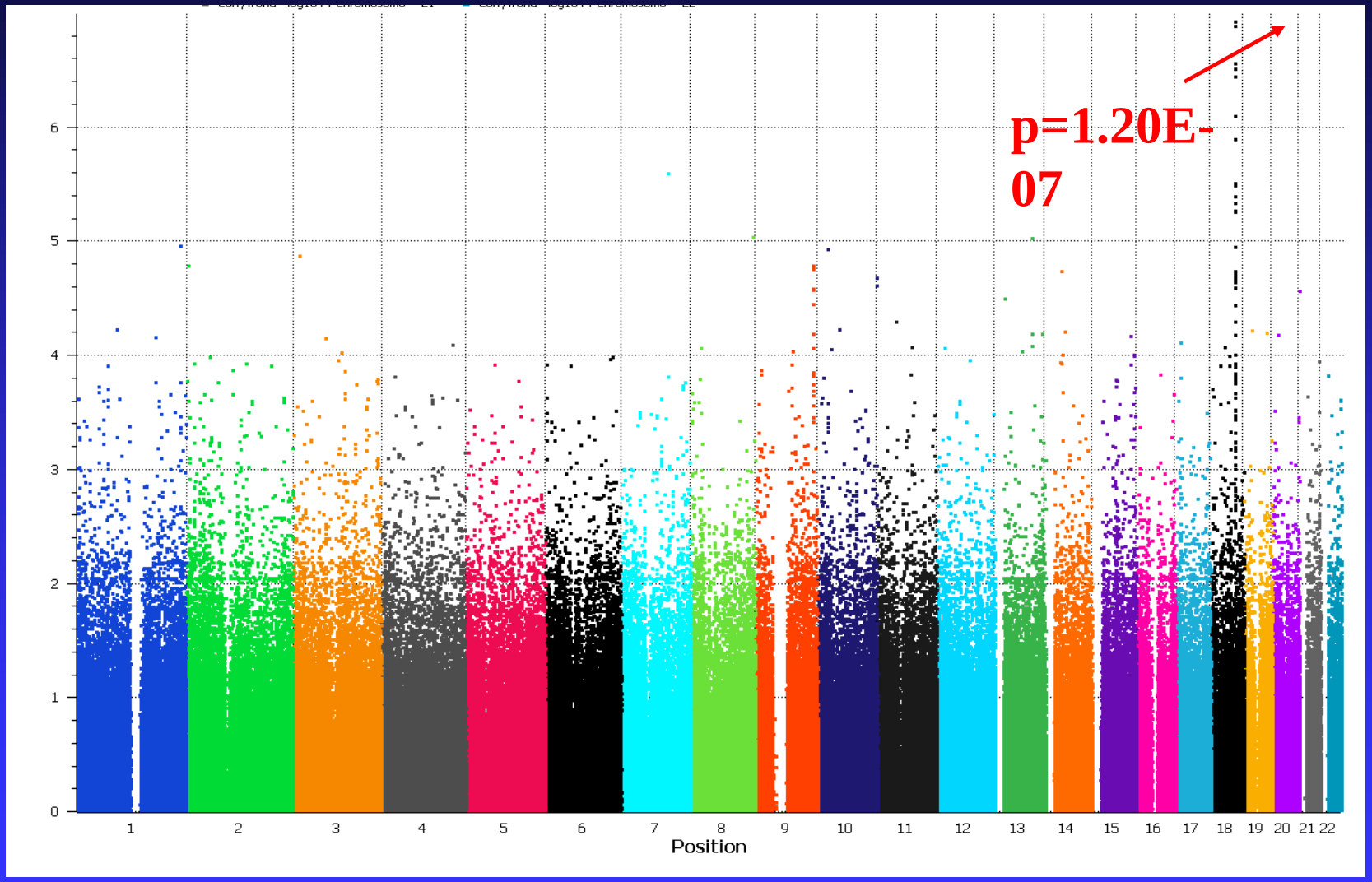
Fasting Glucose



Fasting Triglycerides

Correll CU *et al. JAMA* 2009;302:1765–1773.

Antipsychotic-induced BMI Change in Antipsychotic - Naïve Patients



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

DRUG THERAPY

Adherence to Medication

Lars Osterberg, M.D., and Terrence Blaschke, M.D.

Drugs don't work in patients who don't take them.

—C. Everett Koop, M.D.

ADHERENCE TO (OR COMPLIANCE WITH) A MEDICATION REGIMEN IS generally defined as the extent to which patients take medications as prescribed by their health care providers. The word "adherence" is preferred by many health care providers, because "compliance" suggests that the patient is passively following the doctor's orders and that the treatment plan is not based on a therapeutic alliance or contract established between the patient and the physician. Both terms are imperfect and uninformative descriptions of medication-taking behavior. Unfortunately, applying these terms to patients who do not consume every pill at the desired time can stigmatize these patients in their future relationships with health care providers. The language used to describe how patients take their medications needs to be reassessed, but these terms are still commonly used.[1] Regardless of which word is preferred, it is clear that the full benefit of the many effective medications that are available will be achieved only if patients follow prescribed treatment regimens reasonably closely.

From the General Medicine Division, Veterans Affairs Palo Alto Health Care System, Palo Alto (L.O.); and the Division of Clinical Pharmacology, Stanford University Medical Center, Stanford (T.B.) — both in California. Address reprint requests to Dr. Osterberg at the VA Palo Alto Health Care System, 3801 Miranda Ave., Palo Alto, CA 94304, or at larso@stanford.edu.

N Engl J Med 2005;353:487-97.

Adherence rates are typically disappointingly low in patients with chronic conditions.

- A World Health Organization (WHO) report estimates that 50% of individuals with chronic illnesses in developed countries do not use their medications as recommended:
  - (1) Inadequate adherence to medication regimens accounts for significant exacerbation of disease, increased health care costs and higher mortality rates associated with many different illnesses.
  - (2,3) It has been estimated that of all medication-related hospital admissions in the U.S., 33 to 60 percent are due to poor medication adherence, resulting in $100 billion in direct healthcare costs, $50 billion in lost productivity and $1-2 billion in lost earnings (1,2,4).
  - At the same time the ability of health care providers to recognize nonadherence is generally poor (5)

The risk for psychotic relapse is high

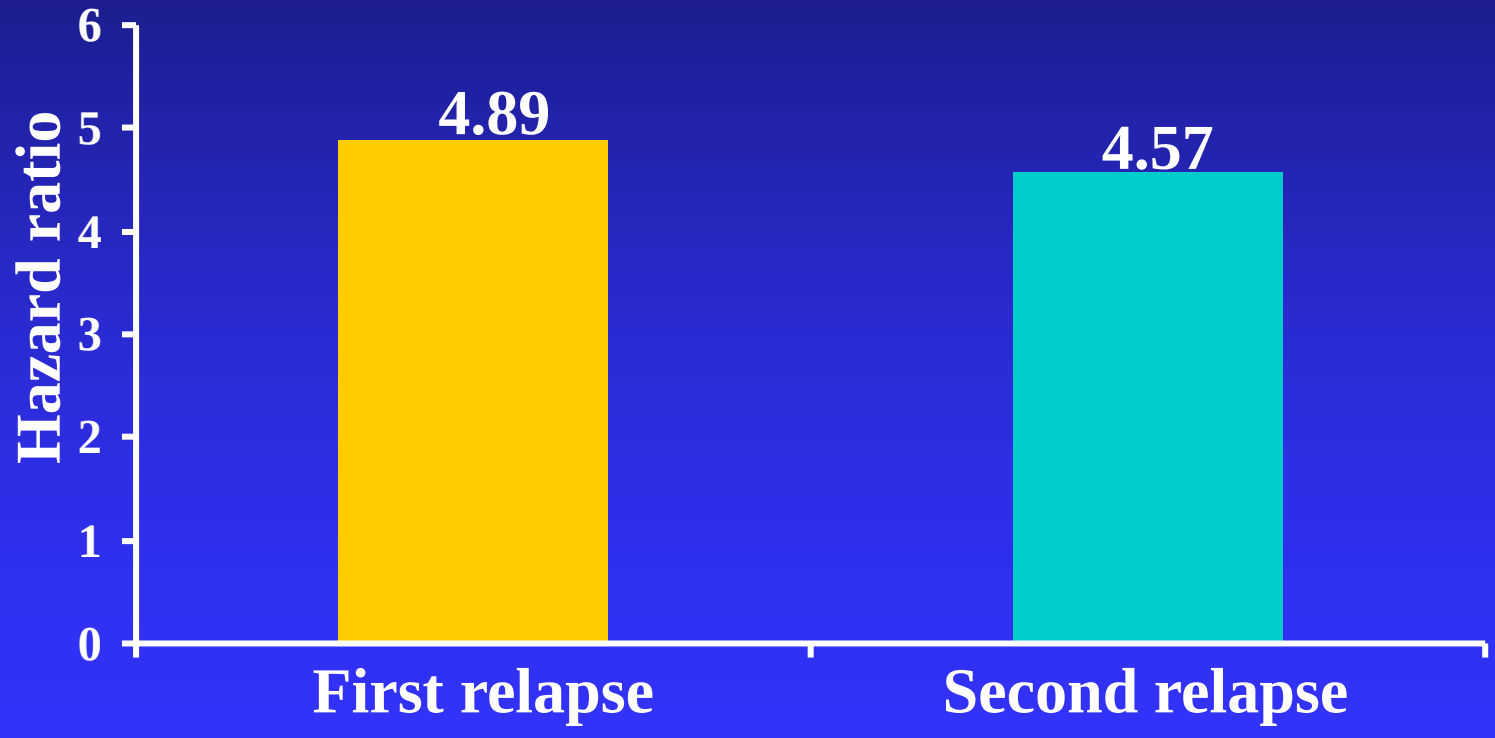
Year*	Relapse rate (%)	95% limit (%)		Patients still at risk at end of year
		Lower	Upper	
1	16.2	8.9	23.4	80
2	53.7	43.4	64.0	39
3	63.1	52.7	73.4	22
4	74.7	64.2	85.2	9
5	81.9	70.6	93.2	4

