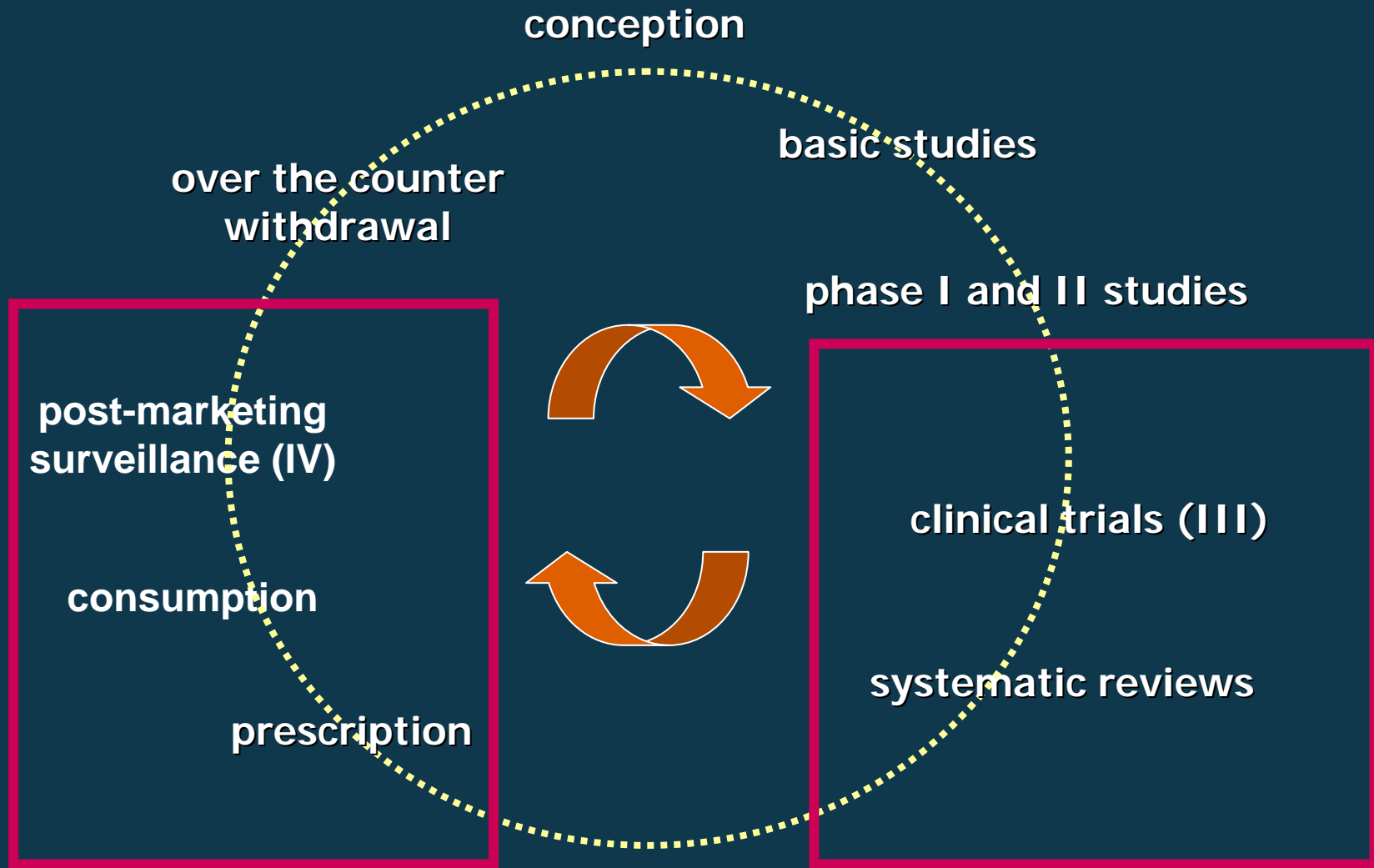


Antipsicotici di vecchia e nuova generazione nelle psicosi schizofreniche

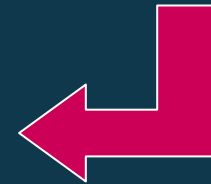
Trieste, 26 Febbraio 2009



DMSP-PSY



LINEE-GUIDA, MANUALI
(società scientifiche,
gruppi di ricerca, ecc ecc)





ANTIPSIKOTICI DI VECCHIA E NUOVA GENERAZIONE

- ❑ **Metanalisi di confronto tra vecchi e nuovi farmaci**
- ❑ **Sperimentazioni chiave: CATIE e EUPHEST**
- ❑ **Antipsicotici e anziani (CATIE + studi epidemiologici)**
- ❑ **Associazioni tra antipsicotici**
- ❑ **Clozapina, e se la risposta è solo parziale?**

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

John Geddes, Nick Freemantle, Paul Harrison, Paul Bebbington for the National Schizophrenia
Guideline Development Group

BMJ VOLUME 321 2 DECEMBER 2000 bmj.com

New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis

Stefan Leucht, Kristian Wahlbeck, Johannes Hamann, Werner Kissling

Lancet 2003; **361**: 1581–89

A Meta-analysis of the Efficacy of Second-Generation Antipsychotics

John M. Davis, MD; Nancy Chen, MS; Ira D. Glick, MD

Arch Gen Psychiatry. 2003;60:553-564

Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis

Stefan Leucht, Caroline Corves, Dieter Arbter, Rolf R Engel, Chunbo Li, John M Davis

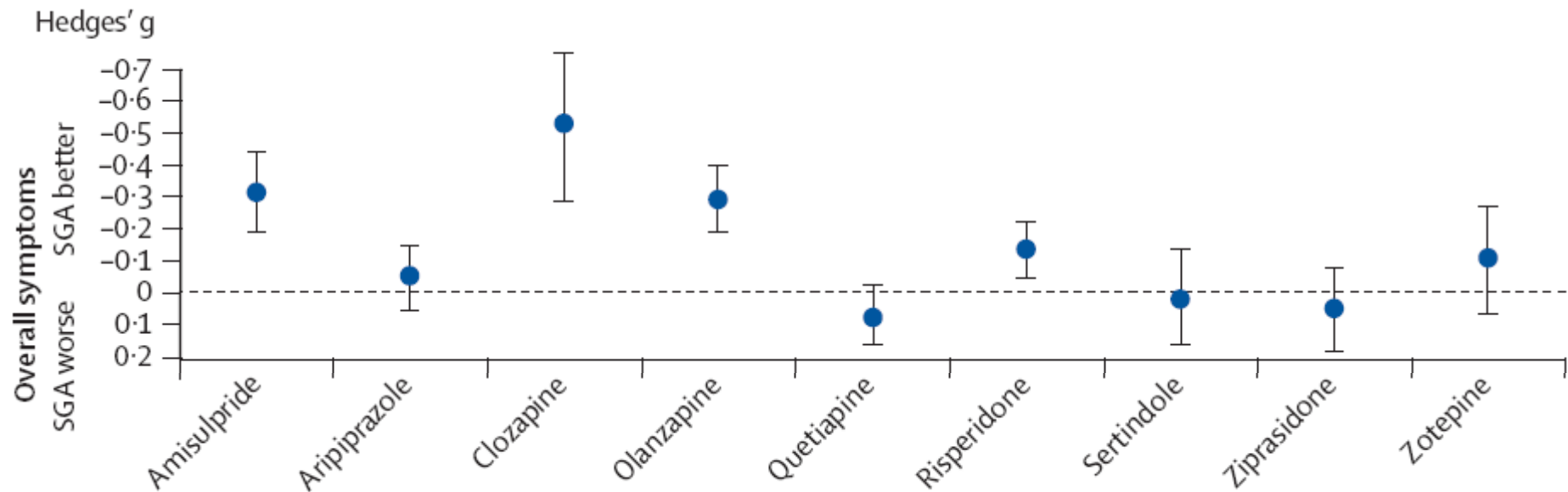
www.thelancet.com Vol 373 January 3, 2009

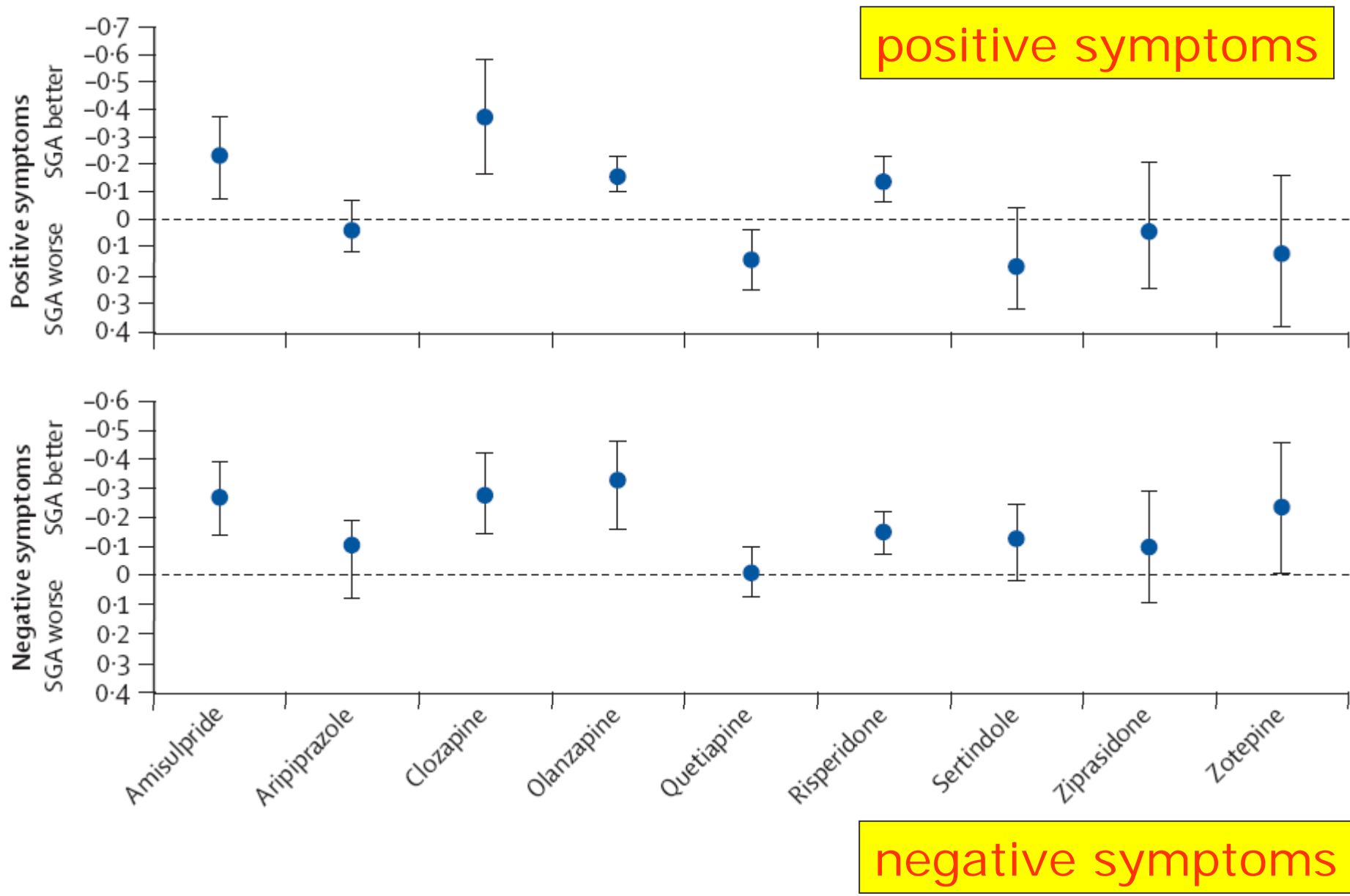
“We compared nine second-generation antipsychotic drugs with first-generation drugs for overall efficacy (main outcome), positive, negative and depressive symptoms, relapse, quality of life, extrapyramidal side-effects, weight gain, and sedation.”

“We included 150 double-blind, mostly short-term, studies, with 21 533 participants.”

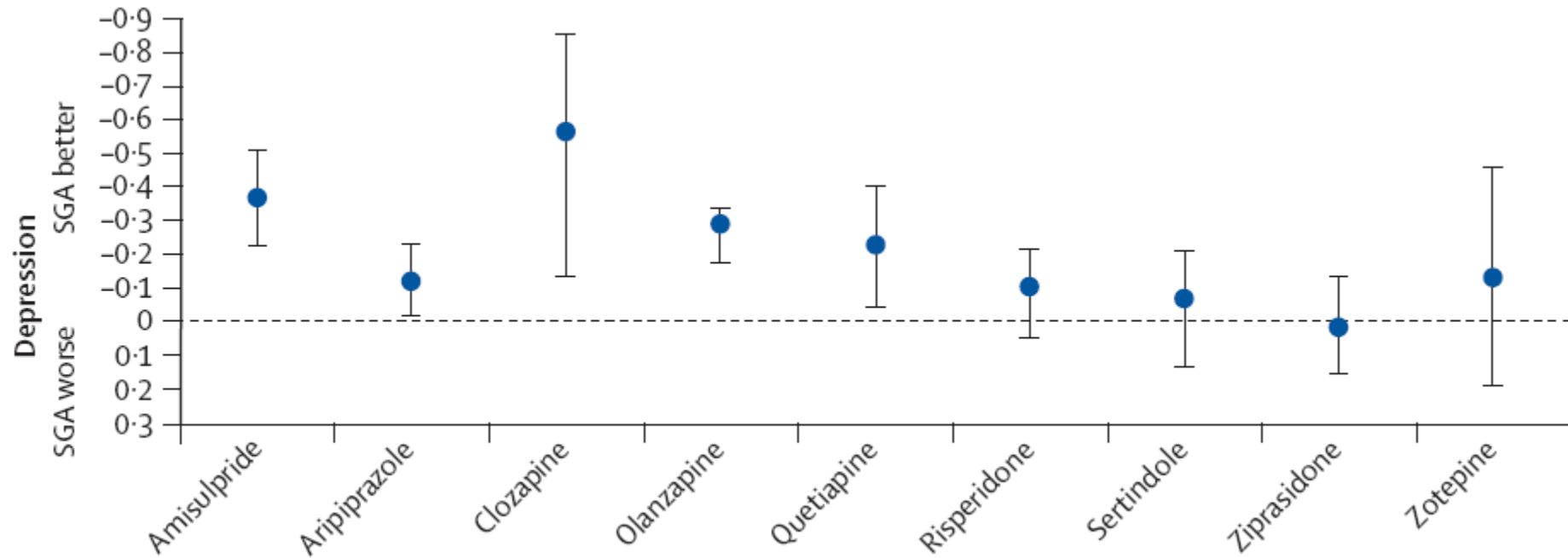
www.thelancet.com **Vol 373** **January 3, 2009**

