# Effectiveness and Cost of Olanzapine and Haloperidol in the Treatment of Schizophrenia

## A Randomized Controlled Trial

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**Context** Although olanzapine has been widely adopted as a treatment of choice for schizophrenia, its long-term effectiveness and costs have not been evaluated in a controlled trial in comparison with a standard antipsychotic drug.

**Objective** To evaluate the effectiveness and cost impact of olanzapine compared with haloperidol in the treatment of schizophrenia.

**Design and Setting** Double-blind, randomized controlled trial with randomization conducted between June 1998 and June 2000 at 17 US Department of Veterans Affairs medical centers.

**Participants** Three hundred nine patients with a *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. Fifty-nine percent fully completed and 36% partially completed follow-up assessments.

**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.

**Main Outcome Measures** Standardized measures of symptoms, quality of life, neurocognitive status, and adverse effects of medication. Veterans Affairs administrative data and interviews concerning non-VA service use were used to estimate costs from the perspective of the VA health care system and society as a whole (ie, consumption of all resources on behalf of these patients).

**Results** There were no significant differences between groups in study retention; positive, negative, or total symptoms of schizophrenia; quality of life; or extrapyramidal symptoms. Olanzapine was associated with reduced akathisia in the intention-to-treat analysis ($P<.001$) and with lower symptoms of tardive dyskinesia in a secondary analysis including only observations during blinded treatment with study drug. Small but significant advantages were also observed on measures of memory and motor function. Olanzapine was also associated with more frequent reports of weight gain and significantly greater VA costs, ranging from $3000 to $9000 annually. Differences in societal costs were somewhat smaller and were not significant.

**Conclusion** Olanzapine does not demonstrate advantages compared with haloperidol (in combination with prophylactic benztropine) in compliance, symptoms, extrapyramidal symptoms, or overall quality of life, and its benefits in reducing akathisia and improving cognition must be balanced with the problems of weight gain and higher cost.

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SCHIZOPHRENIA IS A DISABLING mental illness that affects more than 2 million persons in the United States[1] and was estimated to consume $16 billion of US health care services in 1990.[2] In recent years, a new series of antipsychotic medications has been released, referred to as "atypical" because they have fewer extrapyramidal adverse effects than older agents do.[3-5] The most

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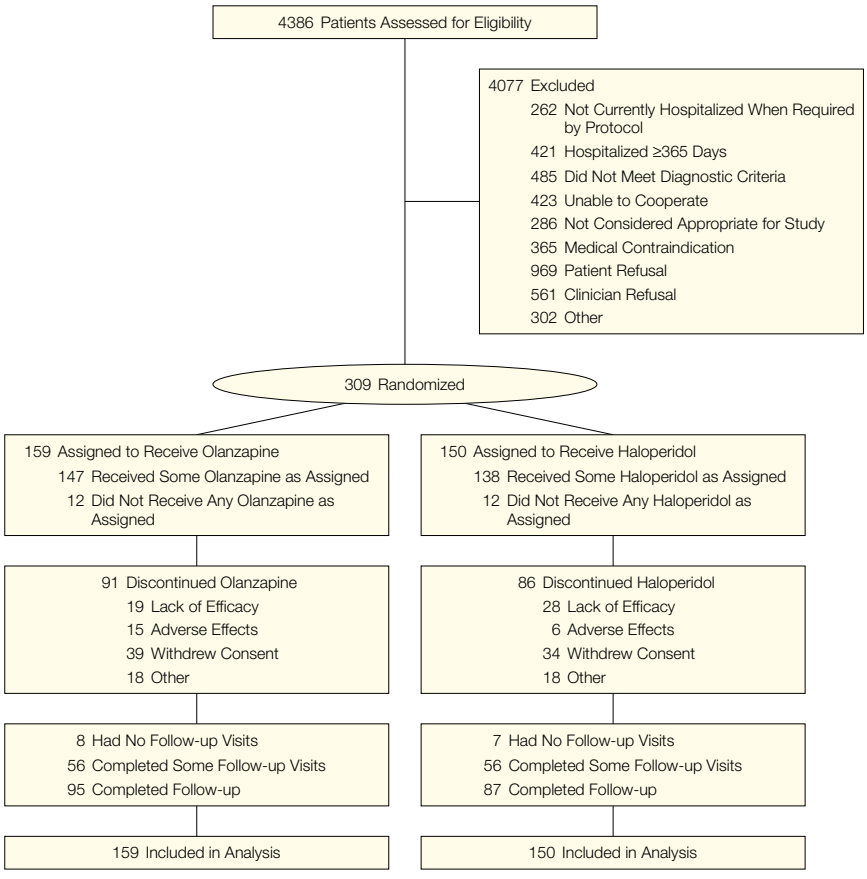
widely used of these medications in the treatment of schizophrenia is olanzapine,[6] with $3.7 billion in 2002 worldwide annual sales.[7] In a series of randomized trials, olanzapine had fewer extrapyramidal adverse effects than haloperidol[8-10] and, in some studies[8,10-13] but not others,[9,14,15] was associated with greater improvement in symptoms and quality of life and lower total health care costs.[15] However, a recent review of 20 olanzapine trials by the Cochrane Collaboration[5] concluded that "the large proportions of participants leaving the studies early . . . make it difficult to draw conclusions on clinical effects. Large long-term randomized trials . . . are long overdue."

