



Medical University of Graz

Effectiveness and Cost of Olanzapine and Haloperidol in the Treatment of Schizophrenia: A Randomized Controlled Trial

R. Rosenheck et al., *JAMA*. 2003;290(20):2693-2702

JAMA[®]

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Philipp Kainz
Michael Mayrhofer-Reinhartshuber



Study Characteristics

- ▶▶ Double-Blind Randomized Controlled Trial

- ▶▶ Duration: 12 months in average (June 1998 – June 2000)

- ▶▶ Ethnicity and Setting: USA

- ▶▶ 17 U.S. Department of Veterans Affairs (VA) medical centers
 - Patient data
 - Cost data
 - Health care services



Objective

- ▶ „To evaluate the effectiveness and cost impact of olanzapine compared with haloperidol in the treatment of schizophrenia.“

Effectiveness (Effizienz):

Bezieht sich auf den Behandlungseffekt unter „realen“ Bedingungen. Alle Patienten, die in die Studie aufgenommen wurden, werden in die Analyse einbezogen (Wechsler, Abbrecher etc.)

→ intention-to-treat Analyse



PICO

▶▶ Patients

- DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*) **diagnosis of schizophrenia or schizoaffective disorder**, serious symptoms and serious dysfunction for the previous 2 years

▶▶ Intervention

- **Olanzapine** (5-20 mg/d) + Placebo Benztropine (1-4 mg/d)

▶▶ Comparison

- **Haloperidol** (5-20 mg/d) + (prophylactic) Benztropine (1-4 mg/d)

▶▶ Outcome (clinical + cost)

- 3 primary endpoints of Olanzapine vs. Haloperidol: fewer symptoms, better quality of life, and lower costs in patients with schizophrenia
- Secondary endpoints: adverse effects, clinical status, neurocognitive status, and premorbid intellectual functioning



Patient Flow & Statistical Methods

▶▶ Power Calculations

- 600 patients for 80% detection of a delta of \$8700 costs

▶▶ Concealment

- Medication kits in sets of 4 (2O + 2H) labeled with a random sequence number
→ Block-Randomization via telephone

▶▶ 2 Analyses

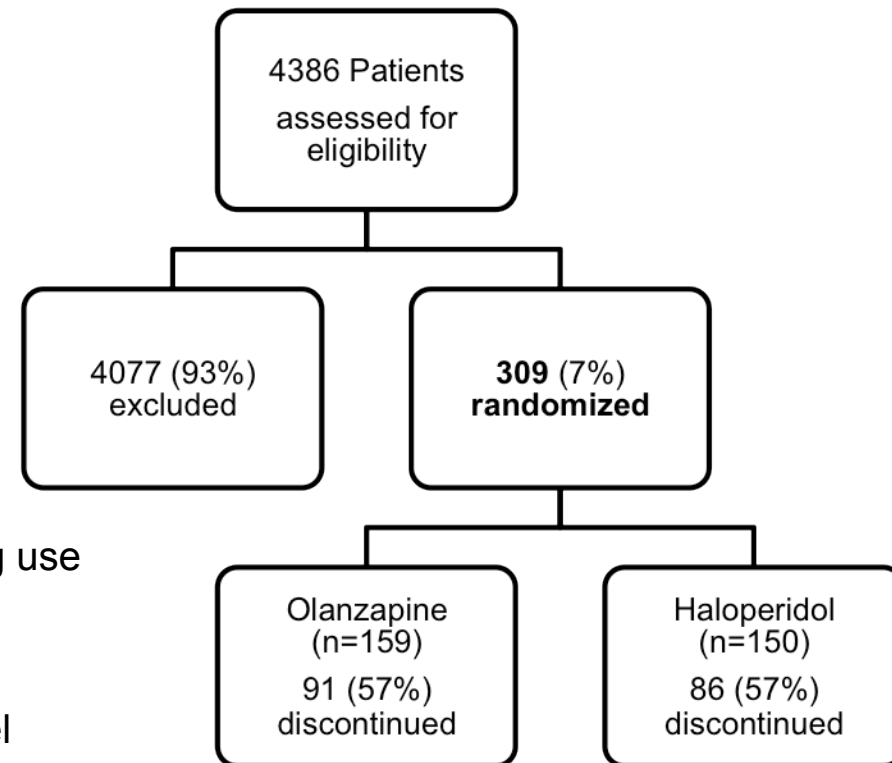
- Intention-to-Treat
- After excluding interruptions of study drug use