overall symptoms

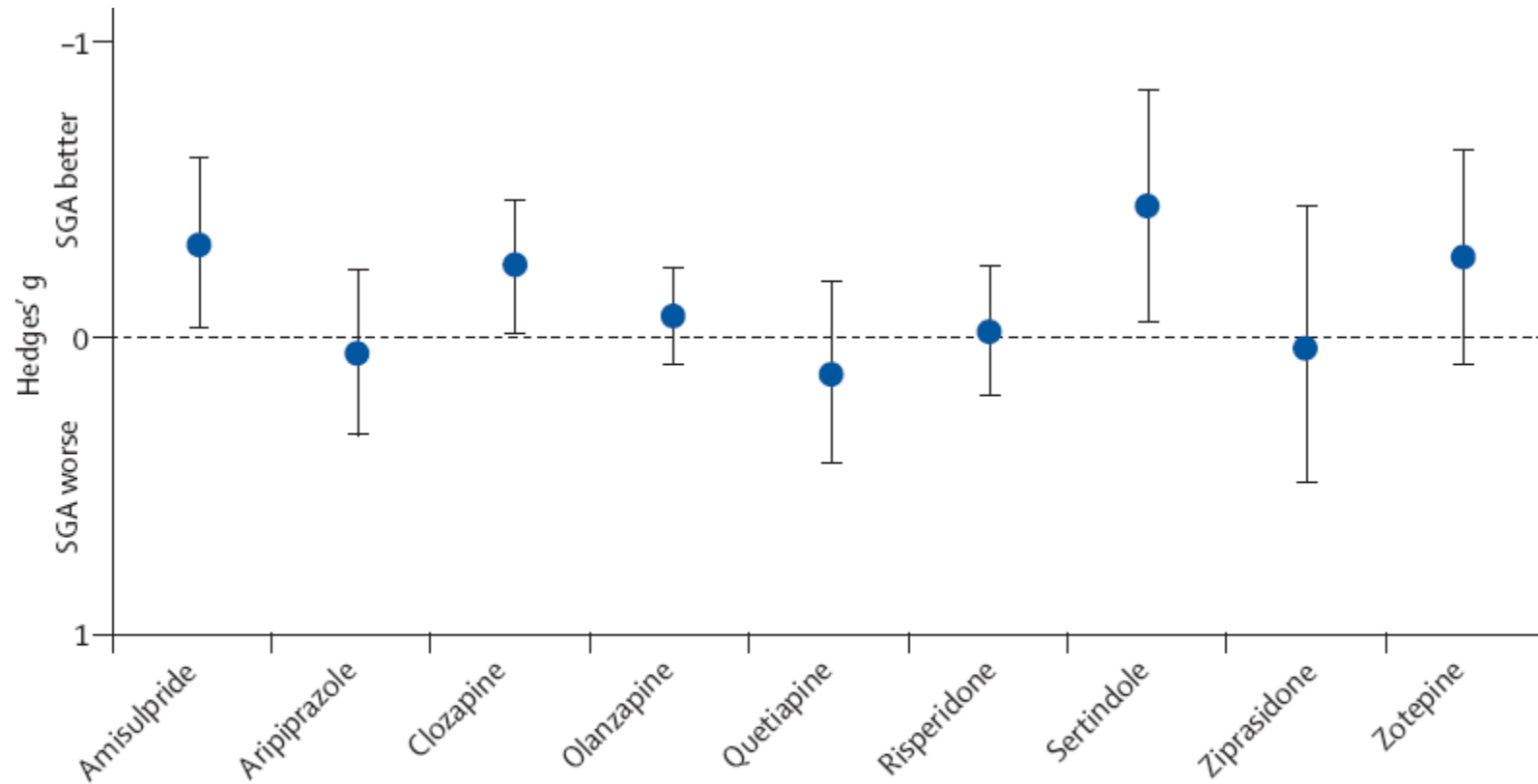




depression

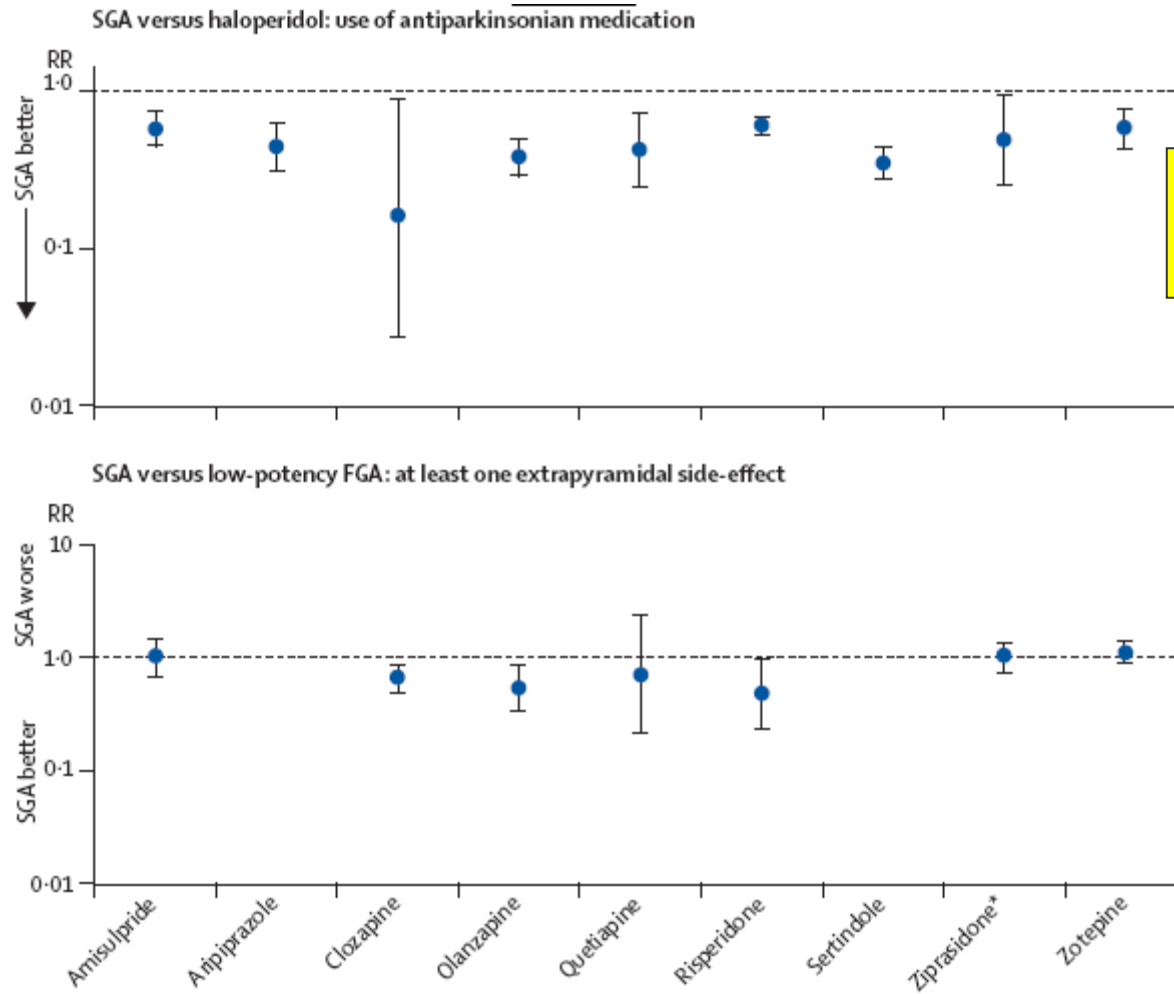


quality of life



Quality of life

www.thelancet.com Vol 373 January 3, 2009



extrapyramidal side-effects

Extrapyramidal side-effects

weight gain

	Number of studies	Number of participants	Mean weight-gain difference (kg; 95% CI)	p value
SGA versus haloperidol				
Amisulpride	2	373	0.9 (0.2 to 1.6)	0.012
Aripiprazole	2	1598	0.6 (-0.1 to 1.2)	0.071
Clozapine	3	170	3.4 (2.0 to 4.9)	<0.0001
Olanzapine	9	2952	3.3 (2.2 to 4.4)	<0.0001
Quetiapine	3	945	1.4 (0.7 to 2.1)	<0.0001
Risperidone	9	1366	1.7 (0.9 to 2.4)	<0.0001
Sertindole	2	779	3.3 (0.2 to 6.4)	0.040
Ziprasidone	1	301	0.1 (-1.2 to 1.3)	0.887
Zotepine	3	321	2.7 (1.7 to 3.7)	<0.0001



DMSP-PSY

Sperimentazioni: CATIE e EUPHEST



CATIE

Clinical Antipsychotic Trials of Intervention Effectiveness

NIMH

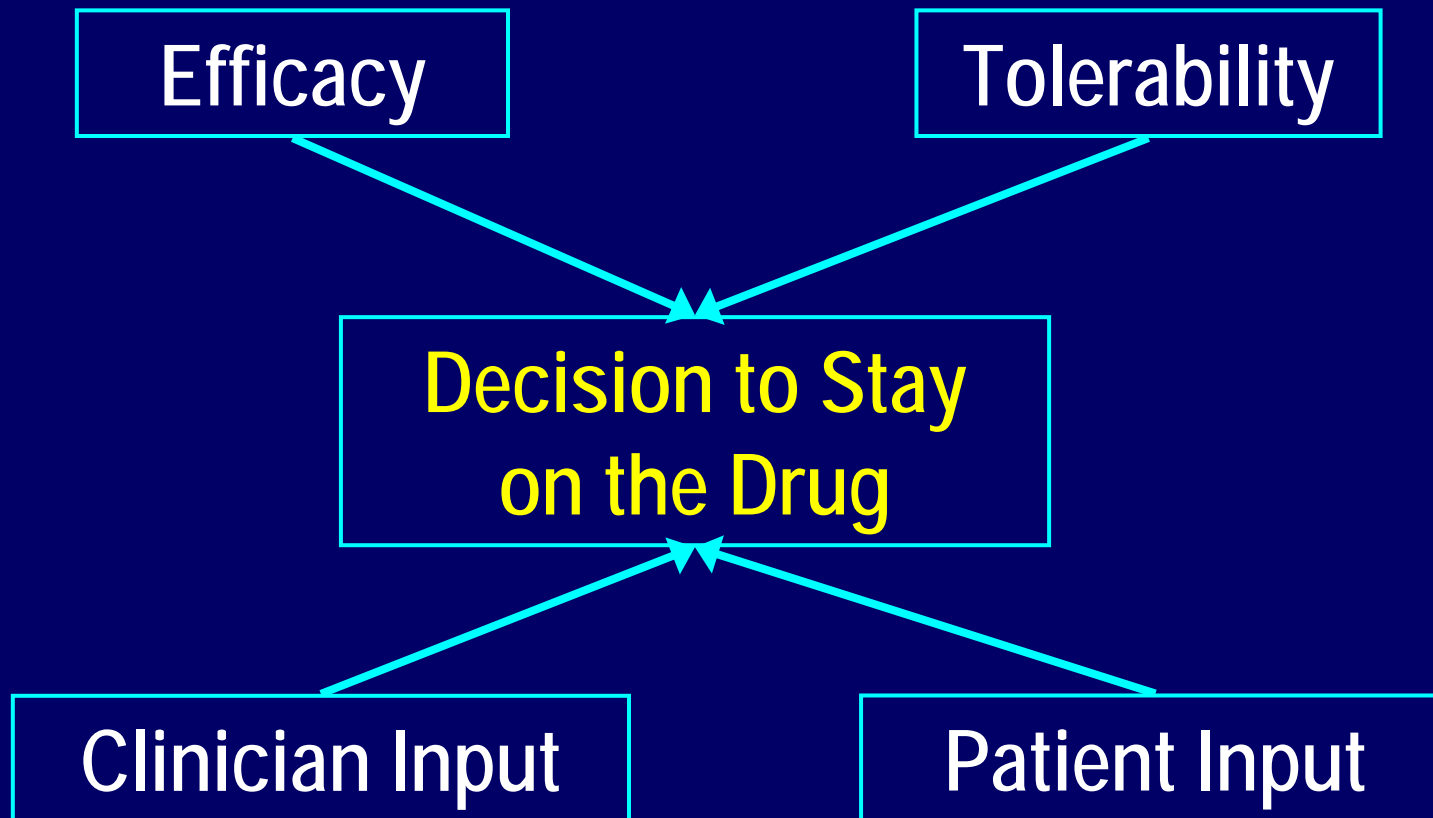
National Institute
of Mental Health

CATIE: Broad Inclusion and Minimal Exclusion Criteria

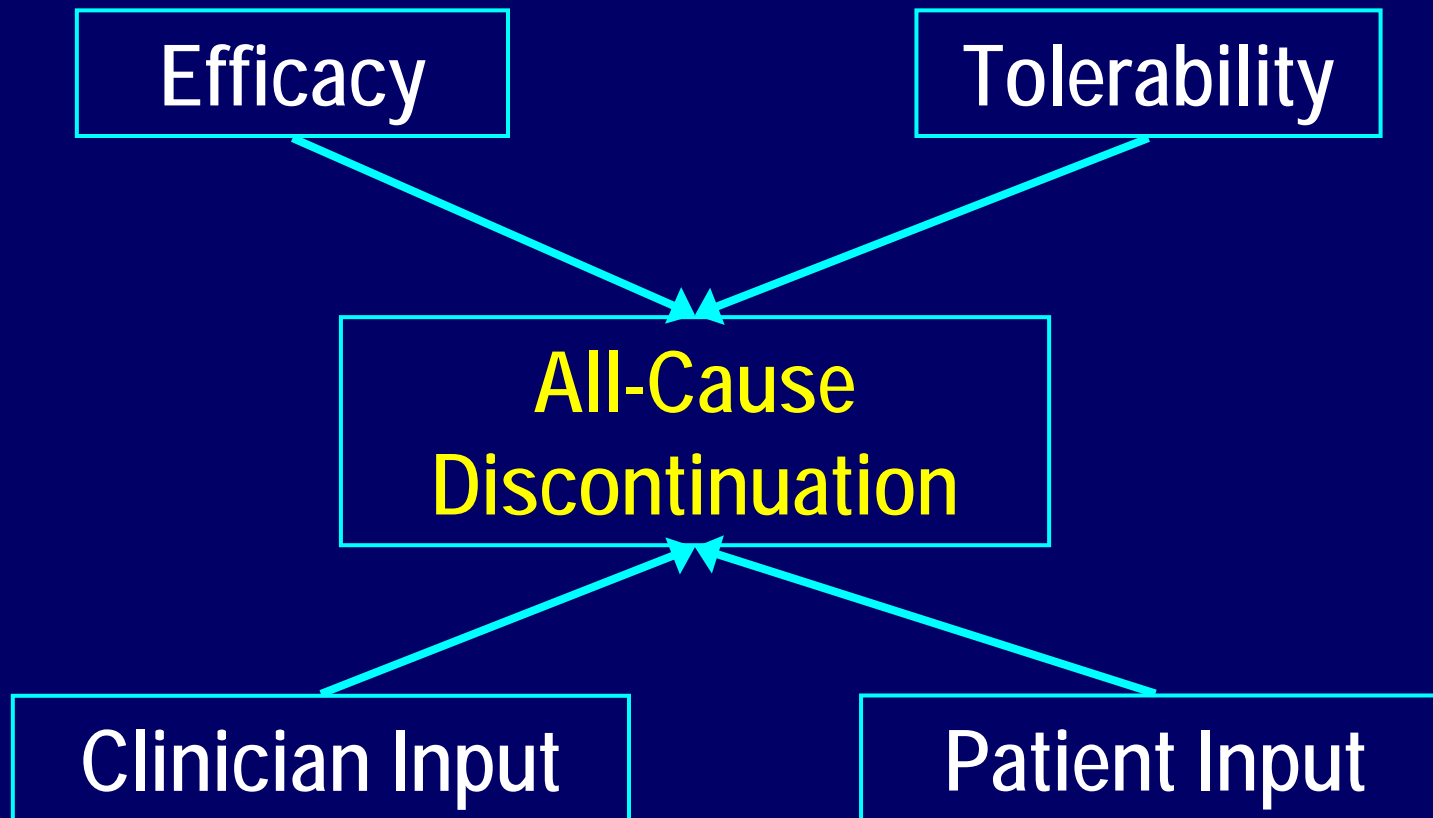
- ◆ DSM-IV schizophrenia, 18-65 years old
- ◆ Not first-episode or treatment-resistant
- ◆ Concomitant medications, medical illnesses, substance use disorders allowed
- ◆ Conducted at 57 geographically, demographically, and organizationally diverse sites

Determinants of Drug Effectiveness

Staying on the Drug Is Critical



Primary Outcome Measure: All-Cause Treatment Discontinuation



Secondary Outcomes

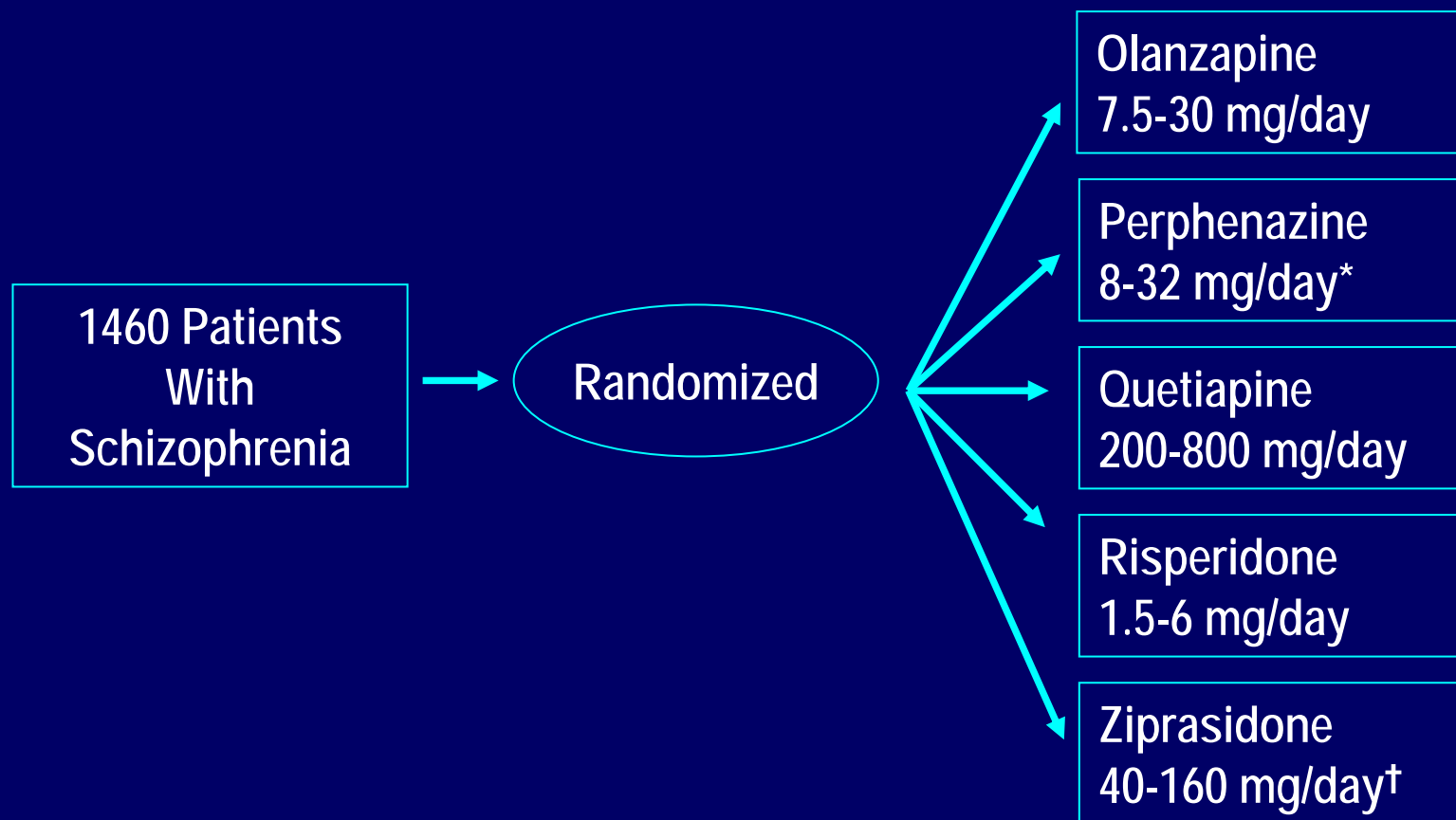
- ◆ Reasons for discontinuation:
 - Efficacy, tolerability, and patient decision
- ◆ Psychopathology
- ◆ Safety
- ◆ Service utilization and costs
- ◆ Neurocognition
- ◆ Treatment adherence
- ◆ Comorbidity
- ◆ Quality of life
- ◆ Substance use
- ◆ Violence

Approaches to EPS in Comparative Studies of First- and Second-Generation Antipsychotic Drugs

- ◆ Anticholinergic drug use as marker of EPS
- ◆ Low-dose strategy (suggested by Geddes et al 2000)
- ◆ Prophylactic anticholinergic drugs with haloperidol (Rosenheck strategy)

EPS=extrapyramidal symptoms.

CATIE Phase 1: Double-Blinded and Randomized



*Persons with TD not assigned to perphenazine.
†Ziprasidone added after 40% sample enrolled.
Stroup TS, et al. *Schizophr Bull.* 2003;29(1):15-31.