Olanzapine, like other atypical antipsychotic agents, can cause serious weight gain[16] and may also be associated with hyperglycemia,[17] diabetes,[18] and hyperlipidemia,[19,20] increasing the importance of evaluating its benefits. No long-term effectiveness study has compared olanzapine or any of the other atypical antipsychotics except clozapine,[21,22] whose use is quite restricted, with a conventional drug. Although olanzapine is more expensive than conventional agents (costing >$4000 more annually at wholesale prices[6]), if it yields equivalent savings in other health costs, these expenditures would be justified. To further evaluate the effectiveness and cost of olanzapine, we conducted a 12-month clinical trial comparing olanzapine with haloperidol, a widely used conventional antipsychotic agent. We hypothesized that olanzapine would outperform haloperidol on 3 primary outcomes, as demonstrated by fewer symptoms, better quality of life, and lower costs in patients with schizophrenia.

**Figure 1.** Enrollment, Allocation, Follow-up, and Analysis




## METHODS

Between June 1998 and June 2000, patients at 17 Department of Veterans Affairs (VA) medical centers were randomly assigned to olanzapine or haloperidol. Medication kits were prepared in sets of 4 (2 olanzapine and 2 haloperidol) and each was labeled with a random sequence number. Patients were assigned a kit at the end of a telephone conversation with the coordinating center. Human rights committees at each participating medical center approved the protocol and all patients provided written informed consent. Data from an 18th site were excluded because of problems with a local institutional review board unrelated to this study.

### Entry Criteria

The study was initially targeted to patients currently hospitalized for schizophrenia for less than 365 days, but the criteria were expanded after 9 months to include patients with schizoaffective disorder and outpatients with any history of psychiatric hospitalization during the previous 2 years.

Eligibility criteria included (1) a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) diagnosis of schizophrenia or schizoaffective disorder on the Structured Clinical Interview for *DSM-IV* Disorders[23]; (2) serious symptoms (ie, score of ≥36 on the Brief Psychiatric Rating Scale[24]); and (3) serious dysfunction for the previous 2 years with inability to work or social constriction. Patients were excluded if they or their clinicians were unable or unwilling to cooperate; if they had a serious medical illness, unexplained seizures, or severe medication allergies; or if they had previously participated in olanzapine research.

The medical records of 4386 patients were reviewed (FIGURE 1). Only 2141 (49%) were eligible for further assessment; 1530 (35%) either refused participation themselves or their clinicians refused participation; 7% could not participate for other reasons; and 309 (7%) provided informed consent and were randomized.

### 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.

### Psychosocial Treatment

A predefined program of psychosocial treatment was offered to both drug treatment groups through a structured treatment planning process.[25]

### Outcome Measures

Symptom outcomes were assessed at baseline, 6 weeks, and 3, 6, 9, and 12 months with the Positive and Negative Syndrome Scale (PANSS),[26] in which high scores reflect worse symptoms and a 20% reduction represents clinically important improvement (possible range of scores, 30-210).[27] The Heinrichs-Carpenter Quality of Life Scale (QOLS), a clinician-rated scale, was used to assess social functioning and severe behavioral deficits, in which higher scores indicate improvement (possible range, 0-126).[28]

Secondary outcomes included adverse effects, assessed with the Barnes scale for akathisia (ie, restlessness and agitation; possible range, 0-5 [ie, none, questionable, mild, moderate, marked, or severe]),[29] the Abnormal Involuntary Movement Scale (AIMS) for tardive dyskinesia (possible range, 0-42),[30] the Simpson-Angus scale for EPS (possible range, 0-4),[31] and a checklist of adverse reactions. Further assessment of clinical status was measured with the Clinical Global Impression scale[32] and quality of life with the Short Form 36-Item Health Survey (SF-36).[33]

Neurocognitive status was assessed at baseline and at 3, 6, and 12 months using the list learning, recall, recognition, and coding subtests from the Repeatable Battery for the Assessment of Neuropsychological Status,[34] along with the Grooved Pegboard,[35] Wisconsin Card Sorting Test–64 Card Version,[36] Trail-Making Test Part B,[35] and the Controlled Oral Word Association Test.[37] The Wide Range Achievement Test–Revised reading subtest was used to assess premorbid intellectual functioning.[38] Principal components factor analysis with varimax rotation identified 3 orthogonal factors: motor function, memory, and the Wisconsin Card Sorting Test. These factors were moderately intercorrelated (Pearson *r* range, 0.42-0.58) and together explained 71% of the variance. They were significantly correlated with age, sex, education, the Simpson-Angus scale for EPS, and the Wide Range Achievement Test, which were included as covariates in analyses of these measures.