n=104 first-episode schizophrenia patients
*Year(s) since previous episode

Robinson D, et al. Arch Gen Psychiatry 1999;56:241–7

Stopping medication is the most powerful predictor of relapse

- **Survival analysis: risk of a first or second relapse when not taking medication ~5 times greater than when taking it**



Robinson D, et al. Arch Gen Psychiatry 1999;56:241–7

What Is the Level of Adherence...

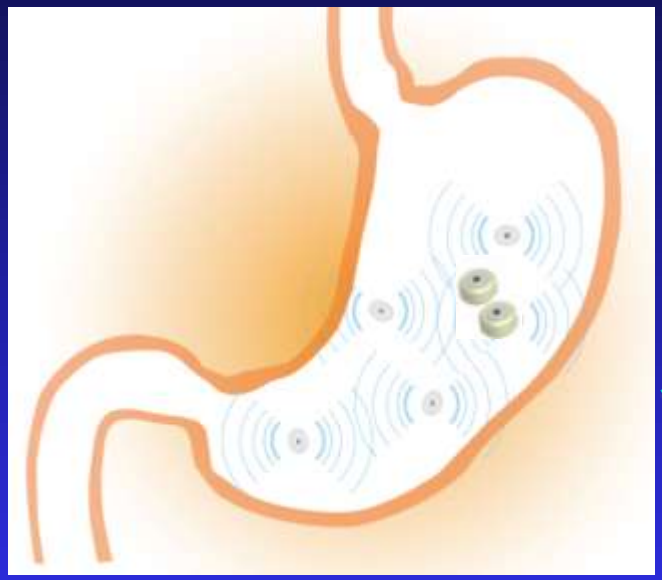
Adherence	….In The Literature?	….In Your Patients?*
	% Patient Population, Average (SD)	
Adherent	**28.0 (11.8)**	**43.1 (20.6)**
Partially Adherent	46.4 (14.4)	38.7 (17.4)
Nonadherent	26.2 (9.8)	19.2 (11.7)

*Patient adherence levels were based on experts' estimates of patient adherence.
SD, standard deviation.

Kane JM, et al. *J Clin Psychiatry*. 2003;64(suppl 12):1-100.

Raisin Intelligent Pharmaceutical System

RAISIN SYSTEM: Theory of Operation



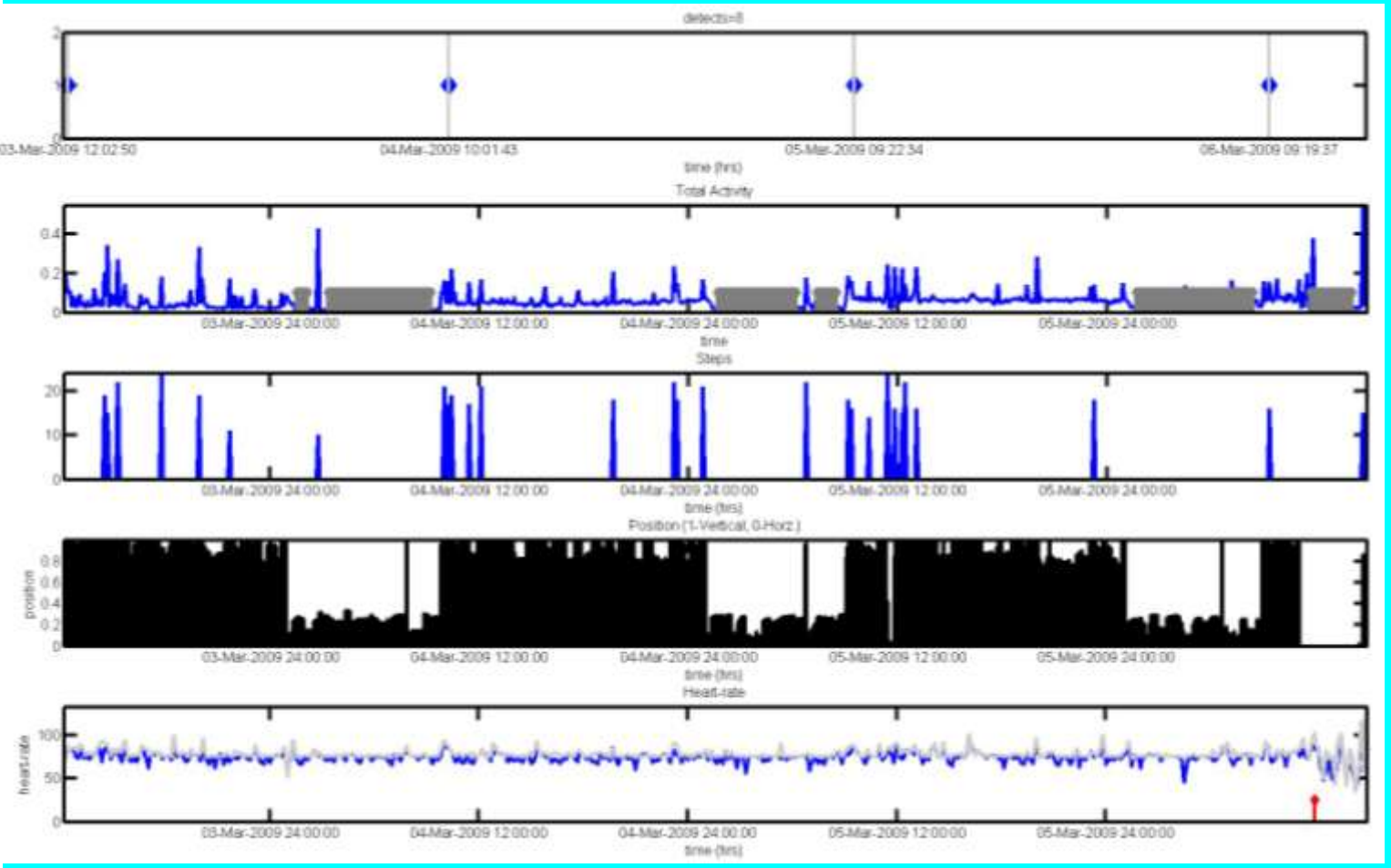
1. Upon ingestion, an Ingestible Event Marker (IEM) is activated by gastric fluid and begins communicating with the Raisin Data Recorder (RDR).

2. RDR gathers information from the IEM. It also collects heart rate, activity, and sleep data via its internal accelerometer.

3. Data from RDR are transmitted to the mobile phone for server upload. Other subjective input can be manually entered using the phone.