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

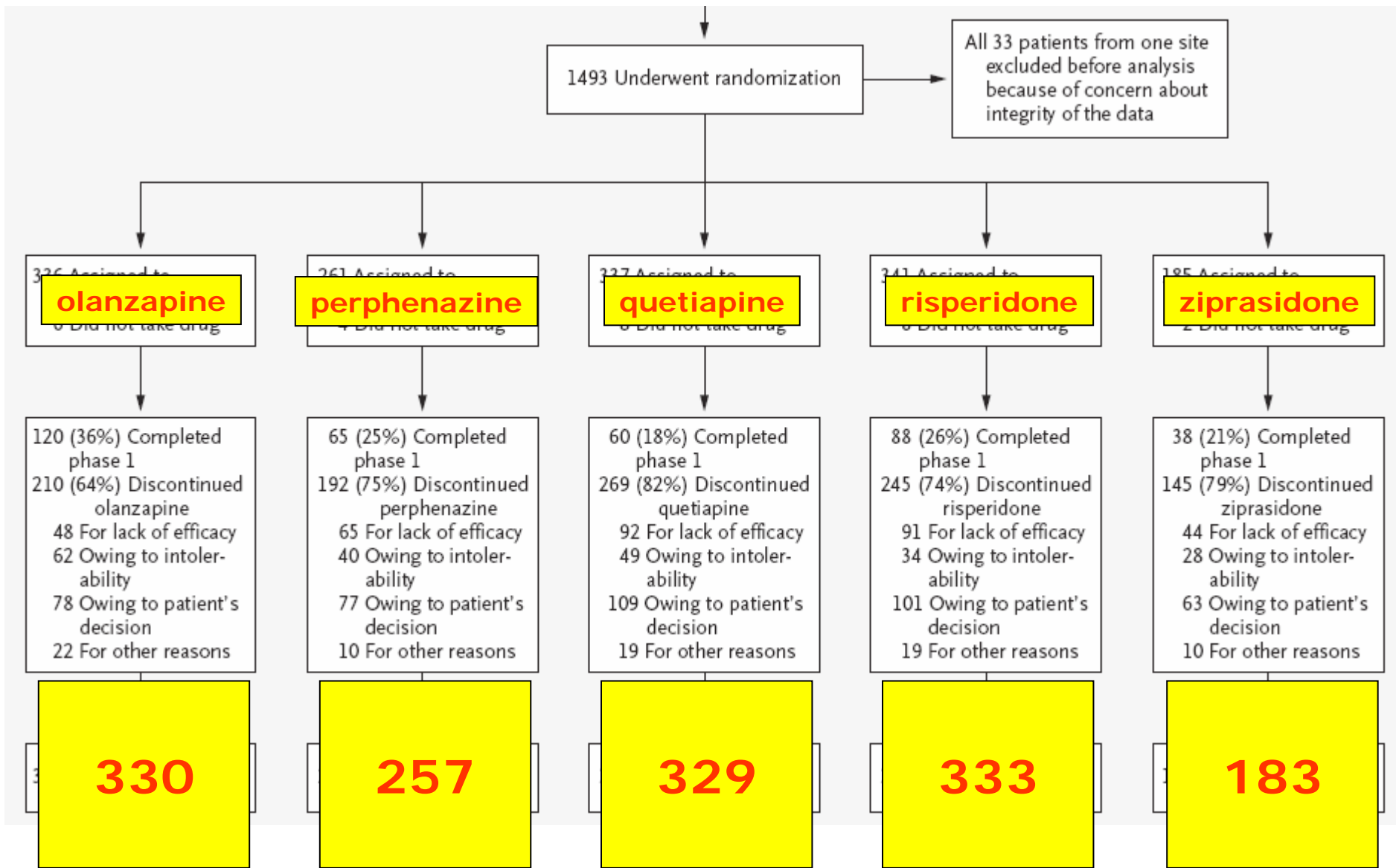
SEPTEMBER 22, 2005

VOL. 353 NO. 12

Effectiveness of Antipsychotic Drugs in Patients
with Chronic Schizophrenia

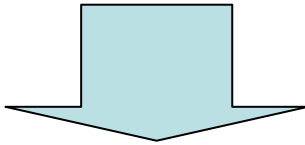
Jeffrey A. Lieberman, M.D., T. Scott Stroup, M.D., M.P.H., Joseph P. McEvoy, M.D., Marvin S. Swartz, M.D.,
Robert A. Rosenheck, M.D., Diana O. Perkins, M.D., M.P.H., Richard S.E. Keefe, Ph.D.,
Sonia M. Davis, Dr.P.H., Clarence E. Davis, Ph.D., Barry D. Lebowitz, Ph.D., Joanne Severe, M.S.,
and John K.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

N ENGL J MED 353;12 WWW.NEJM.ORG SEPTEMBER 22, 2005



METHODS

A total of 1493 patients with schizophrenia were recruited at 57 U.S. sites and randomly assigned to receive olanzapine (7.5 to 30 mg per day), perphenazine (8 to 32 mg per day), quetiapine (200 to 800 mg per day), or risperidone (1.5 to 6.0 mg per day) for up to 18 months. Ziprasidone (40 to 160 mg per day) was included after its approval by the Food and Drug Administration. The primary aim was to delineate differences in the overall effectiveness of these five treatments.



“The primary outcome measure was the discontinuation of treatment for any cause [...]

“... a discrete outcome selected because stopping or changing medication is a frequent occurrence and major problem in the treatment of schizophrenia”

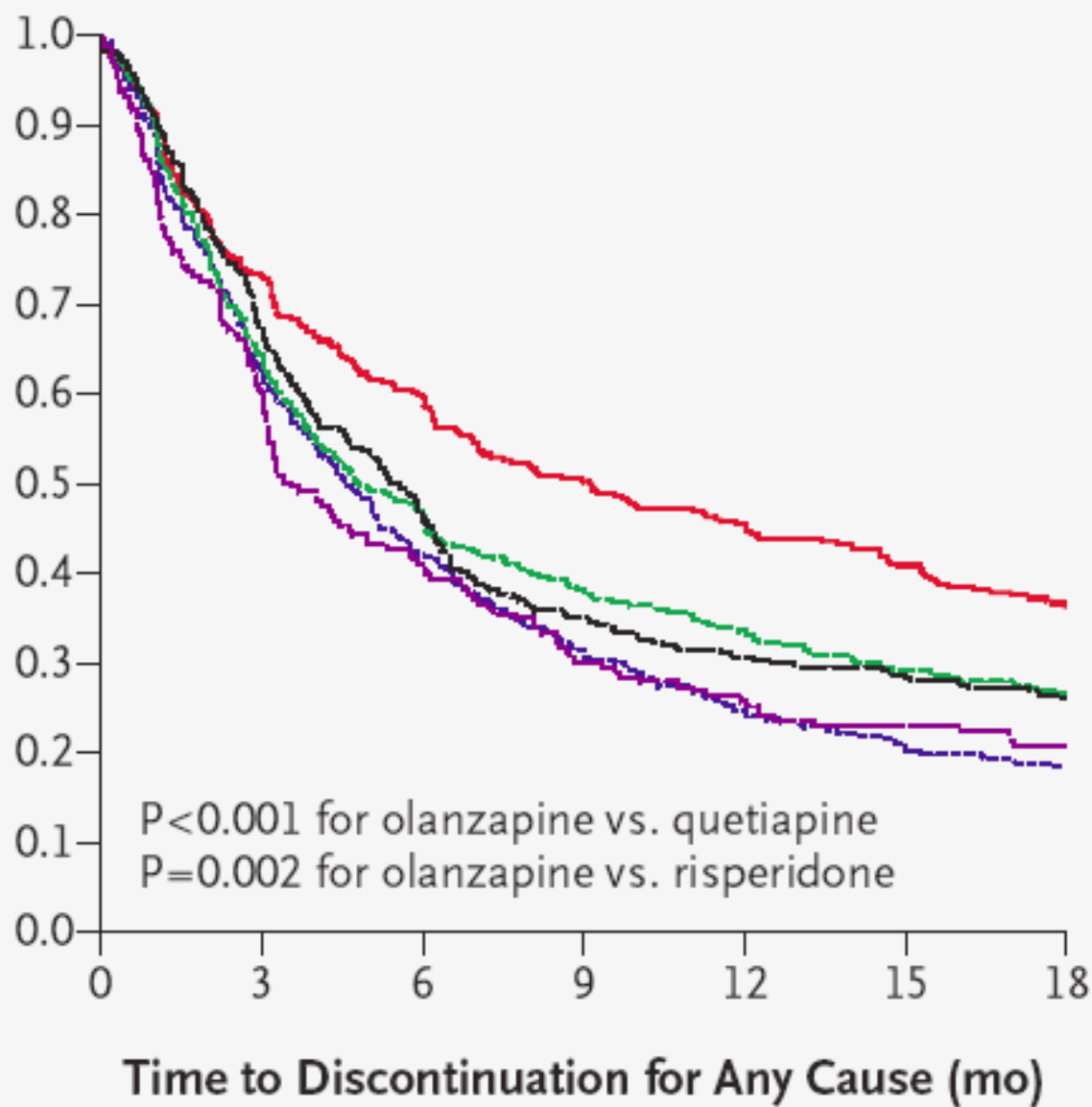
— Olanzapine (N=330)
— Perphenazine (N=257)

— Risperidone (N=333)
— Quetiapine (N=329)

— Ziprasidone (N=183)

N ENGL J MED 353;12 WWW.NEJM.ORG SEPTEMBER 22, 2005

Proportion of Patients without Event



— Olanzapine (N=330) - - - Risperidone (N=333) — Ziprasidone (N=183)
— Perphenazine (N=257) ····· Quetiapine (N=329)

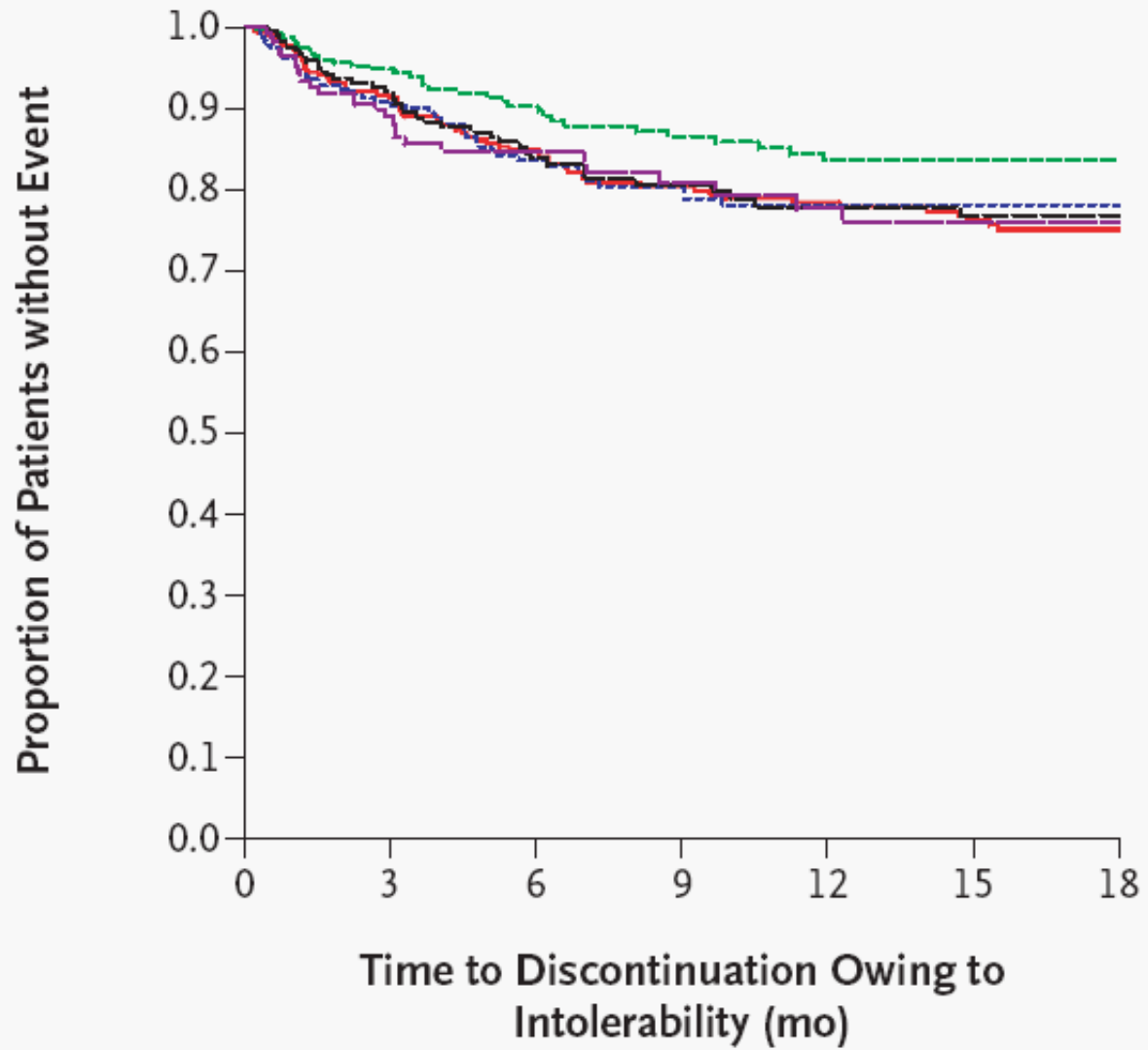


Table 3. Outcome Measures of Safety among Randomized Patients.

Outcome	Olanzapine (N=336)	Quetiapine (N=337)	Risperidone (N=341)	Perphenazine (N=261)*	Ziprasidone (N=185)	P Value†
Hospitalization for exacerbation of schizophrenia						
Hospitalized patients — no. (%)	38 (11)	68 (20)	51 (15)	41 (16)	33 (18)	<0.001
No. of hospitalizations/total person-yr of exposure	81/280	131/199	103/229	89/175	62/109	
Risk ratio	0.29	0.66	0.45	0.51	0.57	
Adverse events — no. (%)						
Any serious adverse event	32 (10)	32 (9)	33 (10)	29 (11)	19 (10)	0.47
Neurologic effects — no./total no. (%)§						
AIMS global severity score ≥2	32/236 (14)	30/236 (13)	38/238 (16)	41/237 (17)	18/126 (14)	0.23
Barnes Akathisia Rating Scale global score ≥3	15/290 (5)	16/305 (5)	20/292 (7)	16/241 (7)	14/158 (9)	0.24
Simpson–Angus Extrapyramidal Signs Scale mean score ≥1	23/296 (8)	12/298 (4)	23/292 (8)	15/243 (6)	6/152 (4)	0.47
Weight change from baseline to last observation¶						
Weight gain >7% — no./total no. (%)	92/307 (30)	49/305 (16)	42/300 (14)	29/243 (12)	12/161 (7)	<0.001
Weight change — lb						
Mean ±SE	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 to 42	-25 to 25	-24 to 24	-29 to 22	-24 to 18	
Weight change — lb/mo of treatment						
Mean ±SE	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 to 9.5	-4.4 to 6.3	-4.6 to 5.7	-4.9 to 4.0	-5.3 to 5.9	

Table 3. Outcome Measures of Safety among Randomized Patients.

Outcome	Olanzapine (N=336)	Quetiapine (N=337)	Risperidone (N=341)	Perphenazine (N=261)*	Ziprasidone (N=185)	P Value†
Change from baseline in laboratory values 						
Blood glucose — mg/dl						
Mean ±SE	15.0±2.8	6.8±2.5	6.7±2.0	5.2±2.0	2.3±3.9	
Median	7.0	4.3	5.5	1.5	2.5	
Exposure-adjusted mean ±SE	13.7±2.5	7.5±2.5	6.6±2.5	5.4±2.8	2.9±3.4	0.59
Glycosylated hemoglobin — %						
Mean ±SE	0.41±0.09	0.05±0.05	0.08±0.04	0.10±0.06	-0.10±0.14	
Median	0.20	0.10	0.05	0.05	0.10	
Exposure-adjusted mean ±SE	0.40±0.07	0.04±0.08	0.07±0.08	0.09±0.09	0.11±0.09	0.01
Cholesterol — mg/dl						
Mean ±SE	9.7±2.1	5.3±2.1	-2.1±1.9	0.5±2.3	-9.2±5.2	
Median	8.5	3.5	-3.0	0.5	-1.0	
Exposure-adjusted mean ±SE	9.4±2.4	6.6±2.4	-1.3±2.4	1.5±2.7	-8.2±3.2	<0.001
Triglycerides — mg/dl						
Mean ±SE	42.9±8.4	19.2±10.6	-2.6±6.3	8.3±11.5	-18.1±9.4	
Median	33.5	17.5	3.0	2.0	-7.0	
Exposure-adjusted mean ±SE	40.5±8.9	21.2±9.2	-2.4±9.1	9.2±10.1	-16.5±12.2	<0.001

Outcome	Olanzapine (N=336)	Quetiapine (N=337)	Risperidone (N=341)	Perphenazine (N=261)*	Ziprasidone (N=185)	P Value†
Change from baseline in laboratory values (cont.)						
Prolactin — ng/dl						
Mean ±SE	-6.1±1.2	-9.3±1.4	15.4±1.5	0.4±1.7	-4.5±1.6	
Median	-0.9	-2.7	9.2	1.4	-2.4	
Exposure-adjusted mean ±SE	-8.1±1.4	-10.6±1.4	13.8±1.4	-1.2±1.6	-5.6±1.9	<0.001
Electrocardiographic findings**						
Mean (±SE) change in corrected QT interval from baseline to last observation — msec	1.2±1.8	5.9±1.9	0.2±1.8	1.4±2.0	1.3±2.2	0.25
Prolonged corrected QT interval — no./total no. (%)	0/231	6/214 (3)	7/218 (3)	2/172 (1)	2/148 (1)	0.03
New cataracts — no./total no. (%)††	3/272 (1)	1/258 (<1)	2/260 (1)	1/210 (<1)	0/142	0.81
Medications added — no. (%)‡‡						
Lithium	1 (<1)	4 (1)	2 (<1)	3 (1)	1 (<1)	0.42
Anticonvulsants	10 (3)	11 (3)	13 (4)	9 (3)	8 (4)	0.63
Antidepressants§§	40 (12)	28 (8)	54 (16)	28 (11)	26 (14)	0.03
Hypnotics, sedatives¶¶	22 (7)	14 (4)	32 (9)	23 (9)	17 (9)	0.03
Anxiolytics	31 (9)	46 (14)	33 (10)	38 (15)	27 (15)	<0.001
Anticholinergic agents	25 (7)	11 (3)	32 (9)	26 (10)	14 (8)	0.01
Oral glucose-lowering drugs, insulin	12 (4)	7 (2)	8 (2)	5 (2)	4 (2)	0.95
Cholestatin drugs	15 (4)	14 (4)	11 (3)	7 (3)	2 (1)	0.28

Effectiveness of antipsychotics

Is the CATIE trial a tsunami?

Emmanuel Stip, MD, MSC, CSPQ Karyne Anselmo

Bottom line

- In general, discontinuation rates were much higher than anticipated.
- Perphenazine is as efficacious as new antipsychotics.
- Olanzapine is superior on several variables but more deleterious metabolically.
- Weight and metabolic parameters were similar among perphenazine and SGAs, except for olanzapine. 🍁

Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial

René S Kahn, W Wolfgang Fleischhacker*, Han Boter, Michael Davidson, Yvonne Vergouwe, Ireneus PM Keet, Mihai D Gheorghe, Janusz K Rybakowski, Silvana Galderisi, Jan Libiger, Martina Hummer, Sonia Dollfus, Juan J López-Ibor, Luchezar G Hranov, Wolfgang Gaebel, Joseph Peuskens, Nils Lindefors, Anita Riecher-Rössler, Diederick E Grobbee, for the EUFEST study group†*

Open randomised controlled trial of haloperidol versus second-generation antipsychotic drugs in 50 sites, in 14 countries.