▶▶ Primary clinical outcomes

- random-effects repeated-measures model

▶▶ Cost outcome

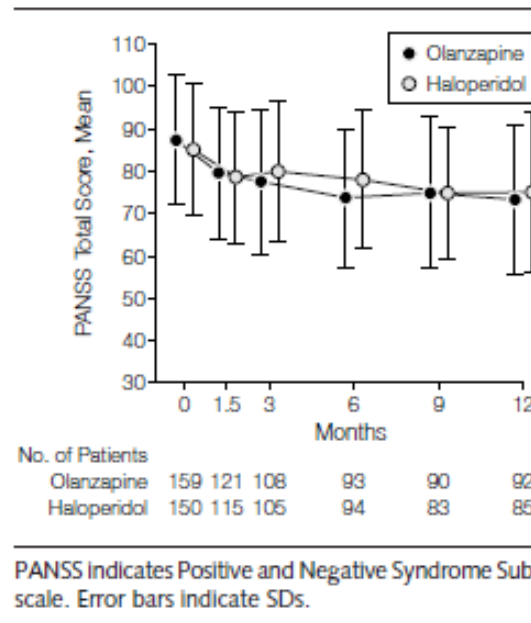
- Analysis of covariance of log-transformed measures and of ranks, controlling for baseline symptoms and service use



Results

- ▶▶ Intention-to-treat analysis showed no significant overall differences during the 12 months of treatment on the PANSS total symptom score ($P=0.35$)

