Olanzapine Versus Haloperidol in the Treatment of Schizophrenia and Schizoaffective and Schizophreniform Disorders: Results of an International Collaborative Trial

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Objective: This international, multicenter double-blind trial was designed to compare the therapeutic profile of an atypical antipsychotic, olanzapine, with that of a conventional dopamine D_2 antagonist, haloperidol. Method: A total of 1,996 patients at 174 sites in Europe and North America were randomly assigned to treatment with olanzapine (N=1,336) or haloperidol (N=660) over 6 weeks. The primary efficacy analysis involved the mean change from baseline to endpoint in total scores on the Brief Psychiatric Rating Scale (BPRS). Secondary analyses included comparisons of the mean change in positive and negative symptoms, comorbid depression, extrapyramidal symptoms, and overall drug safety. Results: Olanzapine demonstrated clinical results superior to those of haloperidol on overall improvement according to the BPRS and on every secondary measure, including depression. Olanzapine was also associated with significantly fewer discontinuations of treatment due to lack of drug efficacy or adverse events. Substantially more olanzapine-treated patients (66.5%) than haloperidol-treated patients (46.8%) completed 6 weeks of therapy. Statistically significant advantages of olanzapine treatment were related to 1) change in negative symptoms, 2) extrapyramidal symptom profile, 3) effect on prolactin levels, and 4) response rate. Conclusions: Olanzapine shows a superior and broader spectrum of efficacy in the treatment of schizophrenic psychopathology, with a substantially more favorable safety profile, than haloperidol. It meets several of the criteria for a novel atypical antipsychotic agent.

(Am J Psychiatry 1997; 154:457–465)

Schizophrenia is a heterogeneous condition that includes positive, disorganized, dysphoric, and negative symptoms. Increasingly, evidence links these symptoms to multiple brain regions, suggesting the underlying disruption of one or more fundamental neural circuits (1). Furthermore, in contrast to earlier theories (e.g., one transmitter, one locus), a broad range of neurotransmitters are now implicated (2).

Received Aug. 8, 1996; revision received Dec. 23, 1996; accepted Dec. 27, 1996. From Lilly Research Laboratories. Address reprint requests to Dr. Tollefson, Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Drop Code 0538, Indianapolis, IN 46285.

The authors thank Suzanne Myers for technical and editorial assistance in the preparation of this manuscript.

Conventional antipsychotic agents show therapeutic limitations. This class of drugs, the by-product of dopamine D_2 receptor screening efforts, is effective in suppressing positive symptoms in some schizophrenic patients; however, nearly one-half of patients experience incomplete or no response (3). Other symptoms (e.g., negative or mood features) are marginally benefited or even exacerbated. Furthermore, neuroleptic-induced adverse events contribute to rates of noncompliance approaching 50% (4). Such generalities serve as a compelling motivation to seek a novel treatment alternative, that is, an "atypical" agent.

An atypical antipsychotic has been characterized as one that exhibits 1) broader efficacy, 2) a lower incidence of extrapyramidal symptoms, 3) minimal perturbation of prolactin levels, and 4) therapeutic efficacy

TABLE 1. Baseline Severity of Illness Scores of Schizophrenic Patients Assigned to Olanzapine or Haloperidol Treatment Who Had at Least One Postbaseline Observation

Variable	Olanzapine Group N	Olanzapine Group Mean	Olanzapine Group SD	Haloperidol Group N	Haloperidol Group Mean	Haloperidol Group SD	Effect Size	p[a]
BPRS total score[b]	1,312	33.1	10.6	636	34.1	11.0	–0.10	<0.02
Positive and Negative Syndrome Scale								
Total score	1,312	90.1	19.2	636	92.1	20.0	–0.10	0.01
Positive symptom score	1,312	21.2	6.1	636	21.5	6.0	–0.05	0.49
Negative symptom score	1,312	24.0	6.8	636	24.5	7.1	–0.07	0.65
Clinical Global Impression severity score	1,318	4.7	0.9	640	4.7	0.9	–0.05	0.53
Montgomery-Åsberg Depression Rating Scale total score	1,053	16.6	8.9	428	16.7	8.7	–0.01	0.55

[a]Analysis of variance (df=1, >1000 for all variables).
[b]Items scored 0–6.