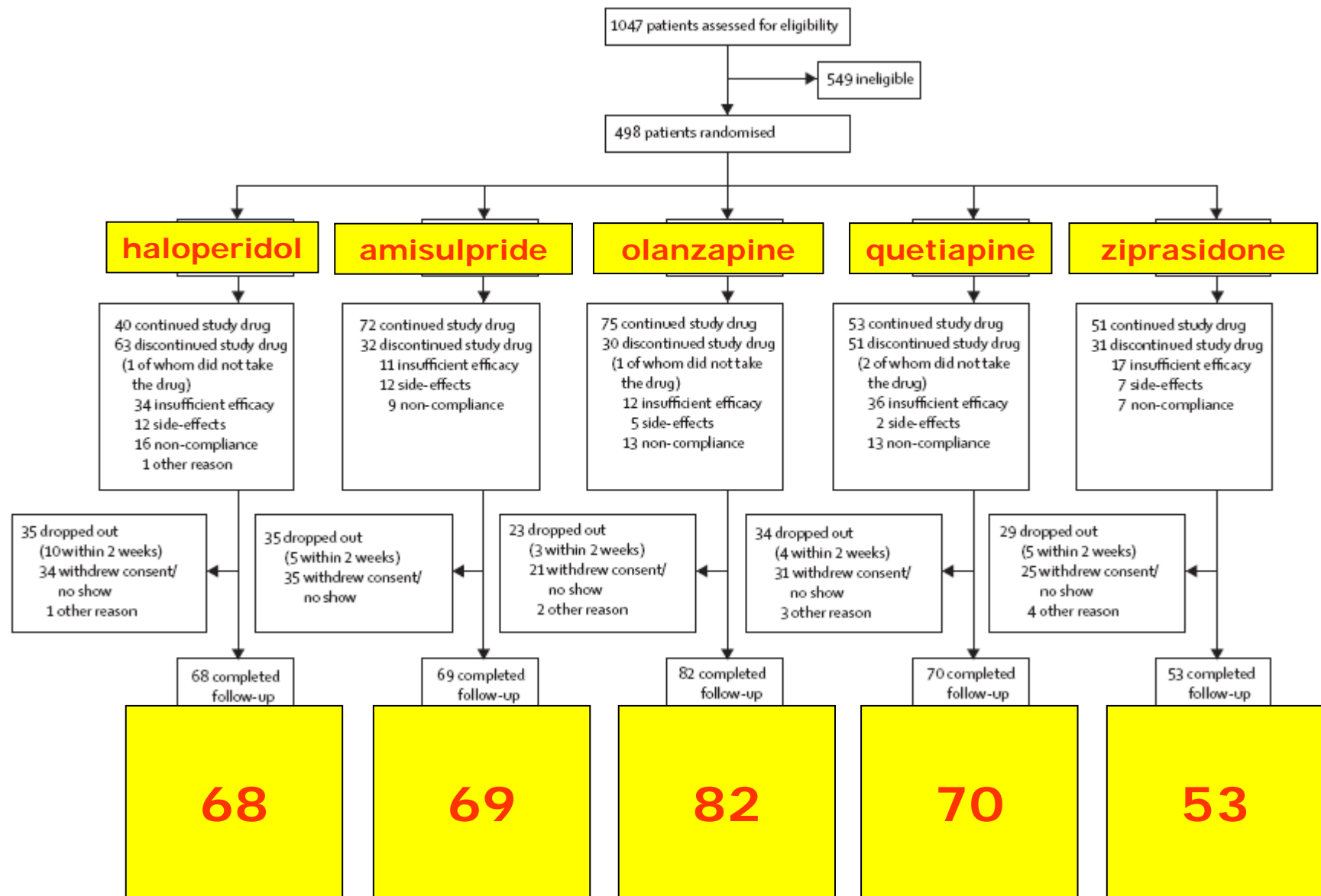
Eligible patients were aged 18–40 years, and met diagnostic criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.

498 patients were randomly assigned to haloperidol (1–4 mg per day; n=103), amisulpride (200–800 mg per day; n=104), olanzapine (5–20 mg per day; n=105), quetiapine (200–750 mg per day; n=104), or ziprasidone (40–160 mg per day; n=82); follow-up was at 1 year.

The primary outcome measure was all-cause treatment discontinuation.

Definizione di first-episode schizofrenia:

“Patients were excluded if more than 2 years had passed since the onset of positive symptoms; if any antipsychotic drug had been used for more than 2 weeks in the previous year, or for 6 weeks at any time.”



	Haloperidol (N=103)	Amisulpride (N=104)	Olanzapine (N=105)	Quetiapine (N=104)	Ziprasidone (N=82)	Total (N=498)
Sociodemographic characteristics						
Age (years)	25.4 (5.6)	25.2 (4.9)	26.3 (5.9)	26.4 (5.7)	26.7 (5.7)	26.0 (5.6)
Women	39/103 (38%)	46/104 (44%)	38/105 (36%)	36/104 (35%)	41/82 (50%)	200/498 (40%)
White	93/103 (90%)	102/104 (98%)	100/105 (95%)	97/104 (93%)	77/82 (94%)	469/498 (94%)
Years of education*	12.4 (2.5)	12.8 (2.9)	12.7 (3.4)	12.0 (2.9)	12.4 (2.6)	12.5 (2.9)
Living alone	14/100 (14%)	12/104 (12%)	12/104 (12%)	20/104 (19%)	8/81 (10%)	66/493 (13%)
Employed or student	42/101 (42%)	55/104 (53%)	46/105 (44%)	46/104 (44%)	42/82 (51%)	231/496 (47%)
Diagnosis†						
Schizophreniform	36/103 (35%)	42/104 (40%)	35/105 (33%)	38/104 (36%)	47/82 (57%)	198/498 (40%)
Schizoaffective	8/103 (8%)	5/104 (5%)	9/105 (9%)	8/104 (8%)	5/82 (6%)	35/498 (7%)
Schizophrenia	59/103 (57%)	57/104 (55%)	61/105 (58%)	58/104 (56%)	30/82 (37%)	265/498 (53%)
Depression (at present)†	9/97 (9%)	5/103 (5%)	9/103 (9%)	17/103 (17%)	6/81 (7%)	46/487 (9%)
Suicidality (at present)†	12/98 (12%)	10/104 (10%)	13/103 (13%)	15/103 (15%)	8/81 (10%)	58/489 (12%)
Substance dependence/abuse (at present)†	23/98 (23%)	16/104 (15%)	24/103 (23%)	29/103 (28%)	20/81 (25%)	112/489 (23%)
Inpatient	87/103 (84%)	97/104 (93%)	101/105 (96%)	89/104 (86%)	71/82 (87%)	445/498 (89%)
Antipsychotic naive	36/103 (35%)	44/104 (42%)	25/105 (24%)	40/104 (38%)	17/82 (21%)	162/498 (33%)
Psychopathology score (PANSS)‡						
Total	88.9 (19.8)	86.4 (19.2)	87.5 (21.1)	91.5 (22.6)	88.3 (20.1)	88.5 (20.6)
Positive scale	22.8 (5.6)	23.0 (6.1)	23.1 (6.3)	23.7 (6.7)	23.0 (6.3)	23.1 (6.2)

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	Haloperidol (N=103)	Amisulpride (N=104)	Olanzapine (N=105)	Quetiapine (N=104)	Ziprasidone (N=82)	p value
Mean dose before discontinuation of treatment (mg/day [SD])	3.0 (1.2)	450.8 (171.9)	12.6 (4.7)	498.6 (201.4)	107.2 (35.0)	
Maximum (or higher) dose received*	56/92 (61%)	26/100 (26%)	54/103 (52%)	39/104 (38%)	37/79 (47%)	<0.0001
Discontinuation for any cause†	63/103 (72%)	32/104 (40%)	30/105 (33%)	51/104 (53%)	31/82 (45%)	
Months to discontinuation (95% CI)‡	0.5 (0.5-0.9)	5.3 (3.0-12+)	6.3 (3.7-12+)	1.2 (0.7-2.0)	1.1 (0.8-8.2)	
Cox-model treatment comparisons (HR [95% CI])§						
Haloperidol		0.37 (0.24-0.57)	0.28 (0.18-0.43)	0.52 (0.35-0.76)	0.51 (0.32-0.81)	<0.0001
Amisulpride			0.74 (0.45-1.23)	1.39 (0.86-2.25)	1.35 (0.79-2.32)	
Olanzapine				1.60 (0.99-2.59)	1.62 (0.92-2.86)	
Quetiapine					1.05 (0.61-1.81)	
Discontinuation because of insufficient efficacy†	34/103 (48%)	11/104 (14%)	12/105 (14%)	36/104 (40%)	17/82 (26%)	
Cox-model treatment comparisons (HR [95% CI])§						
Haloperidol		0.22 (0.11-0.43)	0.20 (0.10-0.38)	0.68 (0.41-1.13)	0.51 (0.27-0.95)	<0.0001
Amisulpride			0.92 (0.40-2.11)	3.04 (1.47-6.32)	2.47 (1.08-5.66)	
Olanzapine				2.95 (1.46-5.95)	2.54 (1.09-5.93)	
Quetiapine					0.89 (0.44-1.79)	

(Continues on next page)

	Haloperidol (N=103)	Amisulpride (N=104)	Olanzapine (N=105)	Quetiapine (N=104)	Ziprasidone (N=82)	p value
(Continued from previous page)						
Discontinuation because of side-effects†	12/103 (20%)	12/104 (20%)	5/105 (6%)	2/104 (3%)	7/82 (14%)	
Cox-model treatment comparisons (HR [95% CI])§						
Haloperidol		0.71(0.32-1.61)	0.26 (0.09-0.75)	0.13 (0.03-0.59)	0.55 (0.20-1.51)	0.023
Amisulpride			0.35 (0.12-1.02)	0.19(0.04-0.89)	0.84 (0.29-2.47)	
Olanzapine				0.38 (0.07-2.10)	1.56 (0.43-5.66)	
Quetiapine					3.13(0.57-17.11)	
Discontinuation because of non-adherence†	16/103 (30%)	9/104 (13%)	13/105 (17%)	13/104 (19%)	7/82 (14%)	
Cox-model treatment comparisons (HR [95% CI])§						
Haloperidol		0.50(0.22-1.15)	0.49 (0.23-1.04)	0.48 (0.22-1.04)	0.50 (0.19-1.32)	0.241
Amisulpride			1.01 (0.42-2.42)	1.04(0.42-2.60)	0.86 (0.30-2.45)	
Olanzapine				0.90(0.40-2.02)	0.84 (0.31-2.32)	
Quetiapine					0.92 (0.31-2.74)	
Discontinuation because of other reasons†	1/103 (4%)	0/104	0/105	0/104	0/82	
HR=hazard ratio. *Proportion of patients who have received the maximum or even a higher dose for at least 1 day. †The percentages are Kaplan-Meier estimates of treatment discontinuation within 12 months. ‡Kaplan-Meier estimates. Months at risk for treatment discontinuation, excluding the first 14 days after randomisation. For amisulpride and olanzapine no upper limit for the CI could be estimated because the upper limit is above the maximum follow-up time. The 95% CI includes the true population 25th percentile with probability 0.95. §Cox proportional-hazards regression models, with adjustments for country.						
Table 2: Treatment doses and treatment discontinuation by allocated treatment						

	Haloperidol	Amisulpride	Olanzapine	Quetiapine	Ziprasidone	p value
Psychopathology score (PANSS)	53.3 (1.7)	52.1 (1.8)	52.4 (1.7)	52.9 (1.7)	53.1 (2.0)	0.70
Severity of illness score (CGI)	3.0 (0.3)	2.3 (0.3)	2.4 (0.3)	2.9 (0.3)	2.5 (0.3)	0.0006
Overall functioning score (GAF)	64.3 (3.5)	74.4 (3.6)	68.3 (3.5)	64.2 (3.5)	66.8 (3.8)	0.006
Depression score (CDSS)	1.9 (0.2)	1.8 (0.2)	1.8 (0.2)	1.9 (0.2)	1.9 (0.3)	0.94
Quality-of-life score (MANSA)	4.7 (0.7)	4.7 (0.07)	4.7 (0.07)	4.7 (0.07)	4.8 (0.08)	0.12
Adherence with antipsychotic drugs	5.8 (0.11)	6.0 (0.11)	6.0 (0.11)	5.8 (0.11)	5.9 (0.13)	0.15

Data are mean (SE) after 12 months follow-up adjusted for baseline values and country. Adherence with antipsychotic drugs was only adjusted for country, since adherence could not be assessed at baseline. PANSS=positive and negative syndrome scale. CGI=clinical global impression. GAF=global assessment of functioning. CDSS=Calgary depression scale for schizophrenia. MANSA=Manchester short assessment of quality of life scale.

Table 3: Outcomes of efficacy

	Haloperidol	Amisulpride	Olanzapine	Quetiapine	Ziprasidone	p value
Admission to psychiatric hospital						
Admitted to hospital after randomisation/at risk for admission	14/64 (22%)	14/88 (16%)	18/89 (20%)	14/60 (23%)	4/60 (7%)	0.094
Admissions to hospital after randomisation/total patient-years at risk for admission (rate)	16/31.5 (0.51)	18/52.4 (0.34)	29/60.0 (0.48)	18/36.0 (0.50)	6/34.0 (0.18)	0.055
Adverse events						
Any serious adverse event	5/103 (5%)	3/104 (3%)	5/105 (5%)	3/104 (3%)	0/82 (0%)	*
Extrapyramidal symptoms (SHRS)[†]						
Akathisia	19/73 (26%)	15/94 (16%)	10/97 (10%)	11/85 (13%)	19/68 (28%)	0.007
Dystonia	1/73 (1%)	3/94 (3%)	0/97 (0%)	1/85 (1%)	2/68 (3%)	*
Parkinsonism	25/73 (34%)	16/94 (17%)	6/97 (6%)	9/85 (11%)	11/68 (16%)	<0.0001
Dyskinesia	2/73 (3%)	1/94 (1%)	0/97 (0%)	0/85 (0%)	0/68 (0%)	*
Sexual dysfunction (UKU)[†]						
Men	15/48 (31%)	14/48 (29%)	15/60 (25%)	16/57 (28%)	19/35 (54%)	0.101
Women	11/24 (46%)	21/45 (47%)	18/38 (47%)	10/28 (36%)	11/33 (33%)	0.774
Weight[‡]						
Overweight (BMI ≥ 25 kg/m ²)	16/43 (37%)	31/72 (43%)	45/83 (54%)	25/55 (45%)	14/43 (33%)	0.585
Weight gain >7% from baseline	23/43 (53%)	45/72 (63%)	71/83 (86%)	36/55 (65%)	16/43 (37%)	0.053
Weight change from baseline (kg)	7.3 (1.8)	9.7 (1.7)	13.9 (1.7)	10.5 (1.8)	4.8 (1.9)	<0.0001

	Haloperidol	Amisulpride	Olanzapine	Quetiapine	Ziprasidone	p value
(Continued from previous page)						
Cholesterol (mmol/L)§						
Hypercholesterolemia**	15/33 (45%)	24/53 (45%)	37/66 (56%)	12/43 (28%)	17/32 (53%)	0.276
Change from baseline						
Mean (SE)	0.5 (0.3)	0.7 (0.2)	0.8 (0.1)	0.6 (0.1)	0.4 (0.2)	
Median (IQR)	0.7 (-0.2 to 1.3)	0.5 (0.1 to 1.4)	0.7 (0.2 to 1.3)	0.6 (0.1 to 1.1)	0.3 (-0.2 to 1.0)	
Per month in study	0.04 (0.05)	0.11 (0.02)	0.11 (0.02)	0.07 (0.02)	0.04 (0.02)	0.144
Prolactin (U/L)§						
Hyperprolactinaemia¶	12/27 (44%)	42/47 (89%)	29/58 (50%)	15/37 (41%)	12/24 (46%)	0.017
Change from baseline						
Mean (SE)	-0.4 (0.3)	0.5 (0.2)	-0.2 (0.1)	-0.2 (0.1)	-1.2 (0.4)	
Median (IQR)	0.0 (-0.3 to 0.1)	0.5 (0.1 to 1.4)	-0.2 (-0.6 to 0.1)	-0.1 (-0.4 to 0.1)	-0.4 (-2.7 to 0.1)	
Per month in study	-0.04 (0.03)	0.12 (0.04)	-0.03 (0.02)	-0.04 (0.02)	-0.16 (0.05)	<0.0001
Fasting glucose (mmol/L)§						
Hyperglycaemia	6/33 (18%)	11/53 (21%)	19/63 (30%)	9/41 (22%)	7/32 (22%)	0.794
Change from baseline						
Mean (SE)	0.4 (0.2)	0.5 (0.1)	0.5 (0.1)	0.5 (0.1)	0.2 (0.2)	
Median (IQR)	0.3 (0.0 to 0.9)	0.5 (0.0 to 1.0)	0.5 (0.1 to 1.0)	0.4 (0.0 to 0.9)	0.3 (-0.2 to 0.9)	
Per month in study	0.04 (0.03)	0.07 (0.02)	0.07 (0.02)	0.06 (0.02)	0.04 (0.02)	0.699
Electrocardiographical findings						
Prolonged QTc interval¶¶	1/19 (5%)	1/42 (2%)	3/43 (7%)	2/22 (9%)	0/21 (0%)	0.459
Concomitant drug						
Lithium	0/103 (0%)	0/104 (0%)	3/105 (3%)	3/104 (3%)	0/82 (0%)	*
Mood stabilisers/anticonvulsants	26/103 (25%)	19/104 (18%)	25/105 (24%)	26/104 (25%)	17/82 (21%)	0.096
Antidepressants	19/103 (18%)	13/104 (13%)	30/105 (29%)	6/104 (6%)	8/82 (10%)	<0.0001
Hypnotics or sedatives	17/103 (17%)	17/104 (16%)	24/105 (23%)	24/104 (23%)	15/82 (18%)	0.366
Anxiolytic drugs	53/103 (51%)	56/104 (54%)	58/105 (55%)	50/104 (48%)	36/82 (44%)	0.170
Anticholinergic drugs	46/103 (45%)	35/104 (34%)	23/105 (22%)	20/104 (19%)	18/82 (22%)	<0.0001

Interpretation This pragmatic trial suggests that clinically meaningful antipsychotic treatment of first-episode of schizophrenia is achievable, for at least 1 year. However, we cannot conclude that second-generation drugs are more efficacious than is haloperidol, since discontinuation rates are not necessarily consistent with symptomatic improvement.

Funding AstraZeneca, Pfizer, Sanofi-Aventis.