### Assessment of Health Care Costs

Health care costs were calculated by multiplying the number of units of service for each patient by estimated 1998 unit costs and were estimated from the perspective of the VA and society as a whole, ie, consumption of all resources on behalf of these patients. Societal costs include not only health care costs and criminal justice costs, for example, but all costs related to these patients for all payors in society.

**Service Utilization.** Health service data from the VA were derived from national workload data systems: the patient treatment file (inpatient care), the extended care file (nursing home and domiciliary care), and the outpatient care file. The Service Use and Resource Form recorded patient reports of non-VA medical and mental health inpatient, residential, and nursing home care and 19 types of medicosurgical and mental health outpatient care.

**VA Unit Costs.** Unit costs for VA inpatient and residential care were estimated on the basis of files created by the VA's Health Economic Resource Center[39,40] using data from the VA's Cost Distribution Report (CDR). The VA medical and mental health outpatient unit cost estimates were also derived from the CDR. Group therapy unit costs were weighted at 20% of the cost of an individual visit, psychosocial rehabilitation at one third, and day treatment at half. Costs of intensive case management were based on cost data from each facility.[41]

**Non–VA Unit Costs.** Non-VA costs were derived from (1) analysis of costs in the 1998 MarketScan data set,[42] a compilation of all insurance claims from more than 500 000 private-sector mental health service users; (2) VA contract payments for private nursing home care available in the CDR; (3) VA payments for contract residential treatment[43]; and (4) published literature presenting unit costs from large non-VA health care systems.[44,45]

**Medication Costs.** The cost of olanzapine was estimated in a sensitivity analysis using both 1999 discounted VA pharmacy cost levels of $2.83 per 5 mg[6] and wholesale community costs of $4.84 per 5 mg.[46] The cost of haloperidol was estimated at $0.02 per 5 mg on the basis of both VA pharmacy data and community prices.[46] Nonstudy medication costs were also estimated using VA and wholesale prices.

**Non–Health Care Costs.** Non–health care costs were derived from individual interview data on use of services and from published literature.[47-50] These costs included the administrative costs of transfer payments (eg, disability, welfare),[47,48] criminal justice system costs (eg, police contacts, arrests),[49,50] and productivity (estimated by employment earnings, included as a negative cost). For transfer payments, only administrative costs were included because they alone represent consumed societal resources.[47]

### Statistical Analyses

The primary analyses for this study are based on intention-to-treat principles including all patients as randomized. Power calculations targeted randomizing 600 patients to yield an 80% chance of de-

**Table 1.** Baseline Characteristics of Patients Assigned to Receive Olanzapine or Haloperidol*

| Characteristics | Olanzapine (n = 159) | Haloperidol (n = 150) |
|---|---|---|
| Demographic | | |
| Age at randomization, y | 46.8 (9.5) | 46.2 (7.7) |
| Male, No. (%) | 154 (96.9) | 144 (96.0) |
| Race/ethnicity, No. (%) | | |
| White | 66 (41.5) | 59 (39.3) |
| African American | 82 (51.6) | 77 (51.3) |
| Hispanic | 8 (5.0) | 13 (8.7) |
| Other | 3 (1.9) | 1 (0.7) |
| Marital status, No. (%) | | |
| Married/cohabitating | 11 (6.9) | 18 (12.1) |
| Never married | 92 (57.9) | 78 (52.3) |
| Divorced/separated | 55 (34.6) | 49 (32.9) |
| Widowed | 1 (0.6) | 4 (2.7) |
| Education, y | 12.4 (1.6) | 12.4 (1.7) |
| Receiving disability payments, No. (%) | 145 (91.8) | 131 (88.5) |
| Employed in past 3 y, No. (%) | 13 (8.3) | 12 (8.2) |
| Clinical | | |
| Lifetime comorbidity, No. (%) | | |
| Major depressive episode | 22 (14.0) | 25 (16.7) |
| Alcohol abuse/dependence | 89 (56.0) | 98 (65.3) |
| Drug abuse | 69 (43.4) | 73 (48.7) |
| Cocaine abuse | 47 (29.6) | 53 (35.3) |
| Current alcohol or drug abuse (past 6 mo), No. (%) | 27 (17.0) | 37 (24.7) |
| Days in hospital in prior year, No. (%) | | |
| 0 | 10 (6.4) | 6 (4.0) |
| 1-30 | 105 (66.9) | 99 (66.0) |
| 31-70 | 28 (17.8) | 28 (18.7) |
| 71-180 | 8 (5.1) | 13 (8.7) |
| >180 | 6 (3.8) | 4 (2.7) |
| Age of onset of schizophrenia, y | 23.7 (4.9) | 24.4 (5.9) |
| Outcome measure scores | | |
| Heinrichs-Carpenter Quality of Life Scale[27] | | |
| Interpersonal relations and social | 16.2 (8.2) | 17.2 (9.2) |
| Instrumental role functioning | 3.5 (4.5) | 3.2 (4.2) |
| Intrapsychic foundations | 17.5 (5.8) | 18.7 (6.5) |
| Total | 44.0 (16.6) | 46.2 (17.4) |
| Brief Psychiatric Rating Scale[24] | | |
| Positive subscale | 14.6 (3.5) | 14.4 (3.6) |
| Negative subscale | 8.8 (2.6) | 8.3 (2.9) |
| Anxiety-depression subscale | 10.9 (3.3) | 11.3 (3.3) |
| Total | 49.7 (8.6) | 48.7 (8.5) |
| Positive and Negative Syndrome Scale[26] | | |
| Positive subscale | 21.7 (5.3) | 21.3 (5.1) |
| Negative subscale | 23.2 (5.5) | 21.7 (5.7) |
| General subscale | 42.5 (7.9) | 42.1 (8.4) |
| Total | 87.5 (15.4) | 85.2 (15.5) |
| Abnormal Involuntary Movement Scale[30] | 5.0 (5.5) | 5.2 (5.9) |
| Simpson-Angus scale for extrapyramidal symptoms[31] | 0.4 (0.4) | 0.4 (0.4) |
| Barnes scale for akathisia[29] | 0.8 (1.0) | 0.8 (1.0) |
| Clinical Global Impression scale[32] | 4.5 (0.8) | 4.5 (0.7) |
| Neurocognitive tests | | |
| Motor function | 0.004 (0.72) | 0.03 (0.83) |
| Memory | –0.01 (0.78) | 0.06 (0.91) |
| Wisconsin Card Sorting Tests[36] | 0.08 (0.94) | –0.03 (0.88) |
| Short Form 36-Item Health Survey[33] | | |
| Physical component scale | 49.4 (10.6) | 49.6 (9.8) |
| Mental component scale | 38.2 (11.7) | 37.4 (12.7) |