Figure 3. PANSS Total Scores

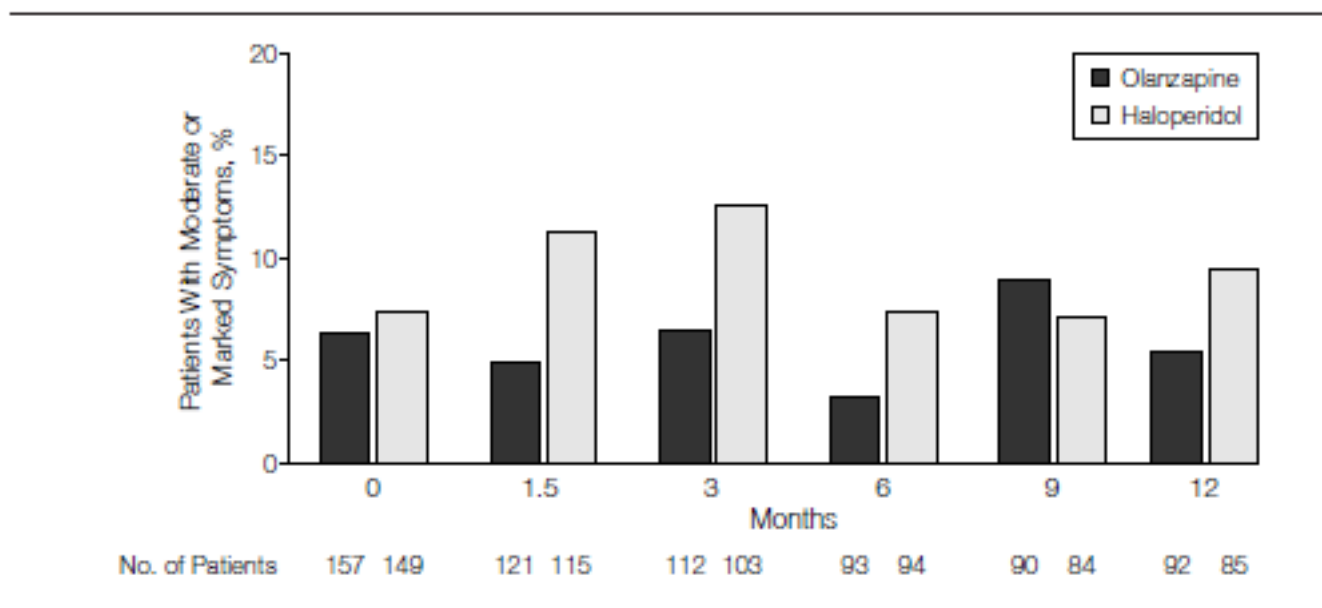


- ▶▶ No significant differences between groups in study retention; positive, negative, or total symptoms of schizophrenia; quality of life; or extrapyramidal symptoms.

Results

- ▶ Olanzapine was associated with significantly lower scores overall on the Barnes scale for akathisia ($P < 0.001$) but not on the AIMS measure of tardive dyskinesia ($P = 0.17$).

Figure 4. Percentage of Patients With Moderate or Marked Symptoms on Barnes Akathisia Global Scale





Results

- ▶ Among patients assigned to olanzapine there were more frequent reports of weight gain attributed by the patient as possibly or probably related to study drug.

Table 2. Adverse Effects Possibly or Probably Attributable to Study Drug*

Adverse Effects	Haloperidol		Olanzapine		P Value†
	No. of Reports/Total	%	No. of Reports/Total	%	
Weight gain					
3 mo	17/101	16.8	29/105	27.6	.07
6 mo	11/88	12.5	28/86	32.5	.002
9 mo	16/75	21.3	29/92	31.5	.16
12 mo	6/72	8.3	21/85	24.7	.01



Results

- ▶ Significant differences in total VA health costs due to medication costs (Olanzapine: \$2.83 / 5 mg; Haloperidol: \$0.02 / 5 mg).

Table 3. Comparison of 1-Year VA Service Use and Cost Data by Intention-to-Treat Analysis (n = 309)

	Olanzapine (n = 159)*	Haloperidol (n = 150)*	Difference	t †	P Value
Medication costs, \$					
VA prices	2224 (1347)	394 (579)	1830	15.70	<.001
Wholesale prices ⁴⁶	4136 (2549)	1068 (1212)	3068	13.60	<.001
Summary costs (service use + medications), \$					
Mental health + medications at VA prices	33 666 (42 386)	26 099 (33 258)	7567	2.23	.03
Median (IQR)‡	18 838 (8269-37 763)	15 466 (6462-28 586)	3372	2.27	.02
Mental health + medications at wholesale prices	35 579 (42 426)	26 773 (33 356)	8806	3.06	.003
Median (IQR)‡	20 499 (10 096-41 517)	15 878 (6899-28 895)	4621	2.96	.003
All VA health + medications at VA prices	41 862 (47 307)	33 116 (34 669)	8746	2.08	.04
Median (IQR)‡	25 898 (13 180-49 148)	22 533 (10 616-41 074)	3365	2.01	.05
All VA health + medications at wholesale prices	43 775 (46 369)	33 790 (34 739)	9985	2.70	.008
Median (IQR)‡	27 942 (14 684-50 692)	23 347 (11 836-75 884)	4595	2.52	.01



Critical Appraisal

- ▶▶ Conflicts of Interest and Financial Disclosure Statements
 - Employees of Lilly participated in the study design and commented on the analysis
 - Different financial disclosures of the authors (Astra-Zeneca and Bristol-Myers Squibb, Janssen)