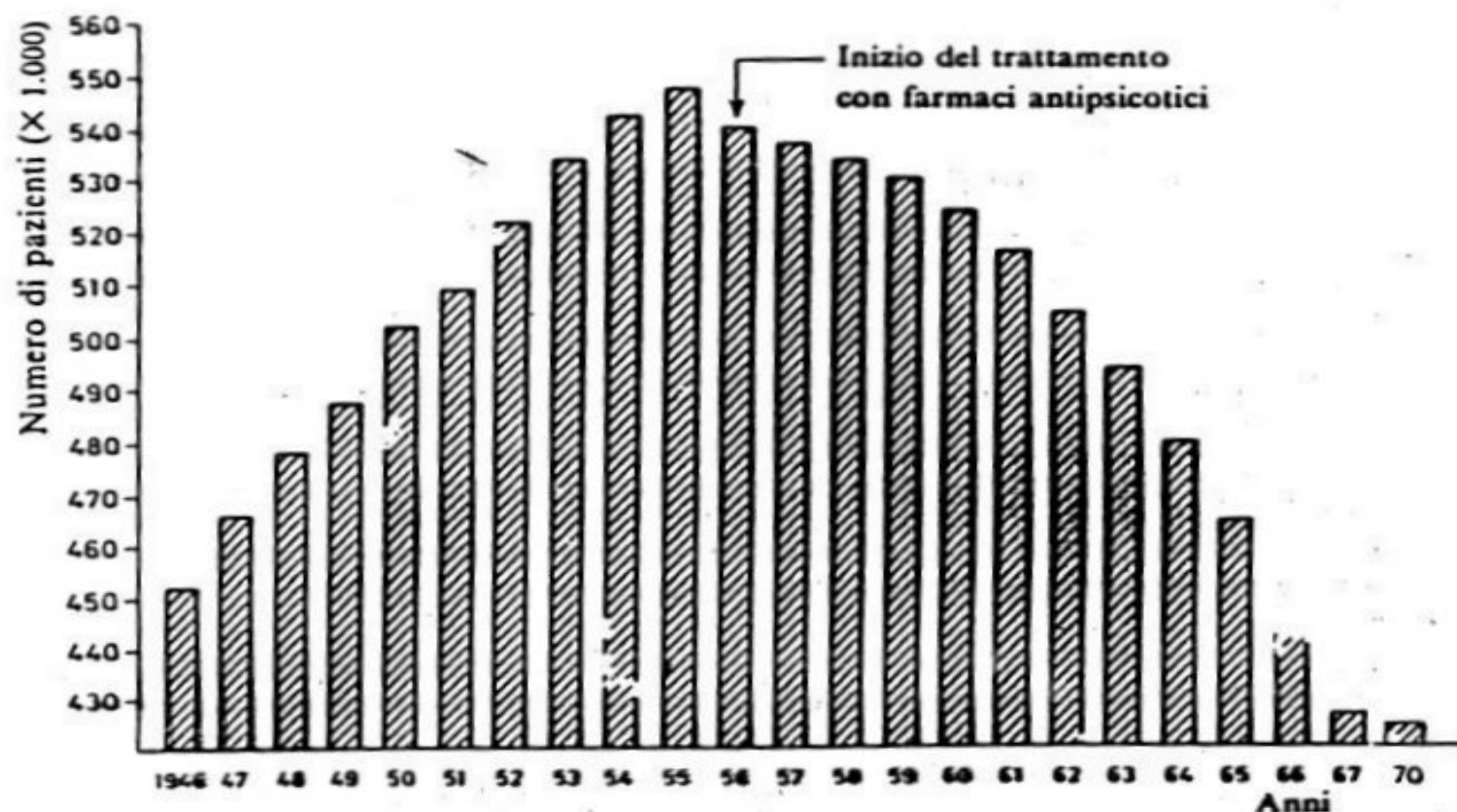


Fig. 1 Effetto della introduzione dei farmaci antipsicotici sul numero di pazienti ricoverati in ospedali psichiatrici americani nel periodo 1946-1970 (modificata da V.G. Longo, *Neuropharmacology and Behavior*, W.H. Freeman and Co., San Francisco, 1972). È da tenere presente che la riduzione dei ricoveri ottenuta attraverso la terapia neurolettica è ancora più vistosa di quanto appaia nella figura, se si considera l'aumento relativo della popolazione generale.



I nuovi antipsicotici differiscono dai vecchi per quanto riguarda il profilo di tollerabilità!

Differenza qualitativa:

- Effetti extrapiramidali**
- Anomalie metaboliche**
- Eventi cerebrovascolari/mortalità**

Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes

AMERICAN DIABETES ASSOCIATION
AMERICAN PSYCHIATRIC ASSOCIATION

AMERICAN ASSOCIATION OF CLINICAL
ENDOCRINOLOGISTS
NORTH AMERICAN ASSOCIATION FOR THE
STUDY OF OBESITY

HT 2004 Physicians Postgraduate Press, Inc.
J Clin Psychiatry 65:2, February 2004.

Table 2.
SGA's and Metabolic Abnormalities

Drug	Weight gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/-	-	-
Ziprasidone*	+/-	-	-

+ = increase effect; - = no effect; D = discrepant results. *Newer drugs with limited long-term data.

Table 3.
Monitoring Protocol for Patients on SGAs*

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually
Personal/family history	X					X
Weight (BMI)	X	X	X	X	X	
Waist circumference	X					X
Blood pressure	X			X		X
Fasting plasma glucose	X			X		X
Fasting lipid profile	X			X		

*More frequent assessments may be warranted based on clinical status

This potential relationship is of considerable clinical concern because obesity and diabetes are important risk factors for CVD, and the relative risk of CVD mortality is significantly greater in people with psychiatric disorders than in the general population.



DMSP-PSY

ANTIPSIKOTICI E ANZIANI

Table 1: Incidence of cerebrovascular events among elderly patients with dementia in placebo-controlled trials of olanzapine⁴

Study no.	Group; % (and no.) of patients with adverse cerebrovascular event	
	Olanzapine	Placebo
HGAO	0 (0/118)	0.8 (1/118)
HGEU*	0.6 (1/159)	0 (0/47)
HGGU	2.5 (5/204)	0 (0/94)
HGIC	2.8 (5/177)	1.1 (1/90)
HGIV†	0.8 (4/520)	0 (0/129)
All	1.3 (15/1178)	0.4 (2/478)

*Street et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. *Arch Gen Psychiatry* 2000;57:968-76.

†De Deyn PP, et al. Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2004;19:115-26.

Table 1: Incidence of cerebrovascular adverse events in elderly patients in placebo-controlled trials of risperidone

Study	Group; % (and no.) of patients with adverse event	
	Risperidone	Placebo
AUS-5	9 (15/167)	2 (3/170)
INT-24	8 (9/115)	2 (2/114)
USA-63	1 (5/462)	1 (2/163)
BEL-14	0 (0/20)	0 (0/19)
Total†	4 (29/764)	2 (7/466)

FDA warns about using antipsychotic drugs for dementia

The US Food and Drug Administration issued a public health advisory warning of fatal adverse events in patients with dementia treated with atypical antipsychotic drugs. Seventeen controlled studies of elderly patients with dementia have shown that patients treated with the drugs were 1.6 to 1.7 times more likely to die than patients given placebo. The causes of death included congestive heart failure, sudden death, and infections, such as pneumonia.

The drugs affected include aripiprazole (Abilify), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), clozapine (Clozaril), and ziprasidone (Geodon). A drug used for depression associated with bipolar disorder, olanzapine (Symbyax), was included in the advisory warning.

bmj.com news roundup

Full versions of these stories are available at: [bmj.com/content/vol330/issue7497/#NEWS_ROUNDUP](https://www.bmj.com/content/vol330/issue7497/#NEWS_ROUNDUP)

Do Atypical Antipsychotics Cause Stroke?

Nathan Herrmann and Krista L. Lanctôt

Division of Geriatric Psychiatry, University of Toronto, Toronto, Ontario, Canada

The association between atypical antipsychotics and cerebrovascular adverse events requires further clarification.

At the present time, this association is another factor that clinicians should consider when weighing the risks and benefits of treating behavioural and psychological disturbances in elderly dementia patients.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications

Philip S. Wang, M.D., Dr.P.H., Sebastian Schneeweiss, M.D., Jerry Avorn, M.D.,
Michael A. Fischer, M.D., Helen Mogun, M.S., Daniel H. Solomon, M.D., M.P.H.,
and M. Alan Brookhart, Ph.D.

N ENGL J MED 353;22 WWW.NEJM.ORG DECEMBER 1, 2005

**retrospective cohort study involving 22,890 patients
65 years of age or older who began receiving a
conventional or atypical antipsychotic medication**

**risk of death within 180 days, less than 40 days, 40
to 79 days, and 80 to 180 days after the initiation of
therapy with an antipsychotic medication**

**we controlled for potential confounding
variables**

N ENGL J MED 353;22 WWW.NEJM.ORG DECEMBER 1, 2005

Table 2. Relative Risk of Death within 180 Days after Beginning Therapy with Conventional as Compared with Atypical Antipsychotic Medications.*

Model	Hazard Ratio (95% CI)
Unadjusted analysis	1.51 (1.43–1.59)
Adjusted analysis†	
Use of any conventional APM	1.37 (1.27–1.49)
Low dose of conventional APM (<median)	1.14 (1.04–1.26)
High dose of conventional APM (>median)	1.73 (1.57–1.90)
Adjusted analysis of death‡	
<40 Days after beginning therapy	1.56 (1.37–1.78)
40–79 Days after beginning therapy	1.37 (1.19–1.59)
80–180 Days after beginning therapy	1.27 (1.14–1.41)
Adjusted analysis of patient subgroups‡	
With dementia	1.29 (1.15–1.45)
Without dementia	1.45 (1.30–1.63)
In a nursing home	1.26 (1.08–1.47)
Not in a nursing home	1.42 (1.29–1.56)

* APM denotes antipsychotic medication, and CI confidence interval.

† Hazard ratios were adjusted for calendar year, age, sex, race, the presence or absence of cardiac arrhythmias, cerebrovascular disease, congestive heart failure, diabetes, myocardial infarction, other ischemic heart disease, other cardiovascular disorders, cancer, HIV infection, dementia, delirium, mood disorders, psychotic disorders, other psychiatric disorders, and the use or nonuse of other psychiatric medications, total number of medications used, hospitalizations, and nursing home stays.

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

OCTOBER 12, 2006

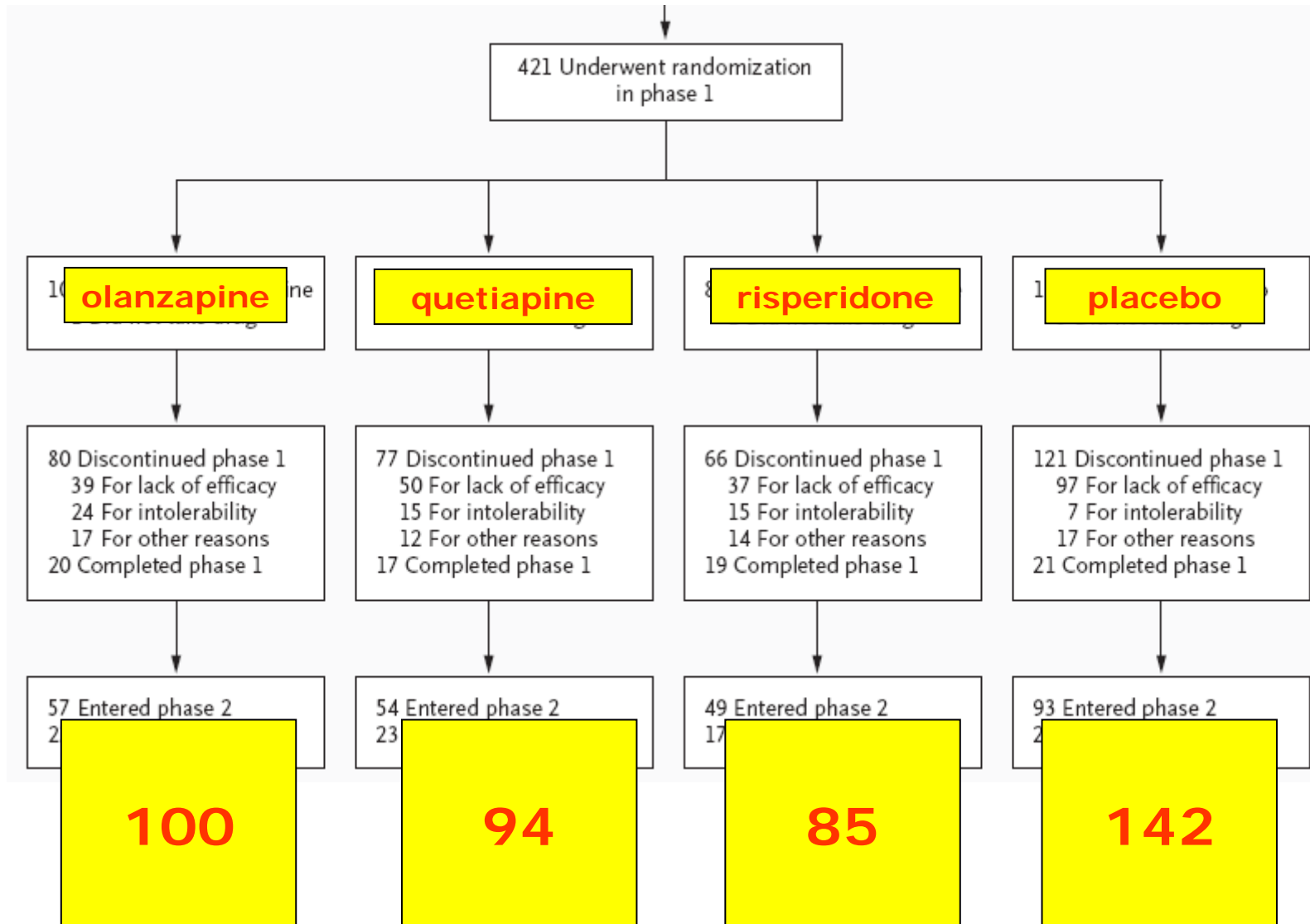
VOL. 355 NO. 15

Effectiveness of Atypical Antipsychotic Drugs
in Patients with Alzheimer's Disease

Lon S. Schneider, M.D., Pierre N. Tariot, M.D., Karen S. Dagerman, M.S., Sonia M. Davis, Dr.P.H.,
John K. Hsiao, M.D., M. Saleem Ismail, M.D., Barry D. Lebowitz, Ph.D., Constantine G. Lyketsos, M.D., M.H.S.,
J. Michael Ryan, M.D., T. Scott Stroup, M.D., David L. Sultzer, M.D., Daniel Weintraub, M.D.,
and Jeffrey A. Lieberman, M.D., for the CATIE-AD Study Group*

METHODS

In this 42-site, double-blind, placebo-controlled trial, 421 outpatients with Alzheimer's disease and psychosis, aggression, or agitation were randomly assigned to receive olanzapine (mean dose, 5.5 mg per day), quetiapine (mean dose, 56.5 mg per day), risperidone (mean dose, 1.0 mg per day), or placebo. Doses were adjusted as needed, and patients were followed for up to 36 weeks. The main outcomes were the time from initial treatment to the discontinuation of treatment for any reason and the number of patients with at least minimal improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks.



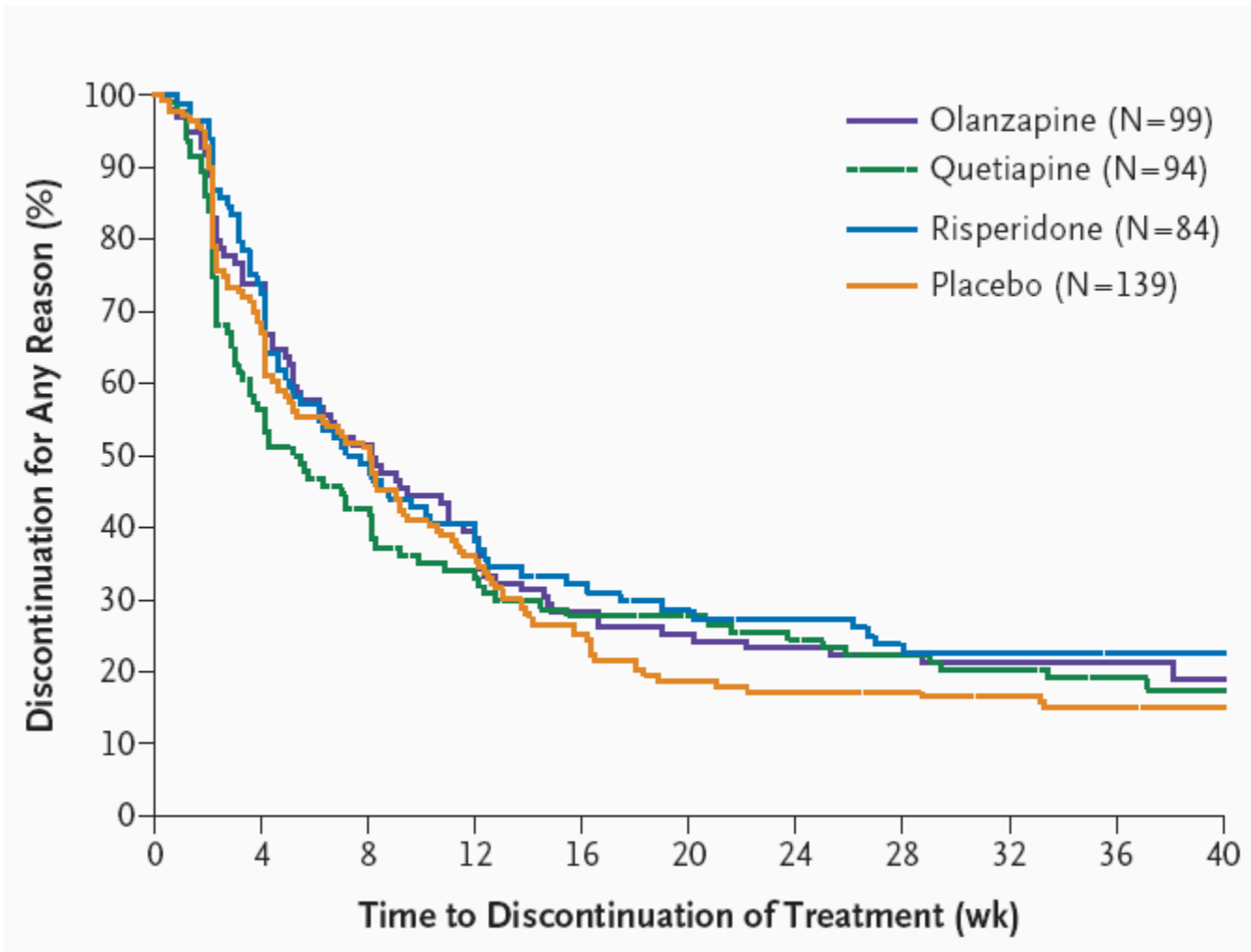


Table 3. (Continued.)