*Data are expressed as mean (SD) unless otherwise indicated.

tecting a difference of $8700 in VA inpatient costs. However, only 309 patients were recruited, yielding an 80% chance of detecting a 5-point (6%) difference in symptoms on the PANSS[26] or a 5-point (11%) difference in the Heinrichs-Carpenter QOLS.[28]

Primary clinical outcomes were analyzed using random-effects repeated-measures models,[51] conducted with PROC MIXED from SAS statistical software, version 8 (SAS Institute Inc, Cary, NC). These models accommodate correlations among the repeated observations and therefore allow the inclusion of available data from individuals with missing observations. Missing data in these models were assumed to be missing at random. In these models, both group assignment and time are modeled as class variables, which allows assessment of both main effects for group assignment (the overall difference between treatment groups across all time points) and group × time interactions (the difference in slopes). All models included adjustment for baseline values of the dependent measures and site effects.

Because cost data were skewed, both mean and median values of aggregated cost data are presented, and analyses of statistical significance were conducted with analysis of covariance of log-transformed measures and of ranks, controlling for baseline symptoms and service use.

Although 177 patients (57.3%) discontinued the assigned study medication because of lack of efficacy, adverse effects, or other reasons (54.1% in the olanzapine group and 60.7% in the haloperidol group; $\chi^2_1=1.37$; $P=.24$), efforts were made to follow up all patients for a full 12 months and to record nonstudy medications; 26.7% of olanzapine discontinuers and 32.1% of haloperidol discontinuers were successfully followed up for the entire 12 months ($\chi^2_1=0.35$; $P=.55$). Outcomes were compared first as randomized (intention-to-treat analysis, for which 63% of all follow-up data were available) and second after excluding all data from time points after the first interruption of study

drug use (for which only 49% of all follow-up data were available). An α value of .05 was used for all statistical tests.

## RESULTS

### Sample and Treatment

Patients randomized to olanzapine (n=159) and to haloperidol (n=150) were significantly different with regard to only 1 measure at baseline: the PANSS negative subscale ($P$=.02) (TABLE 1).

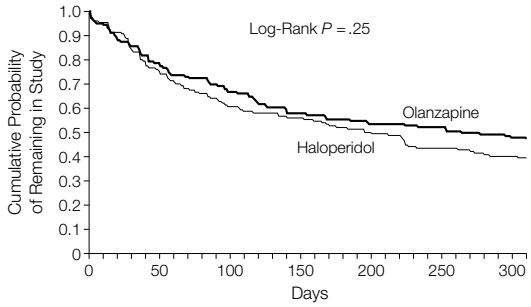
### Treatment

During the first 6 weeks of the trial, the mean (SD) dosages were 11.4 (2.2) mg/d for olanzapine and 11.2 (2.2) mg/d for haloperidol. During the remainder of the first 6 months, they were 14.7 (3.9) mg/d for olanzapine and 13.5 (4.4) mg/d for haloperidol and during the last 6 months were 15.8 (3.9) mg/d for olanzapine and 14.3 (4.6) mg/d for haloperidol.