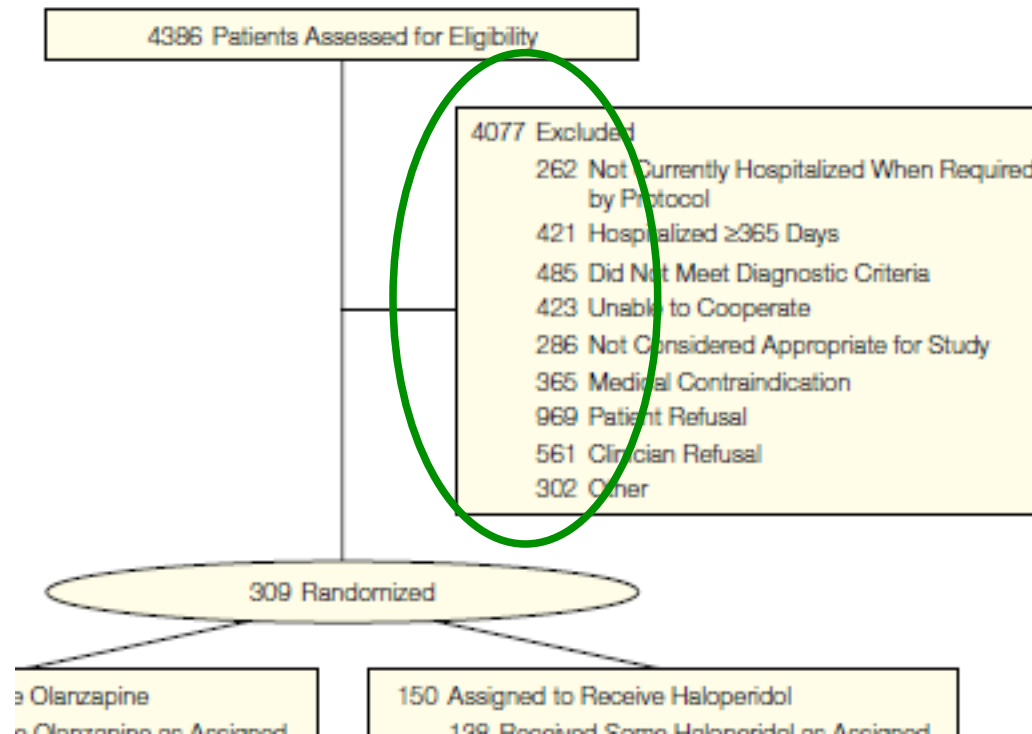
- ▶▶ Why did they reject the 18th center, if the problems were “unrelated to this study”?

- ▶▶ No proper definition of “serious medical illnesses” as an exclusion criterion

- ▶▶ High consent withdrawal rate after randomization, 25% in Olanzapine group and 23% in Haloperidol group

Critical Appraisal

►► Consistency



Taken from Figure 1. Enrollment, Allocation, Follow-up, and Analysis



Critical Appraisal

Interventions Patients were randomly assigned to receive flexibly dosed olanzapine, 5 to 20 mg/d, with prophylactic benztropine, 1 to 4 mg/d (n=159); or haloperidol, 5 to 20 mg/d (n=150), for 12 months.

Taken from Abstract

Pharmacotherapy

After completing baseline assessments, patients were assigned to receive double-blind treatment with oral olanzapine, 5 to 20 mg/d, or haloperidol, 5 to 20 mg/d. Dose adjustments were made as clinically indicated, using 4 fixed dosage levels at 5-mg intervals. Patients assigned to receive haloperidol also received prophylactic benztropine mesylate, 1 to 4 mg/d, for extrapyramidal symptoms (EPS). The olanzapine group received matching placebo benztropine, and both groups could increase the dose with active benztropine. The protocol did not allow concomitant use of other antipsychotic medications, although other psychotropic medications were permitted.

Taken from Methods

▶▶ Consistency: Abstract ≠ Methods

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- ▶▶ Olanzapine + prophylactic Benztropine
 - ▶▶ Haloperidol + prophylactic Benztropine