Variable	Olanzapine Group (N= 100)	Quetiapine Group (N=94)	Risperidone Group (N=85)	Placebo Group (N=142)	P Value (Overall Comparison)
Weight change — lb/mo of treatment	1.0±0.4	0.4±0.6	0.7±0.4	-0.9±0.3	0.003
P value for comparison with placebo	0.001	0.03	0.008		
Change in body-mass index from baseline to last observation					
Change	0.3±0.1	0.2±0.1	0.3±0.1	-0.2±0.1	0.001
P value for comparison with placebo	0.001	0.02	0.001		
Change in laboratory values from baseline to last observation^f					
Glucose — mg/dl	11.2±5.7	2.5±6.4	5.6±6.0	-1.2±5.0	0.28
Total cholesterol — mg/dl	-11.3±4.6	-1.9±5.2	-7.5±4.9	-7.5±4.2	0.67
Triglycerides — mg/dl	20.1±10.2	16.0±11.5	1.3±10.9	11.9±9.4	0.40
Prolactin — mg/dl	4.1±3.6	-4.4±4.2	44.5±3.7	-4.6±3.4	<0.001
Electrocardiographic findings					
Change in corrected QT interval from baseline to last observation — msec	-6.1±5.5	-0.1±4.4	5.1±4.7	4.8±4.9	0.27
Prolonged corrected QT interval — no./total no. (%)	0/37	3/31 (10)	1/32 (3)	4/52 (8)	0.19

Table 3. Adverse Events and Other Safety Outcomes in Phase 1.*					
Variable	Olanzapine Group (N=100)	Quetiapine Group (N=94)	Risperidone Group (N=85)	Placebo Group (N=142)	P Value (Overall Comparison)
Adverse event — no. (%)					
Any serious adverse event†	14 (14)	17 (18)	9 (11)	19 (13)	0.35
Cerebrovascular accident or transient ischemic attack	2 (2)	1 (1)	1 (1)	1 (1)	0.92
Death	1 (1)	3 (3)	1 (1)	3 (2)	0.68
Any severe adverse event	17 (17)	24 (26)	12 (14)	21 (15)	0.11
Any adverse event	71 (71)	59 (63)	62 (73)	83 (58)	0.84
Parkinsonism or extrapyramidal signs	12 (12)	2 (2)	10 (12)	1 (1)	<0.001
Gait disturbance	4 (4)	3 (3)	1 (1)	3 (2)	0.66
Sedation	24 (24)	21 (22)	13 (15)	7 (5)	<0.001
Neurologic effects — no./total no. (%)‡					
AIMS global severity score ≥2	1/73 (1)	2/55 (4)	2/64 (3)	1/96 (1)	0.62
Barnes Akathisia Rating Scale global score ≥3	1/73 (1)	1/55 (2)	0/64	0/96	0.33
Simpson–Angus Extrapyramidal Signs Scale mean score ≥1	10/73 (14)	5/54 (9)	7/64 (11)	2/94 (2)	0.03
P value for comparison with placebo	0.02	0.10	0.04		

CONCLUSIONS

Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease. (ClinicalTrials.gov number, NCT00015548.)

N ENGL J MED 355;15 WWW.NEJM.ORG OCTOBER 12, 2006



DMSP-PSY

Associazioni tra antipsicotici

Antipsychotic Combinations vs Monotherapy in Schizophrenia: A Meta-analysis of Randomized Controlled Trials

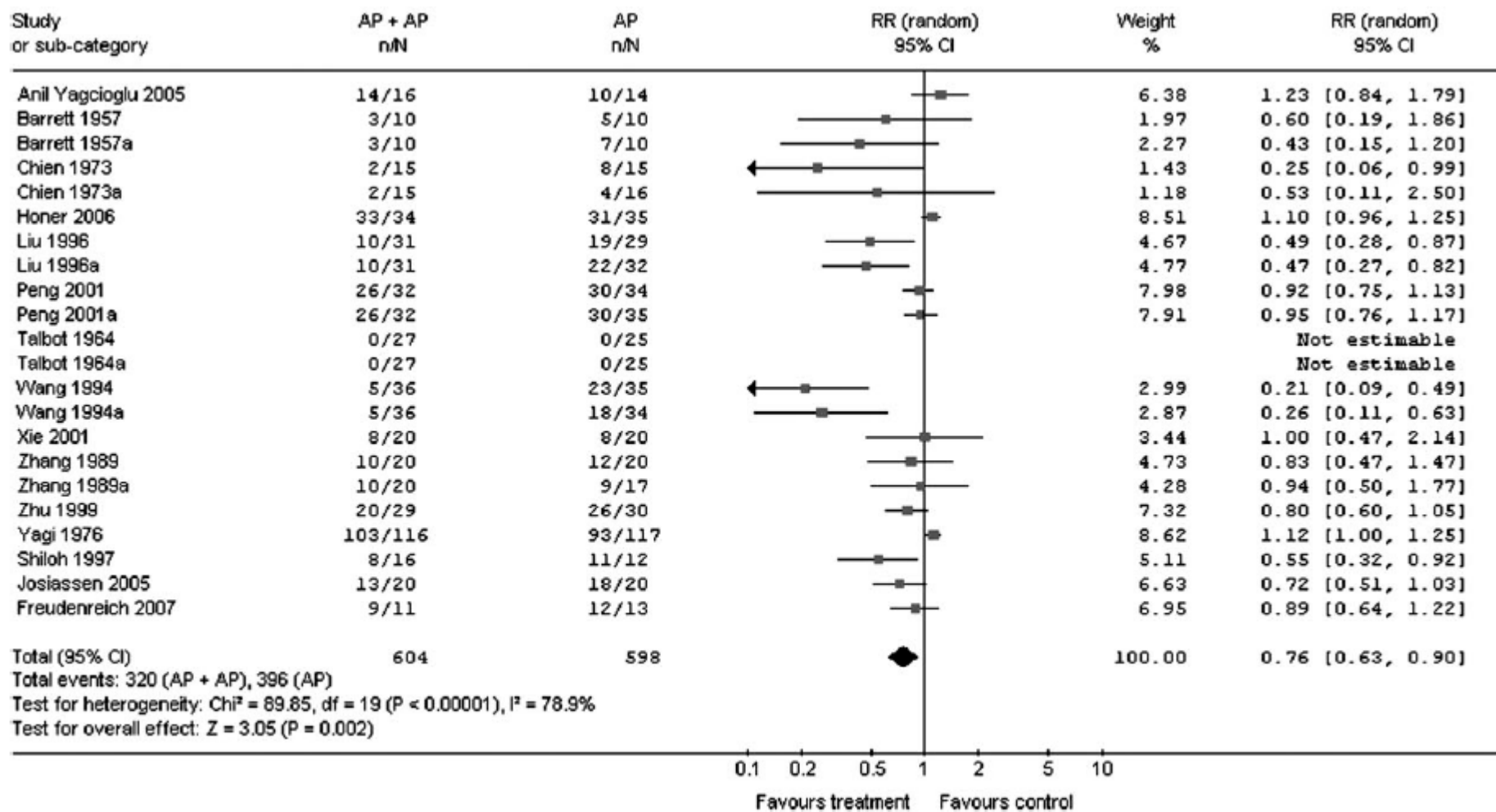
Christoph U. Correll¹⁻⁴, Christine Rummel-Kluge⁵,
Caroline Corves, John M. Kane²⁻⁴, and Stefan Leucht⁵

Objective: To evaluate therapeutic and adverse effects of antipsychotic cotreatment vs monotherapy in schizophrenia.

Data Sources: Cochrane Schizophrenia Group register and hand searches of relevant journals/conference proceedings.

Study Selection: Randomized controlled trials comparing antipsychotic monotherapy to cotreatment with a second antipsychotic.

Results: 19 studies (1229 patients)



2. Lack of Efficacy as Defined in Each Study.

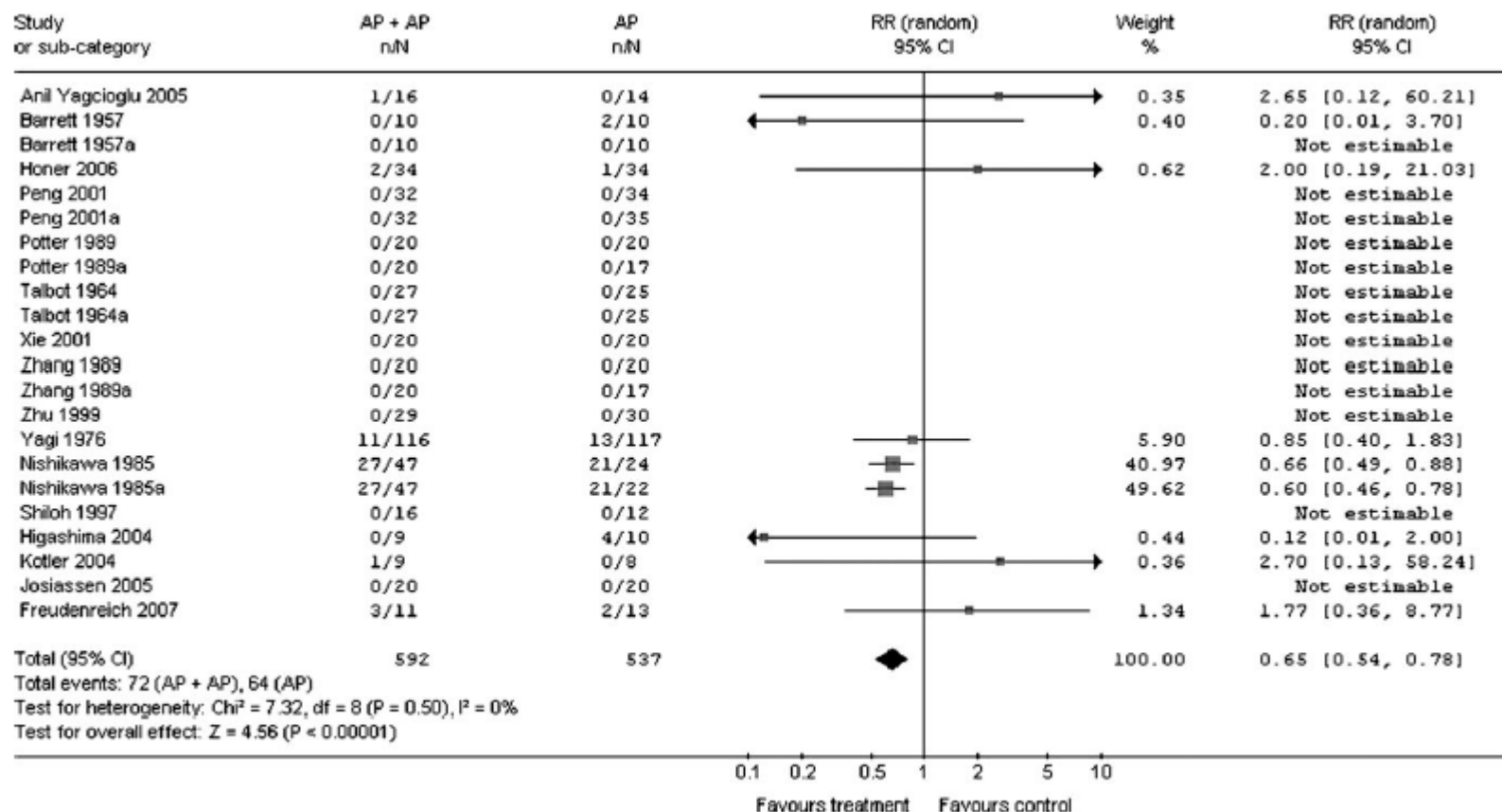
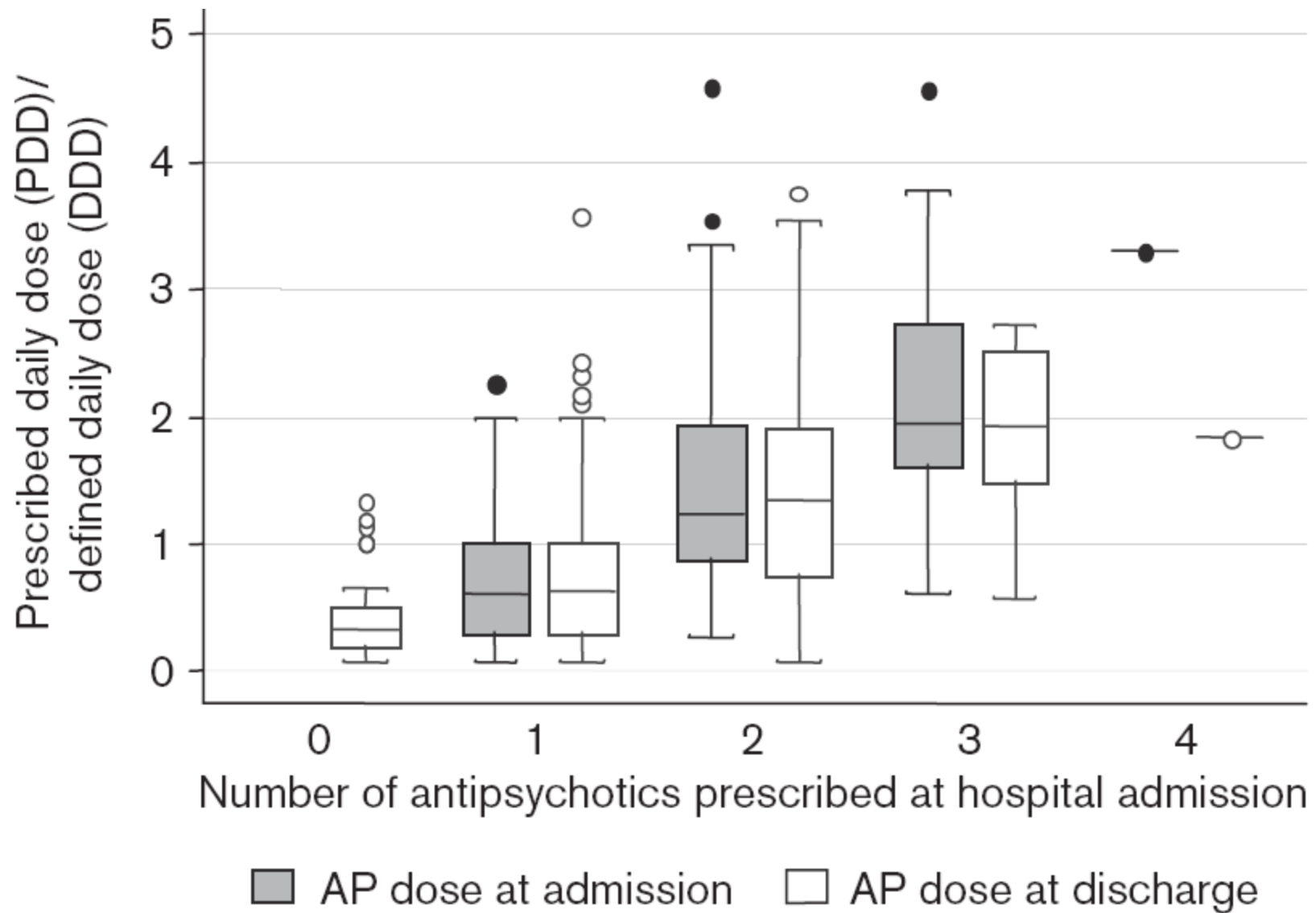


Fig. 3. Leaving the Study Early for any Reason.

Conclusions: In certain clinical situations, antipsychotic cotreatment may be superior to monotherapy. However, the database is subject to possible publication bias and too heterogeneous to derive firm clinical recommendations, underscoring the need for future research.

Factors associated with antipsychotic dosing in psychiatric inpatients: a prospective study

Corrado Barbui^a, Bruno Biancosino^{b,c}, Eleonora Esposito^a, Luciana Marmai^{b,c},
Silvia Donà^{b,c} and Luigi Grassi^{b,c}



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atypical Antipsychotic Drugs and the Risk of Sudden Cardiac Death

Wayne A. Ray, Ph.D., Cecilia P. Chung, M.D., M.P.H., Katherine T. Murray, M.D.,
Kathi Hall, B.S., and C. Michael Stein, M.B., Ch.B.

N ENGL J MED 360;3 NEJM.ORG JANUARY 15, 2009

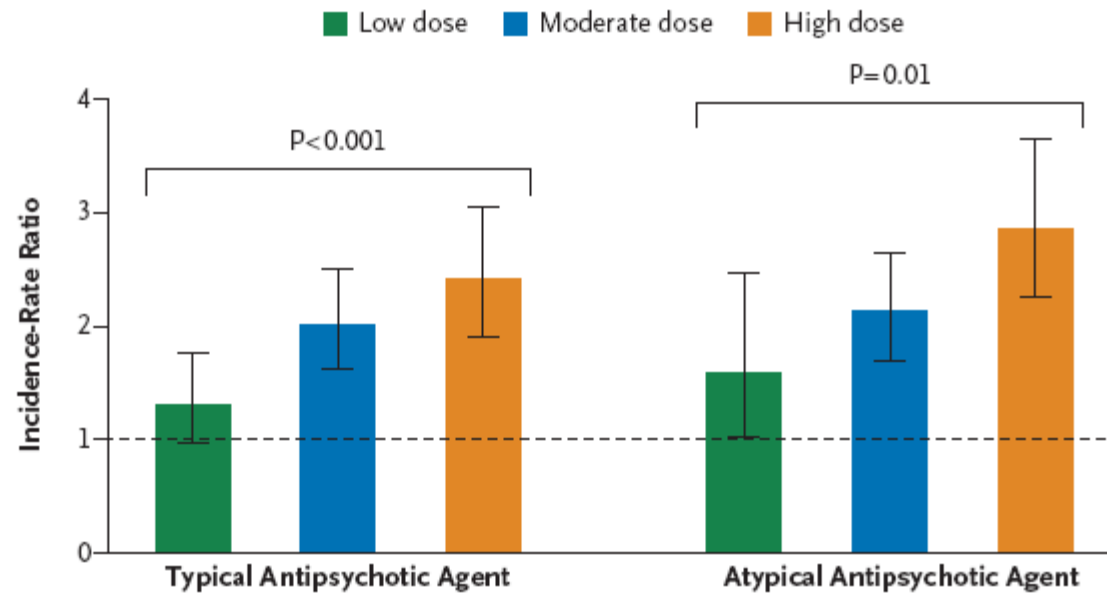
“We calculated the adjusted incidence of sudden cardiac death among current users of antipsychotic drugs in a retrospective cohort study of Medicaid enrollees in Tennessee.”

“The primary analysis included 44,218 and 46,089 baseline users of single typical and atypical drugs, respectively, and 186,600 matched nonusers of antipsychotic drugs.”