### Retention

Survival analysis of participation in the double-blind drug treatment showed no significant difference between groups ($P$=.25 by log-rank test) (FIGURE 2). There were no significant differences in the proportion of patients who completed the entire trial while blinded and receiving study drug (39.3% of patients assigned to haloperidol vs 45.9% assigned to olanzapine; $P$=.25) or in the reasons for discontinuation among those who did not. Patients assigned to haloperidol were only marginally significantly more likely to discontinue because of adverse effects (10.0% vs 4%; $P$=.08) and there were no significant differences in the proportion of haloperidol vs olanzapine patients, respectively, who discontinued because of lack of efficacy or worsening of symptoms (12.7% vs 17.6%; $P$=.27); who were lost to follow-up, missed appointments, or moved (15.3% vs 11.9%; $P$=.41); who withdrew consent or were unhappy with blinded treatment (10.7% vs 8.8%; $P$=.70); or who discontinued for other reasons (12.0% vs 11.3%; $P$=.85). Nor were there significant differences in the use of concomitant medications at any time, including conventional antipsychotics (range, 5%-16% for all patients across time points), nonstudy atypical antipsychotics (5%-17%), antidepressants (18%-25%), and anticholinergics (6%-11%). On average, 7.7% of the olanzapine group and 8.6% of the haloperidol group took open-label anticholinergics.

**Figure 2.** Retention in Trial

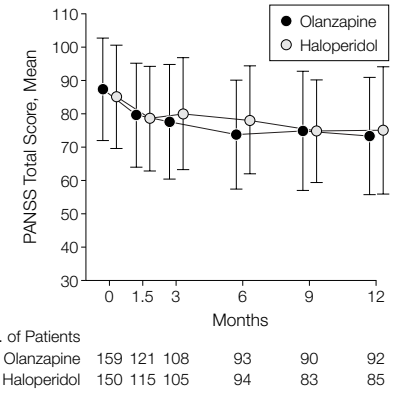



Analyzed by intention to treat ($F=0.87_{1,204}$; $P$=.35).

### Outcomes

Fifty-nine percent of patients fully completed and 36% partially completed follow-up assessments. Intention-to-treat analysis showed no significant overall differences during the 12 months of treatment on the PANSS total symptom score ($F_{1,204}=0.87$; $P$=.35) (average difference, –1.1 points; –1.3% favoring olanzapine; FIGURE 3) or on either the positive ($F=0.22_{1,206}$; $P$=.64) or negative ($F_{1,208}=1.05$; $P$=.31) subscales. There were no significant differences at any time point in the proportion of patients who showed a 20% improvement in PANSS scores. There was also no significant difference between the groups on the QOLS ($F=0.14_{1,211}$; $P$=.71) (average difference, 0.1 points; 0.2% favoring olanzapine). Nor were there any significant differences on specific subscales of the QOLS that address intrapsychic foundations ($F=0.28_{1,207}$; $P$=.59), interpersonal relationships ($F=0.00_{1,213}$; $P$=.97), or instrumental role functioning ($F=0.0_{1,199}$; $P$=.94); on either the physical ($F=1.94_{1,220}$; $P$=.16) or mental ($F=1.44_{1,216}$; $P$=.23) component scales of a secondary measure of quality of life, the SF-36; or on a global measure, the Clinical Global Outcomes scale ($F=0.02_{1,196}$; $P$=.89). Olanzapine was associated with significantly lower scores overall on the Barnes scale for akathisia ($F=14.98_{1,217}$; $P<.001$) but not on the AIMS measure of tardive dyskinesia ($F=1.87_{1,225}$; $P$=.17) or on the Simpson-Angus scale for EPS ($F=0.90_{1,203}$; $P$=.34). Although a smaller proportion of olanzapine patients had moderate or marked akathisia (5.8% vs 9.6% across all assessments, with no patient in either group having a severe rating) (FIGURE 4), this difference was modest in magnitude.

**Figure 3.** PANSS Total Scores




PANSS indicates Positive and Negative Syndrome Subscale. Error bars indicate SDs.

Secondary analysis excluding observations after the first discontinuation of study drug also showed no differences on either PANSS symptoms scores or the QOLS but somewhat more robust overall differences on the Barnes

scale for akathisia ($F=21.0_{1,164}$; $P<.001$) and significant differences on the AIMS ($F=3.95_{1,162}$; $P=.048$).

Because of the substantial amount of missing data in the later months of the trial, analysis of variance was used to compare least-square means at the 6-week and 3-month assessments, controlling for baseline values. These analyses confirmed the overall analysis, showing no significant differences on the PANSS (or any of its subscales), the Simpson-Angus scale for EPS, or the AIMS. The haloperidol group, however, had significantly higher QOLS scores at 6 weeks ($P=.04$) and the olanzapine group had significantly lower Barnes scale for akathisia scores at both 6 weeks ($P=.007$) and 3 months ($P<.001$).