Rich, Integrated Data Set from EMITTER 3.0 CV-HF

Day/Night 1 **Day/Night 2** **Day/Night 3**



Pill detects (8/8)

Activity/Sleep

Step Count

Position

Heart Rate

Schizophrenia Research 127 (2011) 83–92

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Oral versus depot antipsychotic drugs for schizophrenia—A critical systematic review and meta-analysis of randomised long-term trials

Claudia Leucht [a], Stephan Heres [a], John M. Kane [c], Werner Kissling [a], John M. Davis [b], Stefan Leucht [a,*]

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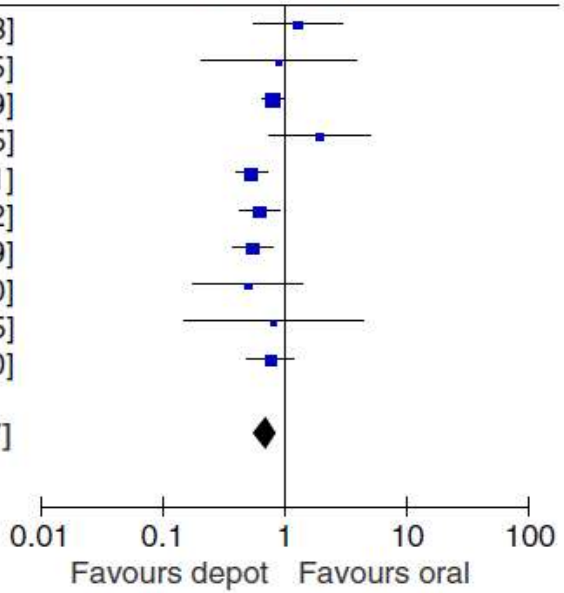
[b] Department of Psychiatry, University of Chicago at Illinois, Chicago, USA
[c] The Zucker Hillside Hospital, Psychiatry Research, North Shore—Long Island Jewish Health System, Glen Oaks, New York, NY, USA

Study or Subgroup	Depot Events	Depot Total	Oral Events	Oral Total	Weight	Risk Ratio M-H, Random, 95% CI
Arango 2005	10	26	6	20	5.2%	1.28 [0.56, 2.93]
Barnes 1983	3	19	3	17	1.9%	0.89 [0.21, 3.85]
Del Guidice 1975	21	27	30	31	22.8%	0.80 [0.65, 0.99]
Falloon 1978	8	20	5	24	4.2%	1.92 [0.74, 4.95]
Gaebel 2010	54	355	102	355	18.6%	0.53 [0.39, 0.71]
Hogarty 1979	22	55	32	50	14.8%	0.63 [0.43, 0.92]
Li 1996	32	155	52	137	15.1%	0.54 [0.37, 0.79]
Potapov 2008	4	20	8	20	3.6%	0.50 [0.18, 1.40]
Rifkin 1977	2	23	3	28	1.4%	0.81 [0.15, 4.45]
Schooler 1979	26	143	35	147	12.4%	0.76 [0.49, 1.20]
Total (95% CI)		**843**		**829**	**100.0%**	**0.70 [0.57, 0.87]**
Total events	182		276			

Heterogeneity: Tau² = 0.04; Chi² = 15.35, df = 9 (P = 0.08); I² = 41%
Test for overall effect: Z = 3.32 (P = 0.0009)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Acting Risperidone and Oral Antipsychotics in Unstable Schizophrenia

Robert A. Rosenheck, M.D., John H. Krystal, M.D., Robert Lew, Ph.D., Paul G. Barnett, Ph.D., Louis Fiore, M.D., M.P.H., Danielle Valley, M.P.H., Soe Soe Thwin, Ph.D., Julia E. Vertrees, Pharm.D., and Matthew H. Liang, M.D., M.P.H., for the CSP555 Research Group*

ABSTRACT

BACKGROUND

Long-acting injectable risperidone, a second-generation antipsychotic agent, may improve adherence to treatment and outcomes in schizophrenia, but it has not been tested in a long-term randomized trial involving patients with unstable disease.

METHODS

We randomly assigned patients in the Veterans Affairs (VA) system who had schizophrenia or schizoaffective disorder and who had been hospitalized within the previous 2 years or were at imminent risk for hospitalization to 25 to 50 mg of long-acting injectable risperidone every two weeks or to a psychiatrist's choice of an oral antipsychotic. All patients were followed for up to 2 years. The primary end point was hospitalization in a VA or non-VA psychiatric hospital. Symptoms, quality of life, and functioning were assessed in blinded videoconference interviews.

RESULTS

Of 369 participants, 40% were hospitalized at randomization, 55% were hospitalized within the previous 2 years, and 5% were at risk for hospitalization. The rate of hospitalization after randomization was not significantly lower among patients who received long-acting injectable risperidone than among those who received oral antipsychotics (39% after 10.8 months vs. 45% after 11.3 months; hazard ratio, 0.87; 95% confidence interval, 0.63 to 1.20). Psychiatric symptoms, quality of life, scores on the Personal and Social Performance scale of global functioning, and neurologic side effects were not significantly improved with long-acting injectable risperidone as compared with control treatments. Patients who received long-acting injectable risperidone reported more adverse events at the injection site and more extrapyramidal symptoms.

CONCLUSIONS

Long-acting injectable risperidone was not superior to a psychiatrist's choice of oral treatment in patients with schizophrenia and schizoaffective disorder who were hospitalized or at high risk for hospitalization, and it was associated with more local injection-site and extrapyramidal adverse effects. (Supported by the VA Cooperative Studies Program and Ortho-McNeil Janssen Scientific Affairs; ClinicalTrials.gov number, NCT00132314.)

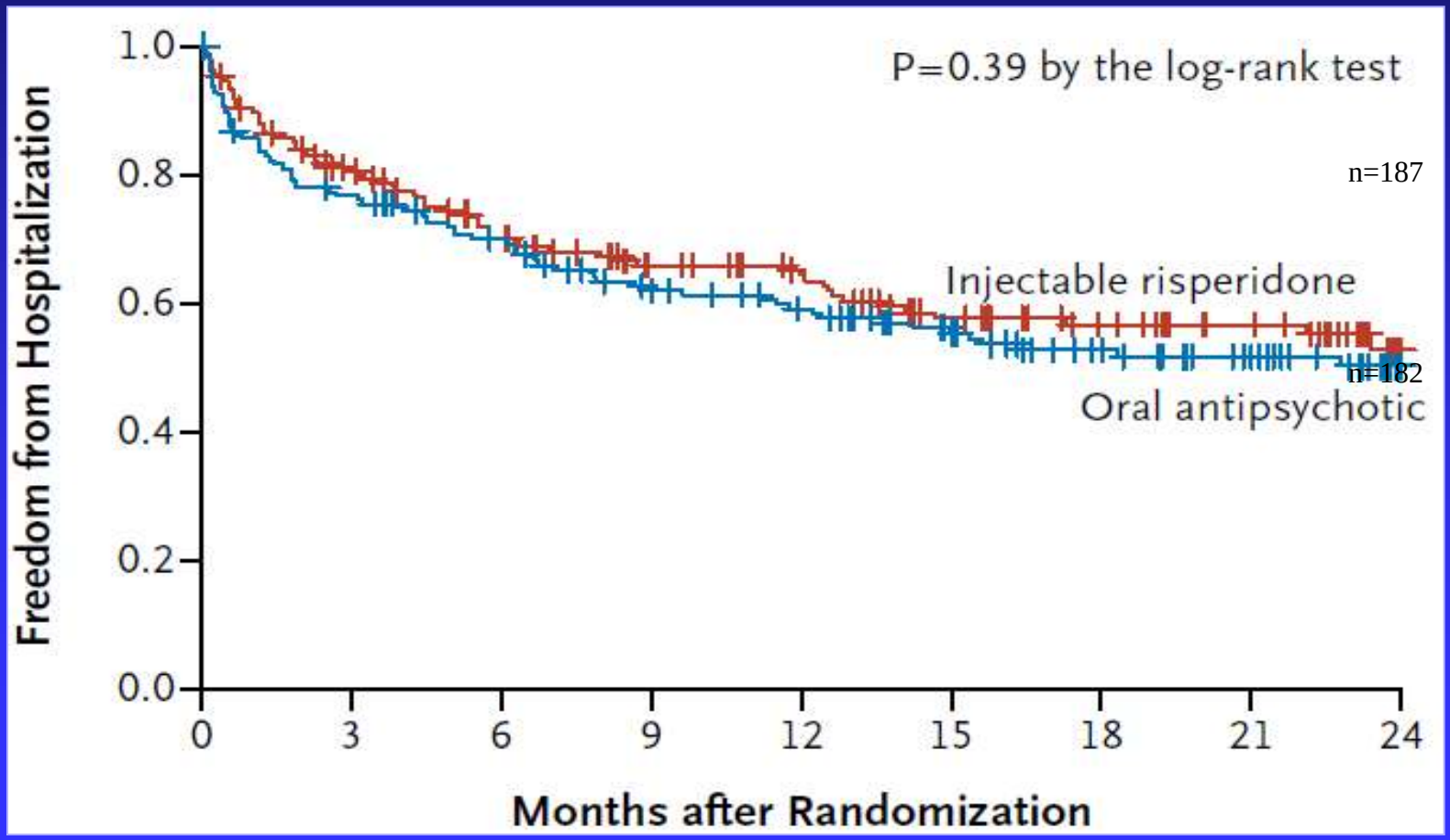
LAI Clinical Study

ORIGINAL ARTICLE

Long-Acting Risperidone and Oral Antipsychotics in Unstable Schizophrenia

Robert A. Rosenheck, M.D., John H. Krystal, M.D., Robert Lew, Ph.D., Paul G. Barnett, Ph.D., Louis Fiore, M.D., M.P.H., Danielle Valley, M.P.H., Soe Soe Thwin, Ph.D., Julia E. Vertrees, Pharm.D., and Matthew H. Liang, M.D., M.P.H., for the CSP555 Research Group*