Age 30-74

Table 2. Adjusted Incidence-Rate Ratios for Sudden Cardiac Death, According to Use or Nonuse of Antipsychotic Drugs.*

User Status	No. of Person-Years	No. of Sudden Deaths	Incidence-Rate Ratio (95% CI)	P Value
Nonuser	624,591	895	Reference group	
Former user	189,981	311	1.13 (0.98–1.30)	0.08
Current user†				
Typical agent				
Any	86,735	255	1.99 (1.68–2.34)	<0.001
Haloperidol	21,728	58	1.61 (1.16–2.24)	0.005
Thioridazine	15,715	65	3.19 (2.41–4.21)	<0.001
Atypical agent				
Any	79,589	223	2.26 (1.88–2.72)	<0.001
Clozapine	4,654	19	3.67 (1.94–6.94)	<0.001
Olanzapine	27,257	75	2.04 (1.52–2.74)	<0.001
Quetiapine	17,355	40	1.88 (1.30–2.71)	<0.001
Risperidone	24,589	85	2.91 (2.26–3.76)	<0.001



No. of Deaths	46	104	105	22	108	93
No. of Person-Years	21,438	33,671	31,626	10,435	41,513	27,641
Incidence-Rate Ratio	1.31	2.01	2.42	1.59	2.13	2.86
95% CI	0.97–1.77	1.62–2.50	1.91–3.06	1.03–2.46	1.70–2.65	2.25–3.65

Figure 1. Adjusted Incidence-Rate Ratios for Sudden Cardiac Death among Current Users of Antipsychotic Drugs, According to Type of Drug and Dose.

Doses are shown as chlorpromazine equivalents: low dose, <100 mg; moderate dose, 100 to 299 mg; high dose, 300 mg or more. The reference category is nonusers of antipsychotic drugs. P values are for a dose–response relationship. I bars indicate 95% confidence intervals.



Risk for suicide

- About 10% schizophrenics commit suicide



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Schizophrenia Research 73 (2005) 139–145

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Suicidal risk during treatment with clozapine: a meta-analysis

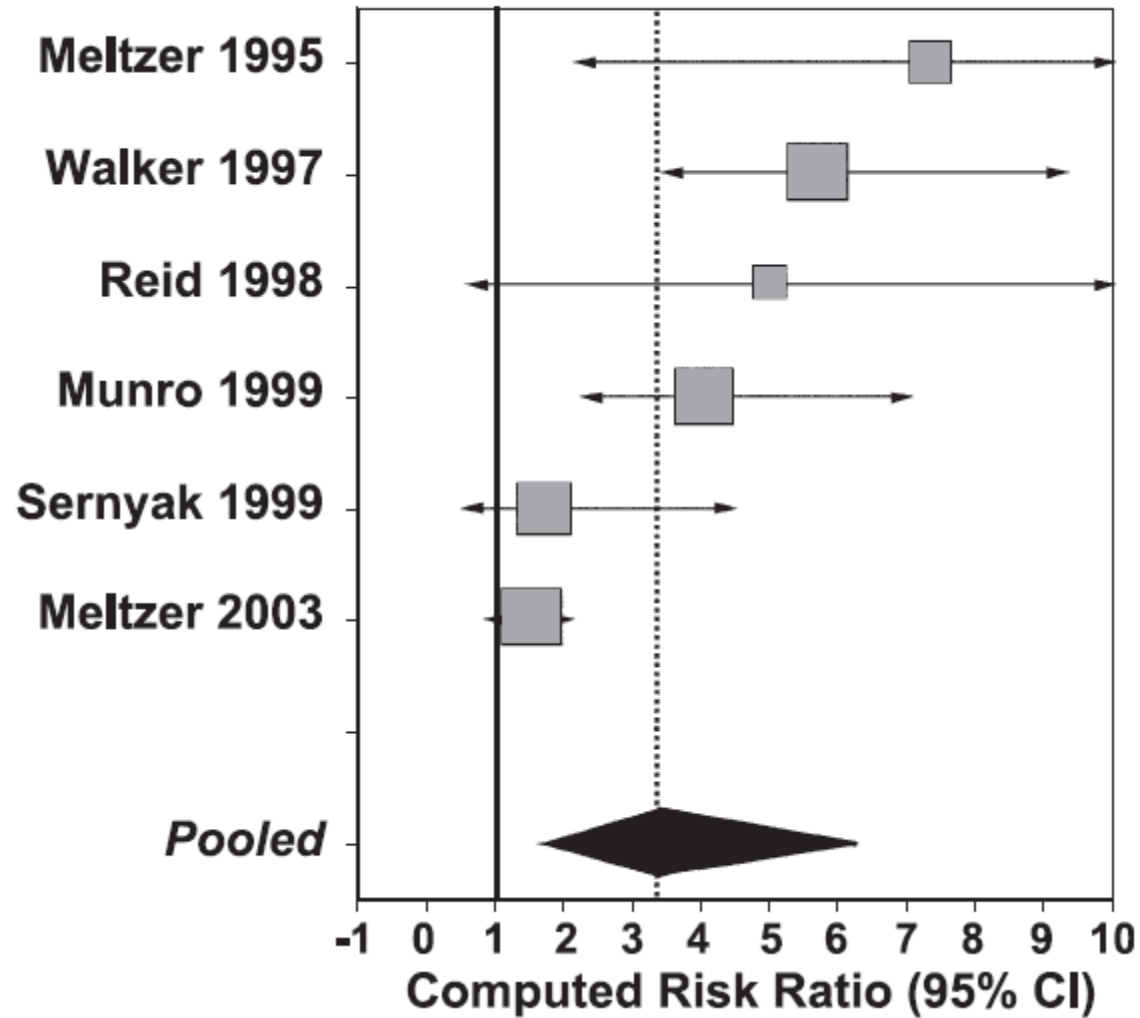
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Received 12 September 2003; received in revised form 25 May 2004; accepted 27 May 2004

Available online 10 July 2004

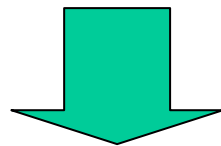


“...Long-term treatment with clozapine was associated with three-fold overall reduction of risk of suicidal behaviors.”

Schizophrenia

Core interventions in the treatment and management of schizophrenia in primary and secondary care

If a service user has had two antipsychotics (including one atypical) each for 6–8 weeks without significant improvement, check out possible causes for a lack of response and consider clozapine. In some circumstances it may be supportable to add a second antipsychotic drug to clozapine if there has been a suboptimal response at standard doses. Do not use more than one antipsychotic drug in other situations, except when changing from one drug to another.



Quale antipsicotico?

*National Institute for
Clinical Excellence*

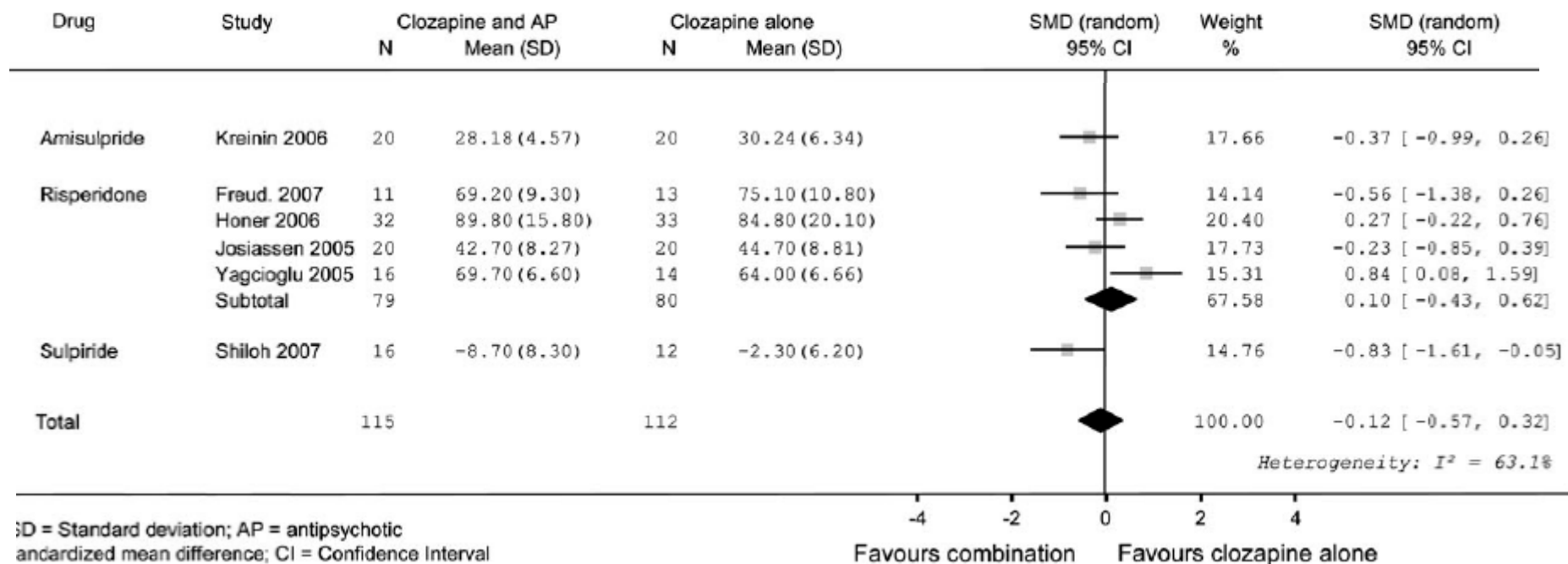
www.nice.org.uk

Does the Addition of a Second Antipsychotic Drug Improve Clozapine Treatment?

Corrado Barbui^{1,2}, Alessandra Signoretti², Serena Mulè²,
Marianna Boso^{2,3}, and Andrea Cipriani²

The search yielded 21 studies suitable for reanalysis. In 3 trials, clozapine was combined with a phenothiazine, in 8 trials with a benzamide, and in the remaining trials with risperidone.

While the majority of randomized trials were not double blind, 6 studies were double-blind placebo-controlled trials.



“Clinicians prescribing a second antipsychotic to people who do not have an optimal response to clozapine should consider that the expected benefit, on the basis of available evidence, is at best modest.”

- ❑ **Pazienti non selezionati**
 - ❑ **Trattamenti simili a quelli erogati in pratica**
 - ❑ **Indicatori di esito clinicamente rilevanti**
 - ❑ **Campioni numerosi**
 - ❑ **Durata adeguata**
 - ❑ **Indipendenza da interessi commerciali**
-

TRIAL PRAGMATICO DI EFFECTIVENESS

C lozapine

H aloperidol

A ripiprazole

T rial

PATIENT POPULATION

Patients with schizophrenia

treated with AP

but still having positive symptoms

AIM: to follow them up for a 12-month period
and assess main clinical outcomes

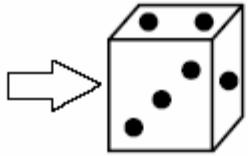
Observational cohort

NESSUNA INCERTEZZA SUL
TRATTAMENTO?

*Randomized
cohort*

INCERTEZZA SUL
TRATTAMENTO?

Patients receiving
clozapine with
psychotic symptoms



Group 1

clozapine + aripiprazole

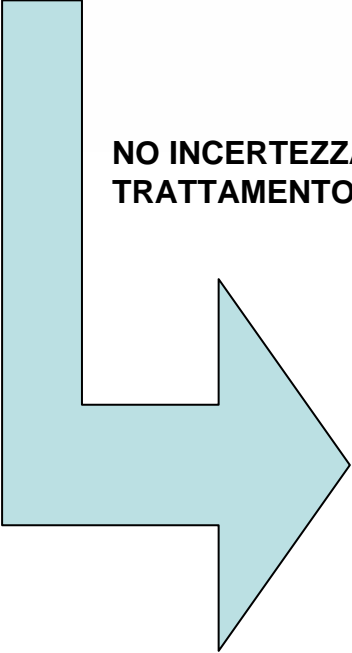
Interruzione
della
"combination"

Group 2

clozapine + haloperidol

Interruzione
della
"combination"

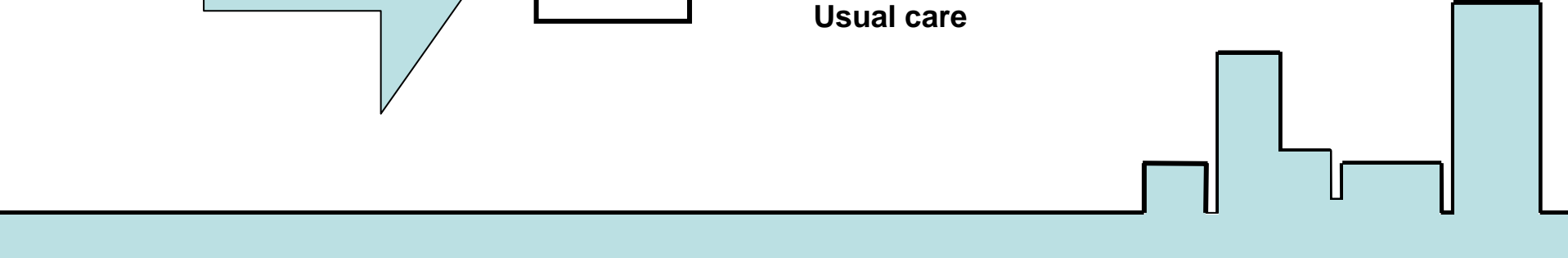
NO INCERTEZZA SUL
TRATTAMENTO



Group 3

Usual care

Outcome



II CHAT è uno studio

INDIPENDENTE

Nessun supporto economico da parte dell'industria farmaceutica.

PRAGMATICO

Non determinerà alcuna modifica delle normali prassi assistenziali.

Al di là della assegnazione casuale dei pazienti alla aggiunta di aripiprazolo o aloperidolo, i medici curanti saranno liberi di seguire la loro consueta pratica clinica, modificando i dosaggi dei trattamenti, aggiungendo o sospendendo i trattamenti sperimentali ed eventuali altri farmaci secondo le necessità cliniche del singolo paziente > logica epidemiologica.

MULTICENTRICO

60 servizi psichiatrici italiani hanno già aderito

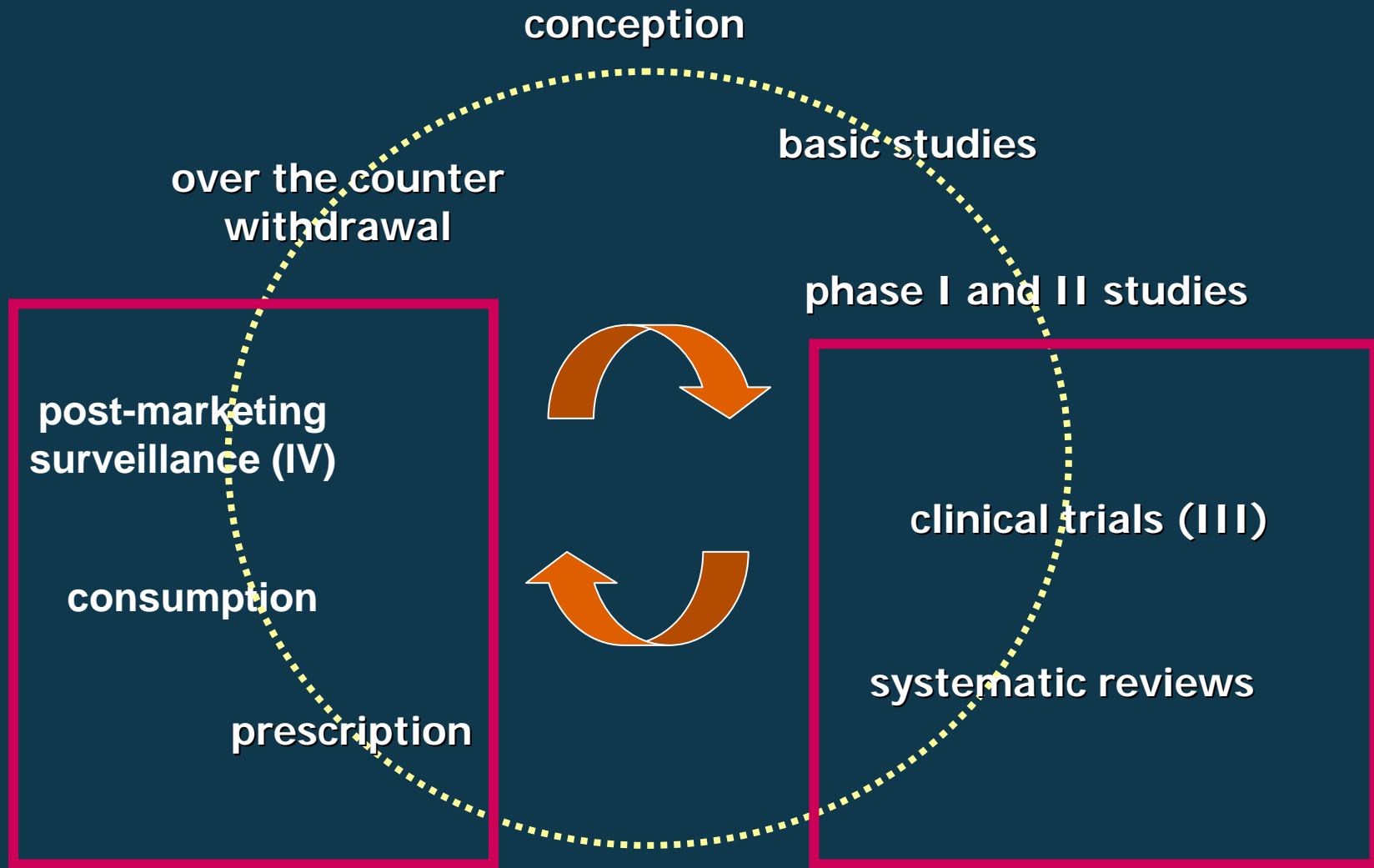
NUOVO!

Rientra tra le sperimentazioni finalizzate a migliorare la pratica clinica quale parte integrante dell'assistenza sanitaria, secondo il Decreto Ministeriale 17/12/2004.