Intention-to-treat analysis of neurocognitive test results showed significantly greater improvement among patients assigned to olanzapine on tests of motor functioning ($F=6.3_{1,176}$; $P=.02$) and memory ($F=5.2_{1,189}$; $P=.03$) but not on the Wisconsin Card Sorting Test ($F=0.01_{1,186}$; $P=.93$). When observations following interruption of blind study medication were excluded, these effects were somewhat more robust for motor functioning ($F=8.3_{1,153}$; $P=.005$) and memory ($F=9.4_{1,163}$; $P=.003$), but the Wisconsin Card Sorting Test remained unimproved ($F=1.09_{1,160}$; $P=.30$). These differences were modest in magnitude, reaching a maximum of 0.16 SD on motor function and 0.22 SD on memory at 9 months (FIGURE 5) but were evidently not of sufficient magnitude to improve overall quality of life, interpersonal relationships, or instrumental role functioning.

Further examination of adverse events shows that 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 that were marginally significant at 3 months ($P=.07$ by Fisher exact test), and significant at 6 months ($P=.002$) and 12 months ($P=.01$) (TABLE 2). There were fewer reports of restlessness with olanzapine, reflecting lower levels of akathisia.

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

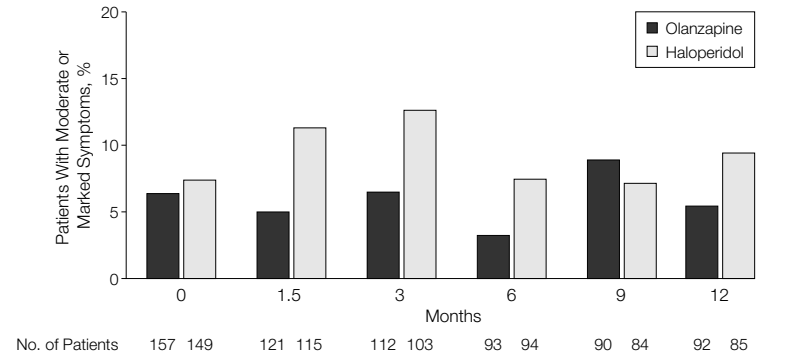
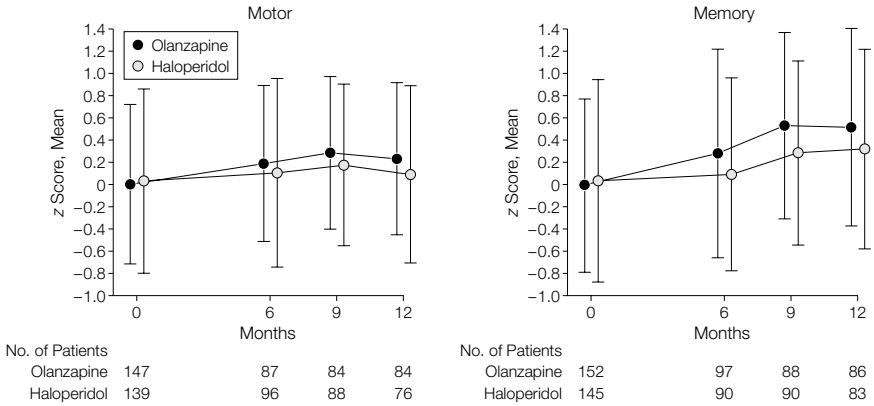



**Figure 5.** Neurocognitive Assessment




Analyzed by intention to treat for motor ($F=6.3_{1,176}$; $P=.02$) and memory ($F=5.2_{1,189}$; $P=.03$) factors. Error bars indicate SDs.

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

| | Haloperidol | | Olanzapine | | |
|---|---|---|---|---|---|
| Adverse Effects | No. of Reports/Total | % | No. of Reports/Total | % | *P* Value† |
| 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 |
| Restlessness | | | | | |
| 3 mo | 20/100 | 30.0 | 18/102 | 17.6 | .047 |
| 6 mo | 25/89 | 28.0 | 13/86 | 15.1 | .04 |
| 9 mo | 23/79 | 29.1 | 15/87 | 17.2 | .10 |
| 12 mo | 23/82 | 28.0 | 13/85 | 15.2 | .06 |

*No significant differences were reported at 3, 6, 9, or 12 months for tachycardia or palpitation, hypotension or lightheadedness, cardiotoxicity, apnea, fever, excess salivation, sedation, seizures, extrapyramidal symptoms, anticholinergic effect, neuroleptic malignant syndrome, other adverse effects, or any adverse effect.
†Determined by the Fisher exact test.

## Service Use and Cost

There were no significant differences between treatment groups on any measure of service use or VA costs, exclusive of medications (TABLE 3). Total

medication costs were 4 to 5 times greater for the olanzapine group than for the haloperidol group, using VA and wholesale prices. With the cost of medications included, both total VA mental health costs and total VA health costs were significantly greater for patients assigned to olanzapine. The magnitude of the differences in cost is reduced when medians rather than means were examined, but nonparametric analysis of ranked cost data still showed statistically significant differences, with higher VA costs for olanzapine ranging from $3000 to $9000 across measures (Table 3).