TABLE 2. Disposition of Schizophrenic Patients Assigned to Olanzapine or Haloperidol Treatment

Variable	Olanzapine Group (N=1,336) N	Olanzapine Group (N=1,336) %	Haloperidol Group (N=660) N	Haloperidol Group (N=660) %	Effect Size	p[a]
Treatment completed	888	66.5	309	46.8	0.40	<0.001
Reason treatment was discontinued						
Adverse event	60	4.5	48	7.3	–0.12	0.01
Lack of efficacy	277	20.7	212	32.1	–0.26	<0.001
Patient lost to follow-up	15	1.1	11	1.7	–0.05	0.31
Patient's decision	48	3.6	49	7.4	–0.17	<0.001
Sponsor's decision	4	0.3	2	0.3	0.00	0.99
Noncompliance	44	3.3	29	4.4	–0.06	0.22

[a]Chi-square test (df=1).

among nonresponders to conventional neuroleptics (5). Such a therapeutic advance should have substantial relevance for the societal costs, personal suffering, and mortality that characterize schizophrenia.

Olanzapine is a novel antipsychotic displaying nanomolar affinity at D_1–D_4, serotonergic (5-$HT_{2,3,6}$), muscarinic (subtypes 1–5), adrenergic (α_1), and histaminergic (H_1) binding sites (6). The pharmacology may further include a glutamatergic mechanism; olanzapine antagonizes phencyclidine- or MK-801-induced behaviors modeling schizophrenia (7). This distinctive profile distinguishes olanzapine from other, conventional antipsychotic agents.

Given this background, we hypothesized that olanzapine would demonstrate a superior safety and efficacy profile in comparison with a conventional neuroleptic, haloperidol. To test this hypothesis, the largest single prospective, blind, and controlled antipsychotic trial undertaken so far was conducted in 17 countries, involving 1,996 patients with schizophrenia or related disorders randomly assigned to treatment.

METHOD

At a total of 174 sites, male and female inpatients and outpatients at least 18 years of age who met the DSM-III-R criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder were randomly assigned to treatment. Patients were required to have a minimum Brief Psychiatric Rating Scale (BPRS) score of 18 (items extracted from the Positive and Negative Syndrome Scale [8] and scored 0–6) and/or be intolerant of current antipsychotic therapy (excluding haloperidol). After a description of the study to the patients, informed written or witnessed oral consent was obtained.

Following a 2- to 9-day screening phase, qualified patients were randomly assigned to treatment with either olanzapine, 5 mg/day, or haloperidol, 5 mg/day (two olanzapine subjects for each haloperidol subject). Either drug could be subsequently increased by 5 mg/week to 20 mg/day or decreased to a minimum of 5 mg/day as clinically warranted.

The protocol established the primary efficacy analysis as the mean change from baseline to endpoint in the Positive and Negative Syndrome Scale-extracted BPRS score. Secondary analyses included scores on the Positive and Negative Syndrome Scale itself, the Montgomery-Åsberg Depression Rating Scale (9), and the Clinical Global Impression (CGI) scale (10).

Analysis of adverse events was based on clinical report form records, administration of an objective scale (Association for Methodology and Documentation in Psychiatry [AMDP-5]) (11), vital signs, standardized instruments for the assessment of extrapyramidal symptoms (12, 13), laboratory tests, ECGs, ophthalmological examinations, and chest X-rays.

All statistical analyses were done on an intent-to-treat basis; that is, data from all randomly assigned patients were included in the analysis. Patients were included in the analysis of change if they had both a baseline and at least one postbaseline observation. Total scores on rating scales were derived from the individual item scores; if any single item score was missing, the total score was treated as missing.

For all continuous efficacy and safety parameters, analysis of variance (ANOVA) was used to compare treatment effects in the olanzapine and haloperidol groups. For last-observation-carried-forward, intent-to-treat analyses of change from baseline, the independent variables in the ANOVA were treatment, geographic region, and treatment-by-geographic region interaction. Geographic region represented the individual countries in Europe and five geographically based regions in the United States chosen a priori.

For selected efficacy parameters, weekly change from baseline was analyzed with the use of ANOVA. In each weekly analysis, the dependent variable was the observed change from baseline, and the independent variables in the ANOVA were treatment and geographic region. For within-subgroup analysis, the independent variables in the ANOVA were treatment and geographic region.

Pearson's chi-square test was used to analyze treatment effects for categorical efficacy and safety. Reports of adverse events were elicited through the use of both directed (with the AMDP-5) and nondirected interviews. Treatment-emergent adverse events were defined as events that worsened from baseline or first appeared during the treatment period.