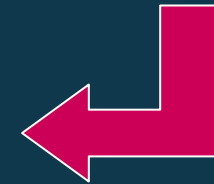
**Come possiamo
tradurre in pratica
queste "evidenze"?**



DMSP-PSY



LINEE-GUIDA, MANUALI
(società scientifiche,
gruppi di ricerca, ecc ecc)



Technology Appraisal

NHS

***National Institute for
Clinical Excellence***

**Guidance on
the use of
newer (atypical)
antipsychotic
drugs for the
treatment of
schizophrenia**

www.nice.org.uk

Guidance on newer antipsychotics for schizophrenia

NICE June 2002. www.nice.org.uk

- Should be part of a comprehensive package of care
- Joint decision making
- Newer drugs **considered** in the choice of first-line treatments for newly diagnosed
- Where joint decision not possible, consider newer drugs as Rx of choice because of lower extrapyramidal side effects
- Switch to newer drugs in established therapy if unacceptable adverse effects, and for relapses if poor response or side effects with previous therapy
- Don't switch if things are going well

Schizophrenia PORT

Treatment Recommendations

- Recommendation 1: *Antipsychotic medications, other than clozapine, should be used as the first-line treatment to reduce psychotic symptoms for persons experiencing an acute symptom episode of schizophrenia.*

GENERAL PRINCIPLES OF PRESCRIBING (I)

Each patient should ideally be prescribed only one antipsychotic, preferably in a single dosage form

Antipsychotics should ideally not be used as "add on" sedatives

The lowest possible effective dose should be used, with patients given a sufficient trial on low doses before any further increase

Doses above 15mg/day haloperidol or equivalent should be the exception rather than the rule

Anticholinergic drugs should be given for parkinsonism or dystonia. Anticholinergics impair memory

Schizophrenia PORT

Treatment Recommendations

- **Recommendation 2:** *The dosage of antipsychotic medication for an acute symptom episode should be in the range of 300-1000 chlorpromazine (CPZ) equivalents per day for a minimum of 6 weeks. Reasons for dosages outside of this range should be justified. The minimum effective dose should be used.*

Table Minimum effective dose/day – antipsychotics

Drug	1st episode	Relapse	References
Chlorpromazine	200 mg*	300 mg	–
Haloperidol	2 mg	>4 mg	1–3
Sulpiride	400 mg*	800 mg	4
Trifluoperazine	10 mg*	15 mg	–
Amisulpride	400 mg*	800 mg	5–7
Aripiprazole	15 mg*	15 mg	8
Olanzapine	5 mg	10 mg	9–10
Quetiapine	150 mg*	300 mg	11–13
Risperidone	2 mg	4 mg	14, 15
Ziprasidone	80 mg*	80 mg	16, 17
Zotepine	75 mg*	150 mg	18, 19

*Estimate – too few data available.

Drug	Maximum dose (mg/day)
Chlorpromazine	1000
Thioridazine	600 (see BNF)
Fluphenazine	20
Trifluoperazine	None (suggest 50)
Flupentixol	18
Zuclopenthixol	150
Haloperidol	30 (see BNF)
Sulpiride	2400
Pimozide	20
Loxapine	250
Amisulpride	1200
Aripiprazole	30
Clozapine	900
Risperidone	16 (see BNF)
Olanzapine	20
Quetiapine	750/800 (see BNF)
Ziprasidone*	160
Zotepine	300



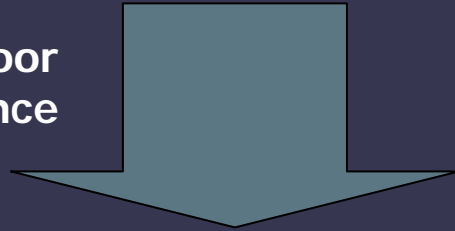
Effective Dosage Range: Acute Treatment



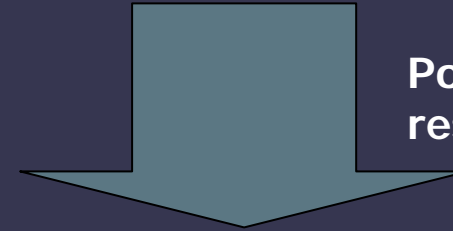
Baldessarini et al. (1988), Arch Gen Psych 45:79-91

**Give antipsychotic,
optimise dosage, assess
over 6-8 weeks**

Poor
compliance



Poor or no
response



**Discuss with
patient/carer, switch to
another antipsychotic or
to depot, assess over 6-8
weeks**

**Switch to another
antipsychotic, switch to
atypicals, assess over 6-8
weeks**

Poor or no response

Switch to clozapine

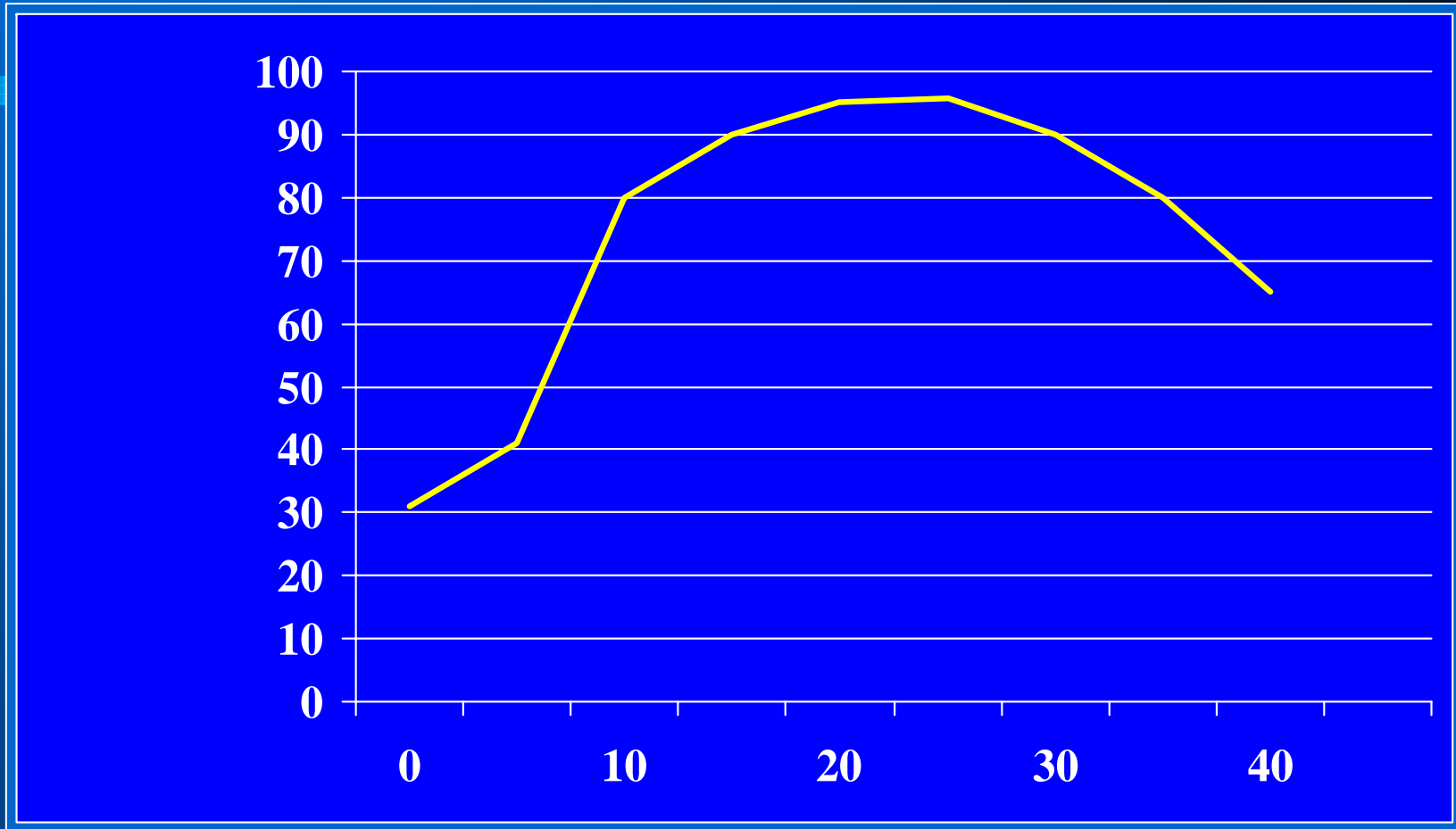
Schizophrenia PORT

Treatment Recommendations

- Recommendation 3: *The maintenance dosage should be in the range of 300-600 CPZ equivalents (oral or depot) per day.*

Effective Dosage Range: Maintenance Treatment

% not
relapsed
(1 yr)



Fluphenazine Decanoate, mg/2 wk

Guideline 6: The Maintenance Phase

Issue	Recommendation
Choice of maintenance antipsychotic	Select and
Duration of maintenance antipsychotic therapy	<p>12–24 months for a first episode. Long-term maintenance therapy is recommended for patients with multiple episodes and/or persistent symptoms (PORT Recommendation 10).</p> <p>For patients with severe symptoms (19)</p>
Dosing of maintenance antipsychotic therapy	<p>Continue the (PO)</p> <p>For re</p>
Use of depot formulation	For patients with
Development of tardive dyskinesia (TD) on conventionals ¹²	<p>For mild TD, switch to newer atypical.</p> <p>For more severe TD, switch to clozapine or newer atypical.</p>

12-24 MESI SE PRIMO EPISODIO

5 ANNI O A LUNGO TERMINE (lifetime) SE EPISODI RIPETUTI O COMPLICATI



The case against antipsychotic drugs: a 50-year record of doing more harm than good[☆]

Robert Whitaker*

19 Rockingham St., Cambridge, MA 02139, USA



Although the standard of care in developed countries is to maintain schizophrenia patients on neuroleptics, this practice is not supported by the 50-year research record for the drugs

A critical review reveals that this paradigm of care worsens long-term outcomes, at least in the aggregate, and that 40% or more of all schizophrenia patients would fare better if they were not so medicated.

Evidence-based care would require the selective use of antipsychotics, based on two principles:

- (a) no immediate neuroleptisation of first-episode patients;**
- (b) every patient stabilized on neuroleptics should be given an opportunity to gradually withdraw from them. This model would dramatically increase recovery rates and decrease the percentage of patients who become chronically ill.**

3B: For Medication Noncompliance⁷

(*Bold italics* = treatment of choice)

Interventions to improve compliance		
Pharmacological	Psychosocial	Programmatic
<p>Base choice of medication on the side effect profile most acceptable to the patient (Guideline 5)</p> <p><i>Consider using a long-acting depot antipsychotic, particularly if the patient has lack of insight into the need for medication</i></p> <p>Monitor symptoms and side effects</p> <p><i>Monitor medication (e.g., direct observation, weekly pill box)</i></p>	<p><i>Family education and support</i></p> <p><i>Patient education and support</i></p> <p>Motivational interviewing (e.g., helping the patient realize that attaining personal goals requires compliance with treatment)</p> <p>Introduce new interventions gradually according to the level of clinical recovery and cognitive impairment</p> <p>Time interventions based on patient's preference and sense of urgency</p>	<p><i>Concurrent treatment of substance abuse</i></p> <p><i>Provide assertive community treatment services</i></p> <p>Continuity of primary clinician across treatment modalities (e.g., inpatient, outpatient, and residential programs)</p> <p>Provide a depot medication clinic</p> <p>Provide more intensive services (e.g., case management, day hospital)</p> <p>Supervised residential services</p>

⁷Medication survey questions 4 & 14; psychosocial survey question 9

GENERAL PRINCIPLES OF PRESCRIBING (II)

Many patients are stabilised on typical therapy and it seems unwise to change medication in such patients. Continuation is appropriate where typicals are effective and well tolerated, but the risk of tardive dyskinesia should be borne in mind.

Only clozapine is effective in refractory schizophrenia

Switching from clozapine to other atypicals is usually unsuccessful or disastrous and should not be attempted unless a severe clozapine-related adverse effect has occurred

8A: When to Switch and When Not to Switch from a Conventional Antipsychotic

	First line	High second line
Factors that favor switching from one antipsychotic to another ¹⁸	<ul style="list-style-type: none"> • Persistent extrapyramidal symptoms that have not responded to treatment with antiparkinsonian or antiakathisia agents • Other disturbing side effects • Risk of tardive dyskinesia • Persistent positive or negative symptoms • Relapse despite adherence to treatment • To improve level of functioning • Patient or family preference • Persistent cognitive problems 	<ul style="list-style-type: none"> • Disruptive or disorganized behavior • Persistent agitation • Persistent severe mood symptoms
Factors that favor NOT switching from one antipsychotic to another ¹⁹	<ul style="list-style-type: none"> • Patient doing well on current medication (good efficacy, few side effects) • Patient on a depot antipsychotic because of history of recurrent compliance problems • Patient for whom exacerbation of psychotic symptoms would present unacceptable risk of danger to self or others • Patient or family preference to remain on current medication 	<ul style="list-style-type: none"> • Inability to obtain or pay for new medications • Inadequate level of clinical follow-up available during the switch • Recent (last 3–6 months) recovery from a relapse • Lack of social supports to provide medication supervision • Concurrent life stressors (e.g., moving, changing treatment programs)

¹⁸Medication survey question 27

¹⁹Medication survey question 28

8B: How to Switch

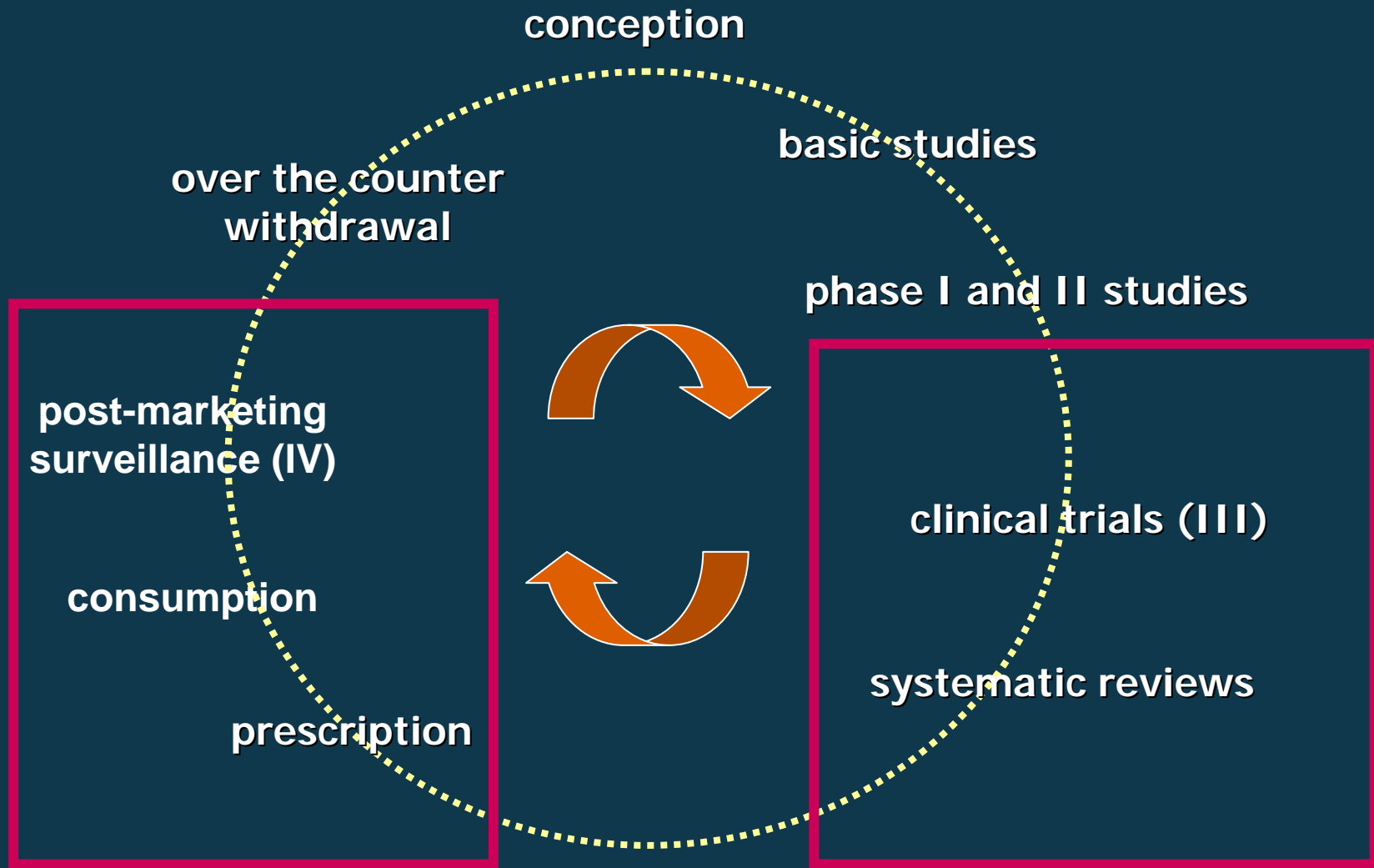
We asked the experts about three possible methods of switching from one antipsychotic to another: 1) stop the old antipsychotic abruptly and immediately start the new antipsychotic, 2) cross-titration—gradually reduce the dose of the first antipsychotic while gradually increasing the dose of the new antipsychotic, 3) overlap and taper—don't reduce the dose of the old antipsychotic until the new antipsychotic is at a full therapeutic dose. Each method has advantages and disadvantages. The stop-the-old/start-the-new method has the advantages of simplicity, a reduced risk of medication errors, and a reduced risk of side effects. Nonetheless, the experts prefer either the overlap and taper or cross-titration methods, citing the advantages of reduced risk of relapse and withdrawal symptoms. Switching from clozapine must be done especially gradually.²⁰

Issue	Recommendation
Preferred methods of switching ²¹	<p>Cross-titration</p> <p>Overlap and taper</p>
Preferred duration of switching ²²	<p>4–5 <u>weeks</u> if the switch does NOT involve clozapine</p> <p>7–8 <u>weeks</u> if the switch does involve clozapine</p>
Factors favoring a very gradual switch from one antipsychotic to another ²³	<ul style="list-style-type: none"> • History of violence or aggression • History of suicide risk • Severe course of illness • Taking high dosage of first antipsychotic • Switching from clozapine to another antipsychotic • Switching from another antipsychotic to clozapine <p><i>Also consider a gradual switch in the following situations:*</i></p> <p><i>Limited availability of clinical monitoring</i></p> <p><i>Patient/family preference</i></p> <p><i>Presence of life stressor</i></p> <p><i>Limited social supports</i></p>

Adverse effect	Suggested drugs	Alternatives	References
Acute EPSEs	Quetiapine Olanzapine Aripiprazole	Risperidone (<6 mg/day) Clozapine Ziprasidone	1–5
Hyperprolactinaemia	Quetiapine Olanzapine <i>(small, transient rise in prolactin⁶, although symptoms rarely observed⁷)</i> Aripiprazole	Ziprasidone Clozapine	8–11
Weight gain	Amisulpride Haloperidol Trifluoperazine Aripiprazole	Quetiapine Ziprasidone Risperidone	12–15
Tardive dyskinesia	Clozapine	Olanzapine Quetiapine Risperidone (<6 mg/day)	16–18
Impaired glucose tolerance	Amisulpride Ziprasidone Aripiprazole	Risperidone	19–22
QT prolongation	Amisulpride Aripiprazole	Olanzapine	23–25
Sedation	Amisulpride Risperidone Sulpiride Haloperidol Aripiprazole		–
Postural hypotension	Amisulpride Sulpiride Haloperidol Trifluoperazine Aripiprazole		–



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LINEE-GUIDA, MANUALI
(società scientifiche,
gruppi di ricerca, ecc ecc)