Time to Hospitalization after Randomization



Rosenheck et al. N Engl J Med 2011

New Results Alter Balance of Evidence of Long-Acting Injectable vs. Oral Antipsychotics Regarding Relapse Prevention in Schizophrenia: A Systematic Review and Meta-Analysis

Taishiro Kishimoto, M.D., Ph.D. [1, 2], Alfred Robenzadeh, M.D. [1], Claudia Leucht, M.D.[3], Stefan Leucht, M.D.[3], Koichiro Watanabe, M.D., Ph.D.[2], Masaru Mimura, M.D., Ph.D.[2], John M. Kane, M.D.[1, 4, 5, 6], Christoph U. Correll, M.D.[1, 4, 5, 6]

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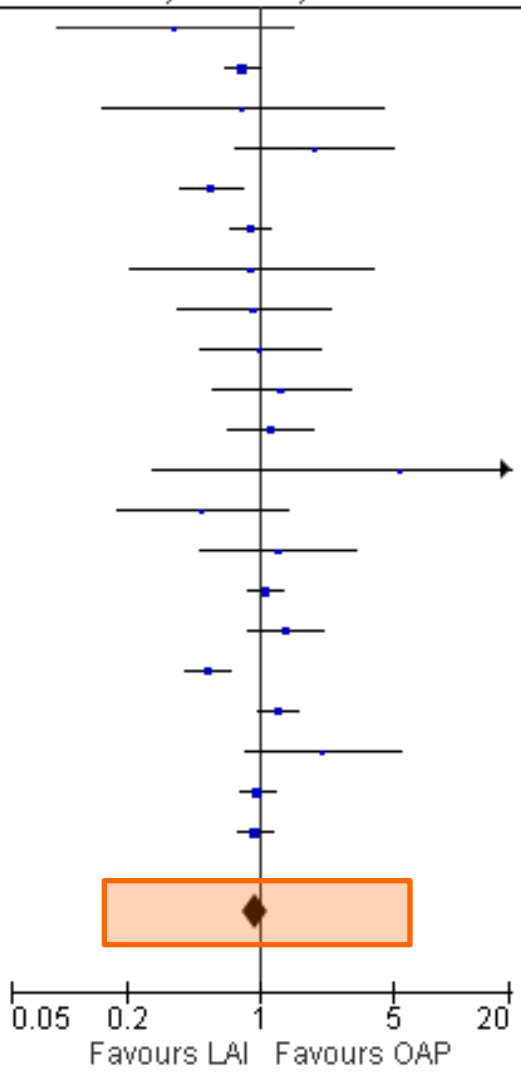
Primary Outcome: LAI Pooled

Relapse (estimated, longest time point)

Study or Subgroup	LAI Events	LAI Total	OAP Events	OAP Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Crawdford 1974	2	14	6	15	1.0%	0.36 [0.09, 1.48]	1974
Del Guidice 1975	21	27	59	61	9.5%	0.80 [0.65, 0.99]	1975
Rifkin 1977	2	23	3	28	0.7%	0.81 [0.15, 4.45]	1977
Falloon 1978	8	20	5	24	2.1%	1.92 [0.74, 4.95]	1978
Hogarty 1979	22	55	36	50	6.8%	0.56 [0.38, 0.80]	1979
Schooler 1980	54	107	61	107	8.8%	0.89 [0.69, 1.14]	1980
Barnes 1983	3	19	3	17	1.0%	0.89 [0.21, 3.85]	1983
Kaneno 1991	8	127	9	132	2.2%	0.92 [0.37, 2.32]	1991
Glick 2005	5	9	9	16	3.1%	0.99 [0.48, 2.04]	2005
Arango 2006	10	26	6	20	2.6%	1.28 [0.56, 2.93]	2006
Keks 2007	25	247	27	300	4.9%	1.12 [0.67, 1.89]	2007
Bai 2007	2	23	0	25	0.2%	5.42 [0.27, 107.20]	2007
Potapov 2008	4	20	8	20	1.8%	0.50 [0.18, 1.40]	2008
Kamijima 2009	18	147	5	51	2.1%	1.25 [0.49, 3.19]	2009
MacFadden 2010	90	177	82	172	9.4%	1.07 [0.86, 1.32]	2010
Kane 2010	58	599	23	322	5.5%	1.36 [0.85, 2.16]	2010
Gaebel 2010	65	327	122	326	8.6%	0.53 [0.41, 0.69]	2010
Schooler 2011	75	146	62	150	8.8%	1.24 [0.97, 1.59]	2011
NCT00246259	11	32	5	31	2.1%	2.13 [0.84, 5.43]	2011
Detke 2011	102	264	104	260	9.4%	0.97 [0.78, 1.19]	2011
Rosenheck 2011	86	187	90	182	9.4%	0.93 [0.75, 1.15]	2011
Total (95% CI)		**2596**		**2309**	**100.0%**	**0.93 [0.80, 1.08]**	
Total events	671		725				

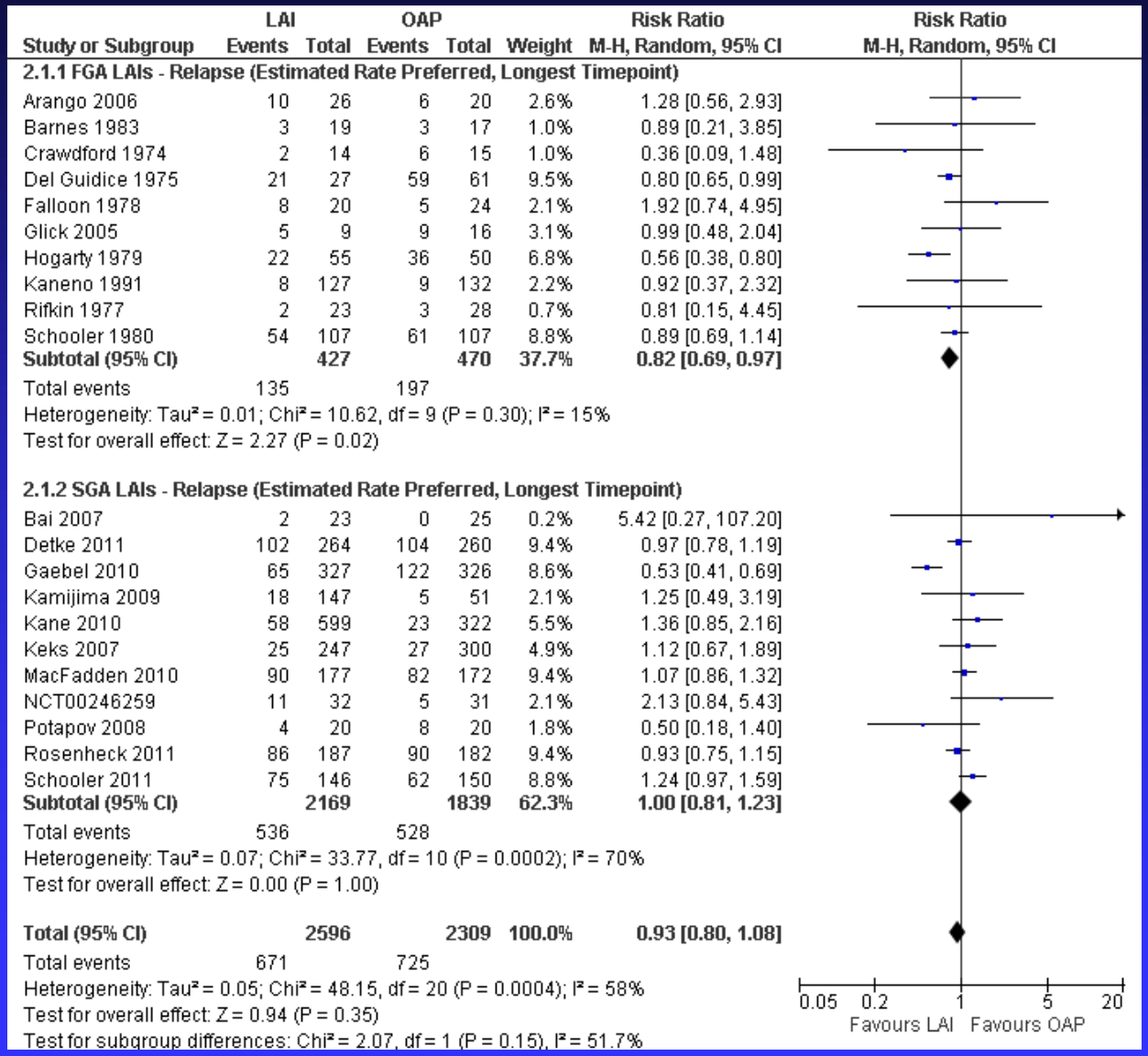
Heterogeneity: Tau² = 0.05; Chi² = 48.15, df = 20 (P = 0.0004); I² = 58%