Estimated effect sizes for continuous and binary variables were calculated to provide a standardized measure of the observed treatment

TABLE 3. Change From Baseline to Endpoint in Severity of Illness Scores of Schizophrenic Patients Treated With Olanzapine or Haloperidol

Variable	Change in Score						Effect Size	p[a]
	Olanzapine Group			Haloperidol Group				
	N	Mean	SD	N	Mean	SD		
BPRS total score[b]	1,312	–10.9	12.9	636	–7.9	12.2	–0.23	<0.02
Positive and Negative Syndrome Scale								
Total score	1,312	–17.7	21.8	636	–13.4	20.6	–0.20	0.05
Positive symptom score	1,312	–4.7	6.8	636	–3.8	6.3	–0.14	0.06
Negative symptom score	1,312	–4.5	6.3	636	–3.2	6.1	–0.21	0.03
Clinical Global Impression severity score	1,318	–1.0	1.2	640	–0.7	1.1	–0.24	<0.03
Montgomery-Åsberg Depression Rating Scale total score	1,053	–6.0	8.7	428	–3.1	8.8	–0.33	0.001

[a]Analysis of variance (df=1, >1000 for all variables).
[b]Items scored 0–6.

effect. For continuous data, the estimated effect size was the difference between treatment means (olanzapine minus haloperidol) divided by the pooled estimate of the standard deviation. For binary data, the estimated effect size was the standardized difference (olanzapine minus haloperidol) between the arc sine square root transformed proportions.

All cited p values were two-tailed, with a significance level of 0.05 as specified in the protocol. All intent-to-treat analyses of efficacy and safety parameters were specified in the protocol. No adjustments in p values for the multiplicity of tests were made; therefore, the error rate was on a comparisonwise basis.

RESULTS

A total of 2,223 patients entered the screening phase of the study. Of these, 1,996 were subsequently randomly assigned to treatment over a 14-month period; the distribution among the 174 investigative sites ranged from 13 sites with one patient to a single site with 73 patients. Of the 1,996 patients, 1,073 were from North America and 923 were from Europe.

The olanzapine group (N=1,336) and the haloperidol group (N=660) were similar with regard to patient and illness characteristics. The mean age was 38.7 years (SD= 11.6) in the former and 38.3 years (SD=11.1) in the latter. The majority of the patients had schizophrenia of the paranoid subtype, and approximately 86% had a chronic course (with or without acute exacerbation).

Treatment histories revealed that many patients had had a suboptimal response to previous conventional therapies. A total of 76.7% of the patients in the olanzapine group and 77.6% of the patients in the haloperidol group either had to discontinue or were otherwise judged unresponsive to their last course of antipsychotic therapy (excluding haloperidol).

The patients randomly assigned to treatment were comparable with regard to baseline disease severity (table 1). Overall, the group was moderately ill. The haloperidol-treated patients showed statistically significant, albeit clinically insignificant, higher mean total scores on the BPRS and the Positive and Negative Syndrome Scale. Other indexes showed nonsignificant differences.

A total of 1,197 patients, or 60%, completed the acute phase of the study. The mean modal dose was 13.2 mg/day (SD=5.8) for olanzapine and 11.8 mg/day (SD=5.6) for haloperidol. The distribution of modal daily doses was as follows: 5 mg, 28% of the olanzapine group and 37% of the haloperidol group; 10 mg, 22% of the olanzapine patients and 27% of the haloperidol patients; 15 mg, 19% of the olanzapine patients and 16% of the haloperidol patients; and 20 mg, 31% of the olanzapine group and 20% of the haloperidol group.

As shown in table 2, a significantly greater proportion of the patients in the olanzapine group than of those in the haloperidol group completed 6 weeks of acute treatment. In addition, the percentage of patients who discontinued treatment because of an adverse event or a lack of efficacy was significantly higher in the haloperidol group than in the olanzapine group.