Non-VA health costs and nonhealth costs showed no significant differences, and differences in societal costs (including both VA and non-VA costs) were slightly smaller than differences in VA costs and were not statistically significant. (VA plus non-VA costs were nonsignificant because while VA costs

**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 |
|---|---|---|---|---|---|
| Service use | | | | | |
| Mental health | | | | | |
| Outpatient visits | 47.0 (64.5) | 61.7 (89.3) | −14.7 | 1.72 | .09 |
| Inpatient days | 42.7 (68.8) | 35.6 (55.0) | 7.1 | 1.62 | .11 |
| Non–mental health | | | | | |
| Outpatient visits | 46.8 (63.9) | 44.7 (71.7) | 2.1 | 0.69 | .49 |
| Inpatient days | 2.4 (9.4) | 2.0 (9.9) | 0.4 | 1.02 | .31 |
| Residential days | 10.5 (34.2) | 14.1 (38.9) | −3.6 | 1.09 | .27 |
| VA health care costs (excluding medications), $ | 39 638 (47 385) | 32 722 (34 640) | 6916 | 0.51 | .61 |
| Mental health | 31 442 (42 513) | 25 705 (33 214) | 5737 | 0.04 | .96 |
| Outpatient visits | 3594 (4247) | 3861 (4366) | −267 | 1.70 | .09 |
| Inpatient days | 27 849 (42 696) | 21 844 (33 278) | 6005 | 1.59 | .11 |
| Non–mental health | 6100 (13 830) | 4584 (8926) | 1516 | 1.12 | .26 |
| Outpatient visits | 3169 (5079) | 2914 (4712) | 255 | 0.89 | .37 |
| Inpatient days | 2931 (12 281) | 1670 (6577) | 1261 | 0.94 | .35 |
| Residential days | 2096 (7505) | 2433 (7689) | −337 | 0.20 | .84 |
| 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 |
| Non-VA costs, $ | 3948 (8236) | 5323 (8584) | −1375 | 0.86 | .39 |
| Non-VA health costs | 2423 (6964) | 3213 (6888) | −790 | 0.85 | .39 |
| Non-VA mental health costs | 1342 (4861) | 2037 (5422) | −695 | 1.02 | .31 |
| Non-VA non–mental health costs | 1080 (2931) | 1175 (2587) | −95 | 0.58 | .56 |
| Nonhealth costs, $ | 1525 (3200) | 2110 (4837) | −585 | 0.04 | .97 |
| Criminal justice | 1260 (2547) | 1711 (4582) | −451 | 0.38 | .70 |
| Administrative costs of public support | 721 (370) | 682 (372) | 39 | 1.58 | .11 |
| Employment (negative cost) | 455 (1485) | 283 (1057) | 172 | 1.42 | .16 |
| Societal costs, $ | | | | | |
| Medication at VA prices | 45 811 (48 079) | 38 439 (35 502) | 7372 | 1.17 | .24 |
| Median (IQR)‡ | 30 693 (15 390-53 309) | 26 383 (15 365-51 403) | 4310 | | .40 |
| Medication at wholesale prices | 47 723 (48 121) | 39 113 (35 561) | 8610 | 1.84 | .07 |
| Median (IQR)‡ | 31 906 (17 556-54 308) | 27 601 (15 985-51 627) | 4305 | | .20 |

Abbreviations: IQR, interquartile range; VA, Department of Veterans Affairs.
*Data are expressed as mean (SD) unless otherwise indicated.
†Analysis of covariance of log-transformed values controlling for preentry service use and symptoms.
‡Nonparametric rank test with adjustment for preentry service use and symptoms.

were significantly different between groups, non-VA costs were not; when combined, these costs were less different between groups.) While the costs of antipsychotic drugs were very different between the groups, the costs of other psychotropic drugs were the same, which tended to neutralize the cost difference for antipsychotic agents, leaving less difference in cost between the 2 groups.

## COMMENT

This 12-month double-blind study found no statistically or clinically significant advantages of olanzapine for schizophrenia on measures of compliance, symptoms, or overall quality of life, nor did it find evidence of reduced inpatient use or total cost. Olanzapine treatment did result in modestly reduced symptoms of akathisia, in less tardive dyskinesia in one secondary analysis, and in small but significant improvements in measures of memory and motor function. Although verbal memory has been reported to be associated with functional capacity,[52] cognitive gains with olanzapine were insufficient to improve QOLS functioning or employment earnings. Olanzapine was also associated with more frequent reports of weight gain and with significantly greater total VA costs, ranging from $3000 to $9000 per patient annually.

These results are substantially less favorable for olanzapine than those reported in previous trials.[8-13,15] Perhaps the most unexpected difference was the lack of any significant advantage for olanzapine on measures of retention, termination due to adverse effects, or EPS other than akathisia. These differences are most likely explained by 2 major differences between this study and others: (1) prophylactic benztropine was prescribed for the haloperidol group (as recommended in a recent treatment overview[53] and as used in typical clinical practice[54]) and (2) outcome data were collected for all patients, even after interruptions of protocol treatment. Studies more favorable to olanzapine,[8-11,13,15] in contrast, allowed use of antiparkinsonian agents only after symptoms arose, increasing the risk of EPS (which is greater for haloperidol than any other antipsychotic and is especially high for men[55]). Rating biases also may have been introduced in those studies because without prophylaxis, haloperidol patients can readily be identified. In addition, since no data were collected after protocol interruptions due to EPS, there could be no documentation of eventual recovery from this highly treatable syndrome.