Test for overall effect: Z = 0.94 (P = 0.35)



Kishimoto T et al.Schiz Bull 2013

Subgroup Analysis: FGA- vs. SGA-LAIs



Study or Subgroup	LAI Events	LAI Total	OAP Events	OAP Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 FGA LAIs - Relapse (Estimated Rate Preferred, Longest Timepoint)						
Arango 2006	10	26	6	20	2.6%	1.28 [0.56, 2.93]
Barnes 1983	3	19	3	17	1.0%	0.89 [0.21, 3.85]
Crawdford 1974	2	14	6	15	1.0%	0.36 [0.09, 1.48]
Del Guidice 1975	21	27	59	61	9.5%	0.80 [0.65, 0.99]
Falloon 1978	8	20	5	24	2.1%	1.92 [0.74, 4.95]
Glick 2005	5	9	9	16	3.1%	0.99 [0.48, 2.04]
Hogarty 1979	22	55	36	50	6.8%	0.56 [0.38, 0.80]
Kaneno 1991	8	127	9	132	2.2%	0.92 [0.37, 2.32]
Rifkin 1977	2	23	3	28	0.7%	0.81 [0.15, 4.45]
Schooler 1980	54	107	61	107	8.8%	0.89 [0.69, 1.14]
Subtotal (95% CI)		**427**		**470**	**37.7%**	**0.82 [0.69, 0.97]**
Total events	135		197			
Heterogeneity: Tau² = 0.01; Chi² = 10.62, df = 9 (P = 0.30); I² = 15%						
Test for overall effect: Z = 2.27 (P = 0.02)						
2.1.2 SGA LAIs - Relapse (Estimated Rate Preferred, Longest Timepoint)						
Bai 2007	2	23	0	25	0.2%	5.42 [0.27, 107.20]
Detke 2011	102	264	104	260	9.4%	0.97 [0.78, 1.19]
Gaebel 2010	65	327	122	326	8.6%	0.53 [0.41, 0.69]
Kamijima 2009	18	147	5	51	2.1%	1.25 [0.49, 3.19]
Kane 2010	58	599	23	322	5.5%	1.36 [0.85, 2.16]
Keks 2007	25	247	27	300	4.9%	1.12 [0.67, 1.89]
MacFadden 2010	90	177	82	172	9.4%	1.07 [0.86, 1.32]
NCT00246259	11	32	5	31	2.1%	2.13 [0.84, 5.43]
Potapov 2008	4	20	8	20	1.8%	0.50 [0.18, 1.40]
Rosenheck 2011	86	187	90	182	9.4%	0.93 [0.75, 1.15]
Schooler 2011	75	146	62	150	8.8%	1.24 [0.97, 1.59]
Subtotal (95% CI)		**2169**		**1839**	**62.3%**	**1.00 [0.81, 1.23]**
Total events	536		528			
Heterogeneity: Tau² = 0.07; Chi² = 33.77, df = 10 (P = 0.0002); I² = 70%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**2596**		**2309**	**100.0%**	**0.93 [0.80, 1.08]**
Total events	671		725			
Heterogeneity: Tau² = 0.05; Chi² = 48.15, df = 20 (P = 0.0004); I² = 58%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Test for subgroup differences: Chi² = 2.07, df = 1 (P = 0.15), I² = 51.7%						

FGA-LAIs vs. OAPs

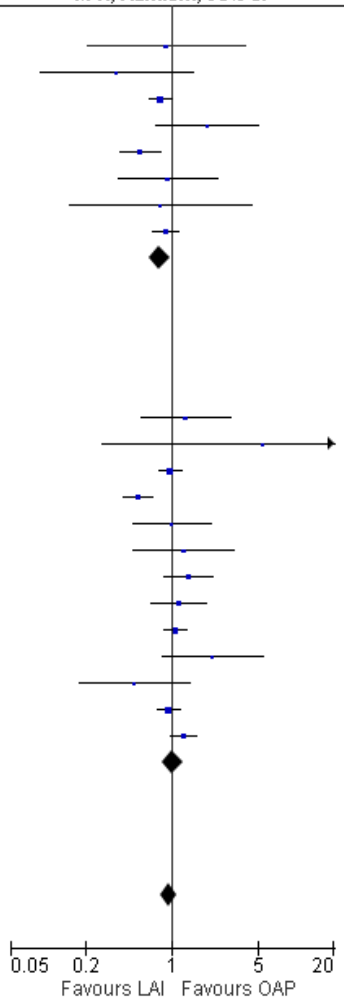
RR=0.82[0.69-0.97]
p=0.02
NNT=15

SGA-LAI vs. OAPs

Kishimoto T et al. Schiz Bull 2013

Subgroup Analysis:
Old studies (≤1991) vs. New studies (≥2005)

Study or Subgroup	LAI Events	LAI Total	OAP Events	OAP Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Subgroup: old studies (</=1991) - Relapse (Estimated Rate Preferred, Longest Timepoint)						
Barnes 1983	3	19	3	17	1.0%	0.89 [0.21, 3.85]
Crawdford 1974	2	14	6	15	1.0%	0.36 [0.09, 1.48]
Del Guidice 1975	21	27	59	61	9.5%	0.80 [0.65, 0.99]
Falloon 1978	8	20	5	24	2.1%	1.92 [0.74, 4.95]
Hogarty 1979	22	55	36	50	6.8%	0.56 [0.38, 0.80]
Kaneno 1991	8	127	9	132	2.2%	0.92 [0.37, 2.32]
Rifkin 1977	2	23	3	28	0.7%	0.81 [0.15, 4.45]
Schooler 1980	54	107	61	107	8.8%	0.89 [0.69, 1.14]
Subtotal (95% CI)		**392**		**434**	**32.1%**	**0.79 [0.65, 0.96]**
Total events	120		182			
Heterogeneity: Tau² = 0.02; Chi² = 9.06, df = 7 (P = 0.25); I² = 23%						
Test for overall effect: Z = 2.33 (P = 0.02)						
2.6.2 Subgroup: new studies (>/=2005) - Relapse (Estimated Rate Preferred, Longest Timepoint)						
Arango 2006	10	26	6	20	2.6%	1.28 [0.56, 2.93]
Bai 2007	2	23	0	25	0.2%	5.42 [0.27, 107.20]
Detke 2011	102	264	104	260	9.4%	0.97 [0.78, 1.19]
Gaebel 2010	65	327	122	326	8.6%	0.53 [0.41, 0.69]
Glick 2005	5	9	9	16	3.1%	0.99 [0.48, 2.04]
Kamijima 2009	18	147	5	51	2.1%	1.25 [0.49, 3.19]
Kane 2010	58	599	23	322	5.5%	1.36 [0.85, 2.16]
Keks 2007	25	247	27	300	4.9%	1.12 [0.67, 1.89]
MacFadden 2010	90	177	82	172	9.4%	1.07 [0.86, 1.32]
NCT00246259	11	32	5	31	2.1%	2.13 [0.84, 5.43]
Potapov 2008	4	20	8	20	1.8%	0.50 [0.18, 1.40]
Rosenheck 2011	86	187	90	182	9.4%	0.93 [0.75, 1.15]
Schooler 2011	75	146	62	150	8.8%	1.24 [0.97, 1.59]
Subtotal (95% CI)		**2204**		**1875**	**67.9%**	**1.01 [0.83, 1.22]**
Total events	551		543			
Heterogeneity: Tau² = 0.06; Chi² = 34.23, df = 12 (P = 0.0006); I² = 65%						
Test for overall effect: Z = 0.07 (P = 0.95)						
Total (95% CI)		**2596**		**2309**	**100.0%**	**0.93 [0.80, 1.08]**
Total events	671		725			
Heterogeneity: Tau² = 0.05; Chi² = 48.15, df = 20 (P = 0.0004); I² = 58%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Test for subgroup differences: Chi² = 2.91, df = 1 (P = 0.09), I² = 65.6%						



LAIs vs. OAPs in old studies

RR=0.79[0.65-0.96]
p=0.02
NNT=13

LAIs vs. OAPs in new studies

RR=1.01[0.83-1.21]

Kishimoto T et al. Schiz Bull 2013

Summary of the Analysis

- FLU-depot was superior to OAPs in preventing relapse.
- Pooled LAIs were not superior to OAPs in preventing relapse as well as other relapse-related outcomes.
- FGA-LAI studies (or older studies) showed superiority of LAIs over OAPs, while SGA-LAI studies (or newer studies) did not.