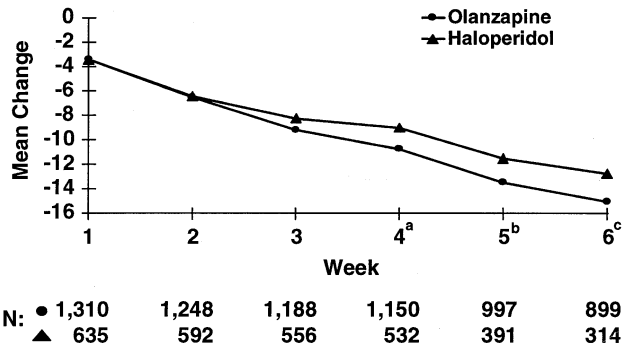
Drug Efficacy

Endpoint analysis. Olanzapine outperformed haloperidol on all six efficacy measures (table 3). Patients in the olanzapine group had a significantly greater mean improvement in the extracted BPRS total score, the primary efficacy measure defined in the study protocol. The comparative changes in Positive and Negative Syndrome Scale total scores confirmed this advantage, which included both positive and negative symptom scores. Furthermore, the treatment effect on associated depressive symptoms revealed that olanzapine-treated patients had a twofold greater improvement in Montgomery-Åsberg Depression Rating Scale total scores than patients in the haloperidol group. Reflecting advantages across these multiple symptom domains, changes in CGI severity scores also favored olanzapine.

No significant treatment-by-gender interactions were noted on these six efficacy measures.

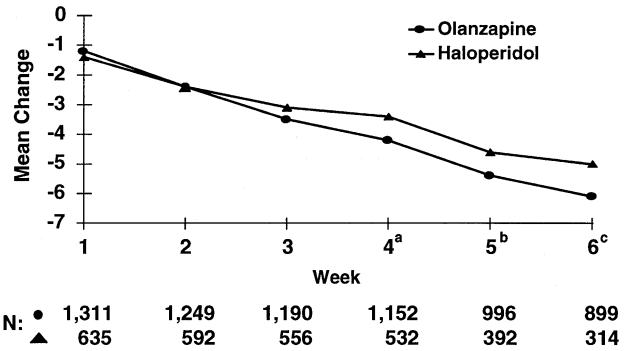
Weekly analysis. The mean change from baseline in weekly BPRS scores and Positive and Negative Syndrome Scale total, positive symptom, and negative symptom scores was also analyzed. The decreases in BPRS total score from baseline to each visit (figure 1) were greater in the olanzapine group than in the haloperidol group from week 3 through week 6 (significantly greater at weeks 4–6). Mean decreases in Positive and Negative Syndrome Scale negative symptom scores from baseline to weeks 4–6 were also significantly

FIGURE 1. Mean Change From Baseline in Weekly BPRS Total Scores of Schizophrenic Patients Treated With Olanzapine or Haloperidol (Observed Case Analysis)



[a]F=10.4, df=1, 1660, p=0.001.
[b]F=9.9, df=1, 1366, p=0.002.
[c]F=11.6, df=1, 1191, p<0.001.

FIGURE 2. Mean Change From Baseline in Weekly Negative Symptom Scores on the Positive and Negative Syndrome Scale of Schizophrenic Patients Treated With Olanzapine or Haloperidol (Observed Case Analysis)



[a]F=7.4, df=1, 1662, p=0.007.
[b]F=5.3, df=1, 1366, p=0.02.
[c]F=9.1, df=1, 1191, p=0.003.

greater in the olanzapine group than in the haloperidol group (figure 2). The mean decreases in Positive and Negative Syndrome Scale positive symptom scores were numerically superior at each week but not statistically significant.

Response rate. An alternative measure of the two respective treatment effects was clinical response. Response was defined as 40% or more improvement in BPRS score from baseline and at least 3 study weeks completed. Olanzapine-treated patients had a significantly higher response rate (52%) than haloperidol-treated patients (34%) (χ^2=42.4, df=1, p<0.001).

Drug Safety

Clinician-solicited adverse events. There was a significant difference between the treatment groups in the incidence of 27 of the 40 AMDP-5 events. Twenty-five events were significantly more common among the haloperidol-treated patients, whereas only two events occurred more frequently among the olanzapine-treated patients (table 4). Among these events, those suggestive of extrapyramidal effects and sleep disruptions, several anticholinergic effects (e.g., palpitations, blurred vision), and hypersalivation were reported significantly more often with haloperidol.

TABLE 4. Significant Differences[a] in Treatment-Emergent Adverse Events Among Schizophrenic Patients Treated With Olanzapine or Haloperidol