Apparent differences in symptom and functional outcomes may also reflect these methodological differences. Clinical descriptions from the pre-atypical era suggest that even in the absence of frank pseudoparkinsonian symptoms, patients taking conventional medications may have akinesia and, as a result, manifest a poor response to conventional antipsychotics until prescribed anticholinergic agents.[56] In the International Collaborative Trial (ICT), one of the manufacturer's US Food and Drug Administration registration trials and the basis for most published comparisons of olanzapine and haloperidol,[10-13] 66.5% of olanzapine patients but only 46.8% of haloperidol patients ($P<.001$) completed 6 weeks of treatment—a substantial difference that was attributed to lack of efficacy.[10] The high failure rate with haloperidol in the ICT, however, may actually reflect the lack of prophylactic antiparkinsonian medication. In contrast with the 46.8% retention rate among haloperidol patients in the ICT, the present study found that 71% of prophylactically treated haloperidol patients were retained during the first 6 weeks of the trial. Thus, the main difference between the 2 studies is the far superior performance of haloperidol in the current trial. Once properly treated for EPS, haloperidol patients in the ICT would most likely have shown further clinical improvement, but such improvement was not documented because data collection was halted. Furthermore, in the absence of prophylactic treatment, haloperidol patients, like their raters, could have recognized which treatment they were receiving, further undoing the double blind.

While the present study relied on mixed models that used all available data and associated each observation with the actual time point at which it was obtained, the ICT relied on a last-observation-carried-forward analysis in which the last rating during assigned study drug treatment was used as the single end point, regardless of when it was obtained. Since patients assigned to olanzapine discontinued later than haloperidol patients, their last observation was likely to have been biased by having more time for either improvement or regression to the mean.

After 6 weeks, the ICT conducted follow-up assessments only on treatment responders.[10] Reports of reduced long-term health costs[13] and improved quality of life[11] with olanzapine in the ICT are thus based on seriously biased last-observation-carried-forward rather than intention-to-treat analyses and follow-up rates of only 28% over the year for the olanzapine group and 15% for haloperidol.[13]

One final difference is that, unlike the ICT, the current trial did not exclude patients with current addictive disorders. However, reanalysis of major outcomes excluding these patients did not reveal any additional differences in symptoms, adverse effects, or quality of life.

The major limitations of this study are the loss of follow-up data, especially in the later phases of the trial, and the use of concomitant nonstudy atypical and conventional antipsychotic agents. However, there were no significant differences between groups in the duration of adherence to the study protocol, reasons for discontinuing study drug, or use of any concomitant medications, including anticholinergic agents. Furthermore, the results based on all data do not differ from those that exclude data collected after treatment protocol violations or from analyses limited to the first 3 months of the trial, when protocol adherence was high.

Also, because the study sample was overwhelmingly male, all treatment was provided in VA facilities, and less than

10% of patients considered for recruitment were enrolled, the generalizability of these findings to other populations and health care systems is unknown. The hospitals involved in this trial had somewhat higher per diem psychiatric inpatient costs than other VA facilities[40] but lower per diem costs than non-VA hospitals.[44,45]

Another possible limitation is that a strict upper limit of 20 mg/d was placed on the dosages of both haloperidol and olanzapine. However, the average dosage of olanzapine used in this study was similar to the average dosages of 14.1 mg/d nationally in the VA[57,58] and to both 12.2 mg/d in a large private sector sample[57,58] and dosages reported in the ICT.[10] Haloperidol dosages averaged 13.6 mg/d in the current trial compared with only 11.8 mg/d in the ICT.

Although we did not meet our power target of 600 patients, we still had 80% power to detect a 6% difference between groups on the PANSS and an 11% difference on the QOLS, both notably smaller than generally accepted difference of 20% needed for clinical significance. Average differences on both measures were, in fact, less than 2%.

A final limitation is that this study did not determine whether the benefits of olanzapine are worth the additional costs and adverse consequences. It is clear that olanzapine is not a dominant choice (ie, it does not have both superior outcomes and lower cost).[59] Our analyses did not indicate, however, whether the clinically modest reduction in akathisia and the improvements on neurocognitive measures are valuable enough to offset the increased cost of olanzapine and the risk of weight gain and, possibly, diabetes.[18] Although methods have been developed to address this kind of question,[59-61] they are not readily applicable to this study because of the discrepant positive and negative findings across measures and because data from a global health utility measure[59,60,62] were not collected. However, in view of the very small average differences between groups in quality of life and the significantly higher quality-of-life scores in the haloperidol group at 6 weeks, when adherence to the research protocol was best, it seems unlikely that olanzapine would have shown significantly higher scores than haloperidol on such measures.

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