Kishimoto T et al. Schiz Bull 2013

AJP in Advance. Published March 1, 2011 (doi: 10.1176/appi.ajp.2011.10081224)

Article

A Nationwide Cohort Study of Oral and Depot Antipsychotics After First Hospitalization for Schizophrenia

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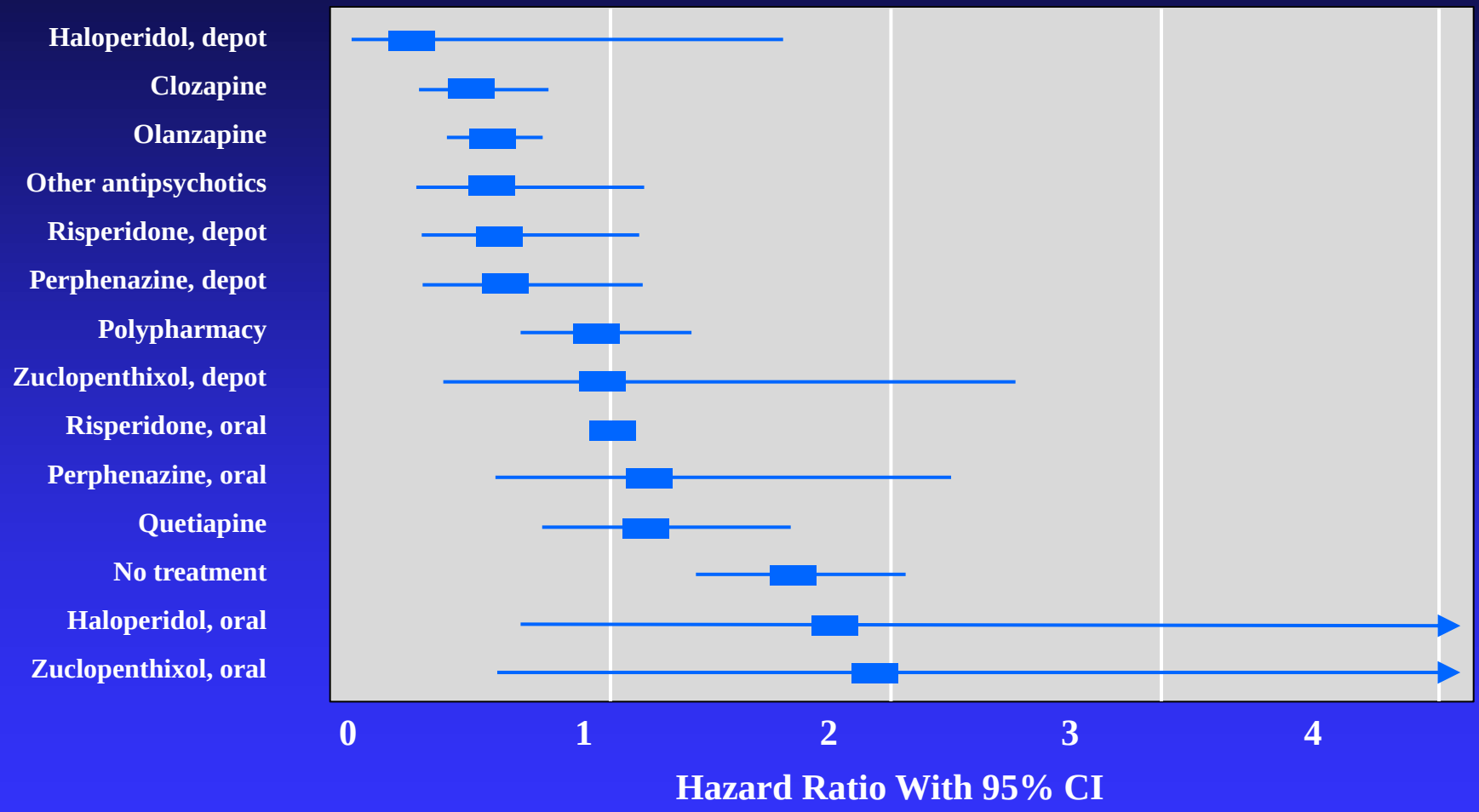
Objective: Data on the effectiveness of antipsychotics in the early phase of schizophrenia are limited. The authors examined the risk of rehospitalization and drug discontinuation in a nationwide cohort of 2,588 consecutive patients hospitalized for the first time with a diagnosis of schizophrenia between 2000 and 2007 in Finland.

Method: The authors linked national databases of hospitalization, mortality, and antipsychotic prescriptions and computed hazard ratios, adjusting for the effects of sociodemographic and clinical variables, the temporal sequence of the antipsychotics used, and the choice of the initial antipsychotic for each patient.

Results: Of 2,588 patients, 1,507 (58.2%) collected a prescription for an antipsychotic during the first 30 days after hospital discharge, and 1,182 (45.7%, 95% confidence interval [CI]=43.7–47.6) continued their initial treatment for 30 days or longer. In a pairwise comparison between depot injections and their equivalent oral formulations, the risk of rehospitalization for patients receiving depot medications was about one-third of that for patients receiving oral medications (adjusted hazard ratio=0.36, 95% CI=0.17–0.75). Compared with oral risperidone, clozapine (adjusted hazard ratio=0.48, 95% CI=0.31–0.76) and olanzapine (adjusted hazard ratio=0.54, 95% CI=0.40–0.73) were each associated with a significantly lower rehospitalization risk. Use of any antipsychotic compared with no antipsychotic was associated with lower mortality (adjusted hazard ratio=0.45, 95% CI=0.31–0.67).

Conclusions: In Finland, only a minority of patients adhere to their initial antipsychotic during the first 60 days after discharge from their first hospitalization for schizophrenia. Use of depot antipsychotics was associated with a significantly lower risk of rehospitalization than use of oral formulations of the same compounds. Among oral antipsychotics, clozapine and olanzapine were associated with more favorable outcomes. Use of any antipsychotic was associated with lower mortality.

Risk of Rehospitalisation After a First Hospitalisation for Schizophrenia, by Antipsychotic Treatment Pattern (N=2,588)



The published results of the Finnish cohort cannot be extrapolated to other markets' antipsychotic clinical study results; do not utilize this guidance when making therapeutic decisions.

Tiihonen J, et al. *Am J Psychiatry.* 2011;168(6):603-609.

What is the most informative design to examine LAI efficacy?

- Randomized Controlled Trial
  - Selection bias (pts in RCT are more adherent), alterations to the ecology of treatment delivery and experience (reminder, adherence assessment etc.)
- Mirror Image Study
  - Expectation bias, influence of independent factors (bed reduction etc.)
- Cohort Study
  - Selection bias (pts on LAI are more severe)

UCLA Recovery Criteria

- Recovery criteria must be met in each of 4 domains
- Improvement in each domain must be sustained concurrently for ≥2 years
- Level of recovery in these 4 domains is measured by
  - Symptom remission
  - Appropriate role function
  - Ability to perform day-to-day living tasks without supervision
  - Social interactions

Liberman RP, Kopelowicz A. *Psychiatr Serv*. 2005;56:735-742.

Cumulative Recovery Rates by Year in Study

Year	Cumulative Recovery Rate (%)	Lower 95% Limit	Upper 95% Limit
3	9.7	3.7	15.8
4	12.3	5.4	19.1
5	13.7	6.4	20.9

Robinson, et al. *Am J Psychiatry*. 2004.