	Olanzapine Group (N=1,306)		Haloperidol Group (N=636)		
Adverse Event[b]	N	%	N	%	Effect Size
More common with olanzapine					
Excessive appetite	313	24.0	79	12.4	0.30
Dry mouth	290	22.2	103	16.2	0.15
More common with haloperidol					
Difficulty falling asleep	299	22.9	183	28.8	–0.13
Interrupted sleep	248	19.0	193	30.3	–0.26
Shortened sleep	197	15.1	158	24.8	–0.24
Increased dreams/nightmares	170	13.0	110	17.3	–0.12
Early awakening	208	15.9	153	24.1	–0.21
Drowsiness	339	26.0	199	31.3	–0.12
Decreased appetite	149	11.4	115	18.1	–0.19
Hypersalivation	113	8.7	124	19.5	–0.32
Nausea	132	10.1	87	13.7	–0.11
Vomiting	67	5.1	57	9.0	–0.15
Palpitations	86	6.6	63	9.9	–0.12
Ataxia	22	1.7	20	3.1	–0.09
Blurred vision	139	10.6	96	15.1	–0.13
Increased perspiration	89	6.8	84	13.2	–0.22
Difficulty with micturition	47	3.6	39	6.1	–0.12
Heaviness in extremities	150	11.5	104	16.4	–0.14
Hot flashes	45	3.4	36	5.7	–0.11
Chills	56	4.3	48	7.5	–0.14
Conversion symptoms	13	1.0	15	2.4	–0.11
Hypertonia	110	8.4	134	21.1	–0.37
Hypotonia	35	2.7	29	4.6	–0.10
Tremor	216	16.5	167	26.3	–0.24
Acute dyskinesia	37	2.8	51	8.0	–0.24
Hypokinesia	67	5.1	86	13.5	–0.30
Akathisia	186	14.2	226	35.5	–0.50

[a]p<0.05, chi-square test.
[b]From the Association for Methodology and Documentation in Psychiatry (AMDP-5) scale (11).

Extrapyramidal symptoms. Further data regarding differences between treatments in extrapyramidal effects were analyzed in two formats: 1) spontaneously reported adverse events (grouped into five categories of extrapyramidal symptoms from the Coding Symbol and Thesaurus for Adverse Event Terminology [COSTART; 14]) and 2) scores on the two extrapyramidal symptom severity rating scales. Dystonic, parkinsonian, akathisia, and residual events were reported significantly less often by the olanzapine-treated patients (table 5).

Ratings on the Simpson-Angus scale (12) and the Barnes Akathisia Scale (13) were analyzed to estimate the rate of

emergence of extrapyramidal symptoms by both baseline-to-endpoint and newly emergent categorical changes. The change in Simpson-Angus scale score from baseline to endpoint reflected a 1-point improvement in extrapyramidal symptoms among the olanzapine-treated patients and a 1-point worsening among the haloperidol-treated patients, a significant difference ($F=38.9$, $df=1, 1868$, $p<0.001$). A similar pattern was seen with the Barnes Akathisia Scale results ($F=34.7$, $df=1, 1903$, $p<0.001$), where olanzapine-treated patients' scores improved and haloperidol-treated patients' scores worsened from baseline.

The percentage of patients with treatment-emergent parkinsonism (a total score >3 on the Simpson-Angus scale) was significantly smaller in the olanzapine group (14.1%) than in the haloperidol group (37.9%) ($\chi^2=101.6$, $df=1$, $p<0.001$). Similarly, significantly fewer olanzapine-treated patients (12.3%) than haloperidol-treated patients (40.3%) had a treatment-emergent Barnes scale global score of 2 or more at any postbaseline visit ($\chi^2=167.0$, $df=1$, $p<0.001$). Both of these treatment differences were clinically meaningful.

Concomitant medication use. The proportion of olanzapine-treated patients taking at least one dose of a permitted concomitant drug was significantly smaller than the proportion of their haloperidol-treated counterparts for both a benzodiazepine and benztropine. A meaningful difference in rates was evident with the latter (table 6).

Vital signs. Assessments of vital signs revealed no clinically significant differences between treatment groups. A slight increase in weight was associated with olanzapine therapy, the endpoint mean weight increase being 1.88 kg (SD=3.54); for haloperidol, the mean increase was 0.02 kg (SD=2.79). This difference was significant ($F=38.0$, $df=1, 1894$, $p<0.001$). However, a post hoc analysis revealed that body mass index was a relevant predictor of weight gain. Patients with a low prestudy body mass index were significantly more likely to have gained weight during treatment with olanzapine. Haloperidol-treated patients experienced more weight loss (7% or more of baseline weight), 4.6% versus 2.5% ($\chi^2=5.8$, $df=1$, $p<0.02$). There was no significant treatment-by-gender interaction, indicating that the treatment effect in weight change was consistent between male and female patients.