“Tread softly because you tread on my dreams”

WB Yeats


RAISE
Early Treatment Program
A Research Project of the NIMH

RAISE – ETP Executive Committee

- John Kane, - Principal Investigator
  - The Zucker Hillside Hospital (ZHH)
- Delbert Robinson ZHH
- Nina Schooler SUNY Downstate Medical Center
- Jean Addington University of Calgary
- Sue Estroff University of North Carolina
- Christoph Correll ZHH
- Kim Mueser Boston University
- David Penn University of North Carolina
- Robert Rosenheck Yale University
- Patricia Marcy ZHH Project Director

Targets for Psychosocial Interventions

- Isolation from families and friends
- Damage to social and working relationships
- Risk of self-harm and aggression
- Substance abuse
- Self stigma
- Demoralization and depression
- Family disruption and distress
- Disrupted developmental trajectory
- Coping with symptoms and poor cognition

Essential Elements in First Episode Intervention

- Specialized track with trained team
- Strategies for initial and sustained engagement
- Personalized psychopharmacologic treatment
- Medical management and liaison with primary care
- Psychosocial treatments
  - Psychoeducation
  - Cognitive Behavior Therapy
  - Phase Specific Groups
  - Interventions for Substance Misuse
  - Vocational and Educational Programs
  - Family Work
- Substance abuse treatment

Components of NAVIGATE Intervention

- Personalized psychopharmacological treatment and medical management
- Family psychoeducation/treatment
- Supported education/employment
- Individual resiliency training
- Team of professionals share responsibility for treating clients in NAVIGATE program
- All components individually tailored to client and family goals established early in treatment
- Shared decision making model informs all treatment

RAISE –ETP
Key Study Methods

- Sites randomly assigned to
  - NAVIGATE - Our integrated intervention
  - Community Care - current treatment program
- Masked clinical raters conduct live, two-way video interviews to assess
  - Diagnosis – SCID
    - At enrollment and one year
  - Symptoms – PANSS and CDRS
  - Functional Outcome - QOLS
- Insure expert assessment and high reliability at non-academic clinical settings
- Subjects are assessed every 6 months for a minimum of 2 years

Computerized Decision Support System
Longitudinal Symptom Assessment

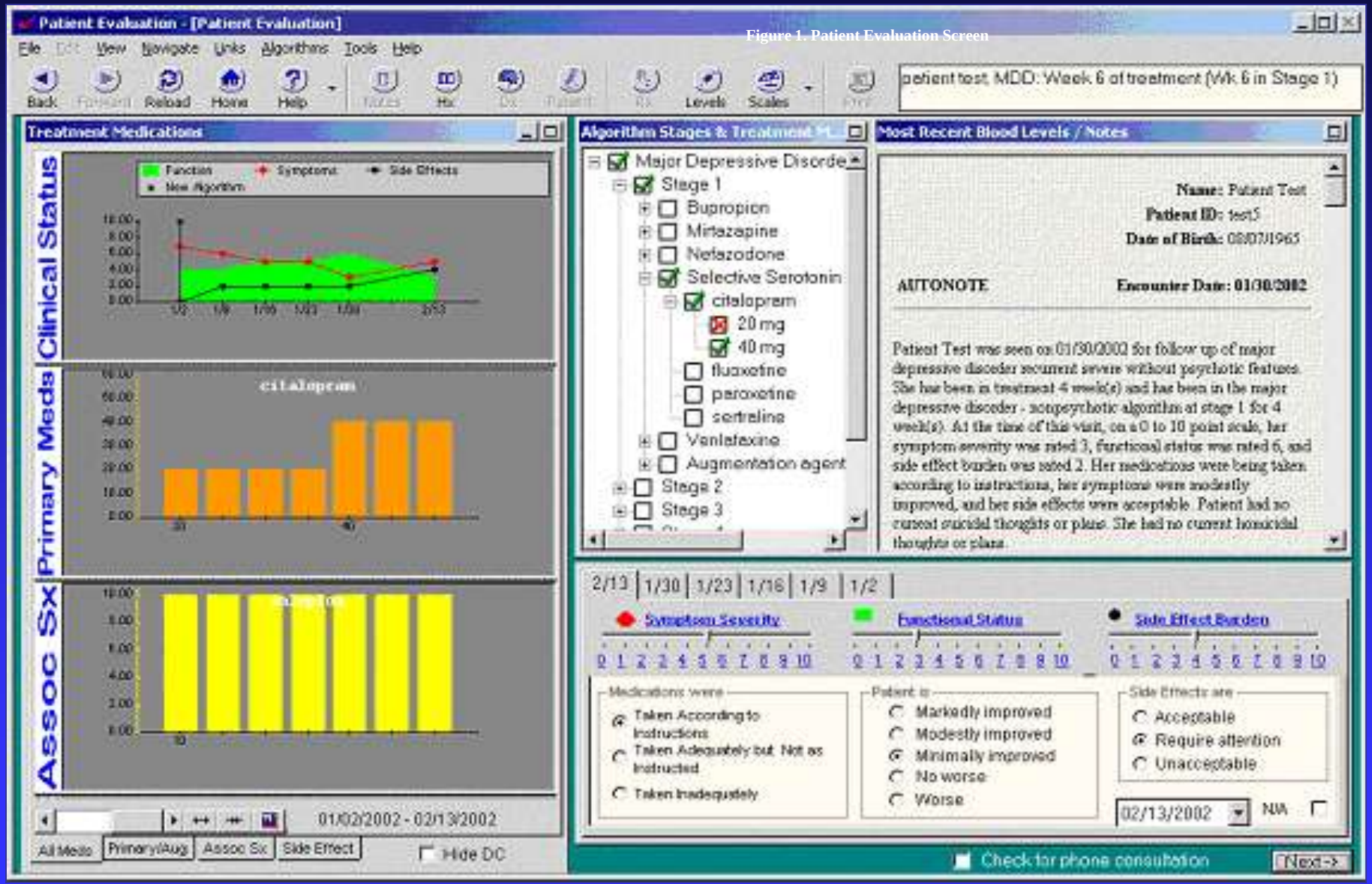


Figure 1. Patient Evaluation Screen

Primary and Secondary Outcome Measures

- **Primary Outcome Measure – Total Score QOLS**
- **Secondary outcome measures**
  - **Cost from Societal and Health care system perspective**
  - **Psychopathology**
  - **Participation in work and school**
  - **Quality Adjusted Life Years (QALYS) based on PANSS & side effect data**
  - **Cost effectiveness and cost-benefit of NAVIGATE and Community Care services.**
  - **Client self evaluation of recovery, stigma and satisfaction**

RAISE – ETP Site Distribution

34 sites in 21 states

Improving Care and Reducing Cost (ICRC) Program

THE NEW YORKER

MEDICAL REPORT

THE HOT SPOTTERS

Can we lower medical costs by giving the neediest patients better care?

BY ATUL GAWANDE

JANUARY 24, 2011

If Camden, New Jersey, becomes the first American community to lower its medical costs, it will have a murder to thank. At nine-fifty on a February night in 2001, a twenty-two-year-old black man was shot while driving his Ford Taurus station wagon through a neighborhood on the edge of the Rutgers University campus. The victim lay motionless in the street beside the open door on the driver's side, as if the car had ejected him. A neighborhood couple, a physical therapist and a volunteer firefighter, approached to see if they could help, but police waved them back.

"He's not going to make it," an officer reportedly told the physical therapist. "He's pretty much dead." She called a physician, Jeffrey Brenner, who lived a few doors up the street, and he ran to the scene with a stethoscope and a pocket ventilation mask. After some discussion, the police let him enter the crime scene and attend to the victim. Witnesses told the local newspaper that he was the first person to lay hands on the man.

In Camden, New Jersey, one per cent of patients account for a third of the city's medical costs. Photograph by Phillip Toledano.

Home Healthcare

1. In home self assessment
2. Physiologic monitoring
3. Telemedicine evaluations
4. Video assessment of adherence
5. Early detection of exacerbation/relapse
6. Cost-saving
7. Decrease patient burden, increase patient satisfaction

Program Overview

- **Goal:**
  - To reduce ER visits and hospital days while providing better care, better health and increased patient satisfaction. This will be done by fostering innovation in the use of technology and by training and deploying a new cadre of personnel in the behavioral health field: Mental Health/Health Technology (MH/HT) Case Managers.

Program Overview

- **Aims:**
  - Demonstrate significant reduction in total health care costs over 6 months
  - Produce significant advantages in measures of health outcomes, quality of life and patient satisfaction.
  - Demonstrate the applicability of the model in a broad range of treatment settings and patient populations across the United States
  - Compare the new model to standard care in the patient population.
  - Train and deploy a new cadre of health care workers who will help implement the model and transform health care

Overall Design

- Enroll 100 standard reference patients
  - 10 at each site
  - Receive standard care and complete assessments
- Enroll 770 patients into the ICRC program
  - 200 clients at The Zucker Hillside Hospital
  - 570 clients at 9 community mental health centers
  - Receive the ICRC programs and complete assessments
- All patients will participate in the program for 6 months

Inclusion and Exclusion Criteria

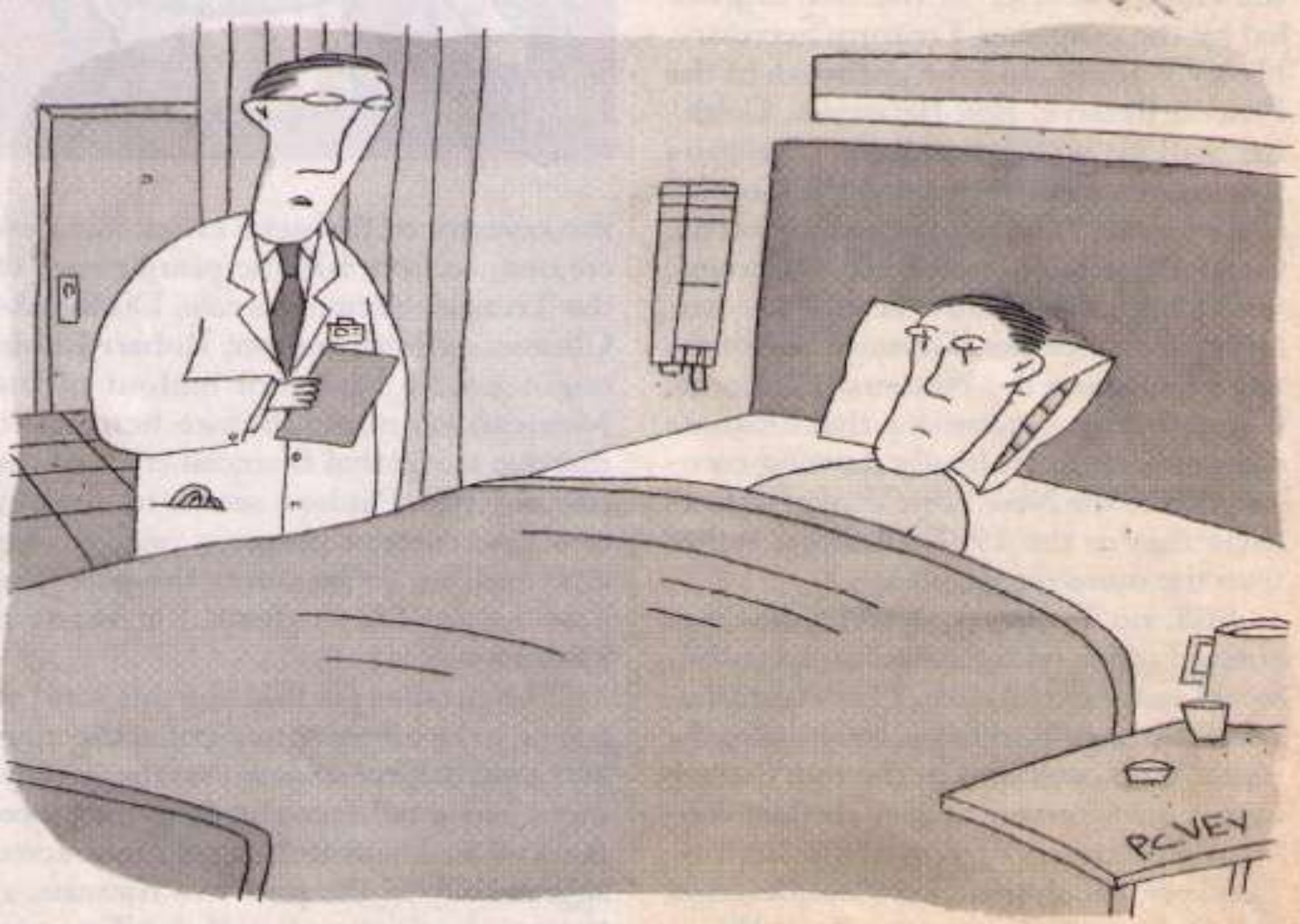
- Inclusion criteria:
  - Age 18 to 50
  - Clinically confirmed diagnoses of schizophrenia or schizoaffective disorder
  - Patients who are currently in the hospital or have been discharged from a psychiatric hospital within the last 30 days
  - Ability to participate in research assessments in English and ability to provide fully informed consent.
- Exclusion criteria include:
  - Individuals who cannot provide fully informed consent will be excluded
  - Any other serious medical condition that in the opinion of the investigator would seriously impair assessment
  - Patients who would likely find it burdensome and/or have difficulty sustaining the use of a laptop computer and /or smart phone due to issues of security, consistent connectivity or other factors.

ICRC Program

- Each center will have project director, a mental health/health technology case manager (MH/HT CM), and a prescriber
- Patients will meet regularly with the MH/HT CM who will offer them the components of the ICRC program:
  - A relapse prevention plan
  - Smart phone technology to manage adherence and symptoms
  - Online CBT therapy for voices or paranoia
  - Technology to Extend Care and Support to Schizophrenia (TECSS) - a web-based program for patients and families that provides psychoeducation and offers social support through the use of web-based therapist facilitated sessions.
  - For a subset of patients -medication sensor technology.
  - A prescriber decision assistant - a web-based prescriber decision support system

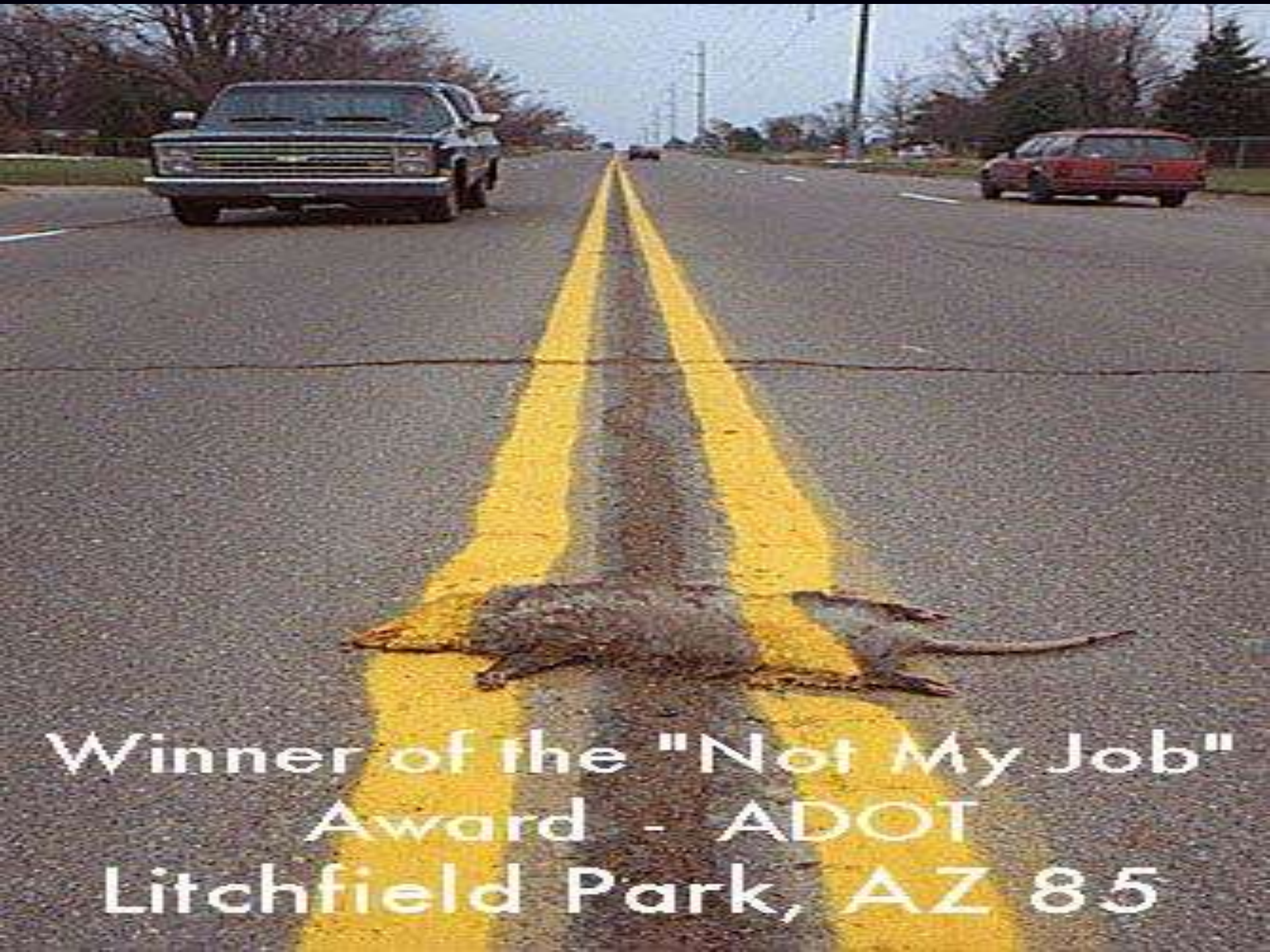
10 Participating Mental Health Centers

- Burrell Behavioral Health – Springfield, MO
- CEI Mental Health Authority – Lansing, MI
- Cherry Street – Grand Rapids, MI
- Henderson Behavioral Health – Ft. Lauderdale, FL
- Human Development Center – Duluth, MN
- PeaceHealth – Eugene, OR
- The MHC of Greater Manchester- Manchester, NH
- Terrebonne MHC – Terrebonne, LA
- The Zucker Hillside Hospital – Glen Oak, NY
- University of New Mexico – Albuquerque, NM



"We're moving you to a room with a better pillow."


1490


Winner of the "Not My Job"
Award - ADOT
Litchfield Park, AZ 85