Laboratory analytes. While mild, transient increases in prolactin levels were observed in both treatment groups, these elevations (change from baseline to maximum prolactin level) were significantly smaller in the olanzapine treatment group ($F=110.3$, $df=1, 1309$, $p<0.001$) and typically nonpersistent.

Neither compound showed evidence of hematotoxicity. Both leukopenia and neutropenia were less frequently associated with olanzapine than with haloperidol. No case of agranulocytosis was encountered.

Olanzapine treatment was associated with early transient increases (mean change from baseline=5.91 U/liter, SD=27.8) in hepatic transaminase (ALT; 7.9% of patients); however, these elevations were not associated with clinical symptoms, were modest in scope, and did not necessitate the discontinuation of olanzapine. Overall, on a time-adjusted basis, the incidence of transaminasemia with olanzapine was comparable to that seen with haloperidol.

Treatment-by-gender analysis showed no clinically significant differences in laboratory analytes between male and female patients.

TABLE 5. Treatment-Emergent Extrapyramidal Adverse Events Among Schizophrenic Patients Treated With Olanzapine or Haloperidol

Category of Extrapyramidal Events[a]	Olanzapine Group (N=1,336)		Haloperidol Group (N=660)		Effect Size	p[b]
	N	%	N	%		
Dystonic[c]	19	1.4	35	5.3	–0.23	<0.001
Parkinsonian[d]	128	9.6	177	26.8	–0.46	<0.001
Akathisia[e]	104	7.8	149	22.6	–0.42	<0.001
Dyskinetic[f]	26	1.9	15	2.3	–0.03	0.63
Residual[g]	21	1.6	19	2.9	–0.09	0.05
Any extrapyramidal event	256	19.2	298	45.2	–0.57	<0.001

[a]From the Coding Symbol and Thesaurus for Adverse Event Terminology (COSTART) (14).
[b]Chi-square test (df=1).
[c]Patients with the following symptoms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.
[d]Patients with the following symptoms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.
[e]Patients with the following symptoms were counted in this category: akathisia, hyperkinesia.
[f]Patients with the following symptoms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.
[g]Patients with the following symptoms were counted in this category: movement disorder, myoclonus, itching.

TABLE 6. Use of Other Medications by Schizophrenic Patients Treated With Olanzapine or Haloperidol

Variable	Olanzapine Group (N=1,336)		Haloperidol Group (N=660)		Effect Size	p[a]
	N	*%*	*N*	*%*		
Benzodiazepine used at least once	808	60.5	437	66.2	–0.12	0.01
Benztropine used at least once	228	17.1	315	47.7	–0.67	<0.001
	Mean	*SD*	*Mean*	*SD*		
Dose of benztropine (mg/day)	0.33	1.12	1.29	2.44	–0.58	<0.001

[a]Analysis of variance (df=1, 1954) for continuous data; chi-square test (df=1) for categorical data.

DISCUSSION

As stated earlier, conventional neuroleptics, while widely prescribed as treatment for psychotic disorders, present three primary weaknesses. First, the therapeutic benefits of conventional antipsychotics in schizophrenia are principally limited to positive symptoms, and the effect sizes are variable. Hegarty et al. (3) reviewed 821 international studies conducted between 1895 and 1992 and found an average overall response rate of 40% among patients with schizophrenia. When studies done prior to the midpoint of the century were excluded, only one-half of schizophrenic patients achieved acceptable symptom reductions.

Negative symptoms impose great suffering on patients by impeding their rehabilitation and psychosocial functioning (15). Crow (16) has characterized these symptoms (type II syndrome) as unresponsive to neuroleptic treatment. Lack of therapeutic efficacy for negative symptoms, be they primary or secondary, is a major deficiency among the conventional D_2-blocking agents and may explain their limitations in mediating the chronic course of schizophrenia (17). Meltzer (18) recently commented on data suggesting that a pleotrophic pharmacology (similar to that of olanzapine) may convey a therapeutic advantage in the treatment of negative symptoms and that "sorting out primary versus secondary issues may be less important than providing assistance in the recovery of normal function."

Second, depressive signs and symptoms are also evident in 25%–75% of schizophrenic patients (19). In these patients they have been associated with higher rates of mortality, a poor long-term prognosis, and more frequent rehospitalizations. Because conventional neuroleptics are of limited benefit for depressive signs and symptoms, cyclic antidepressants are often added as therapeutic adjuncts. Moreover, conventional D_2 antagonists may cause a neuroleptic-induced dysphoria.

Third, extrapyramidal symptoms are among the leading causes of poor compliance with antipsychotic treatment. Casey (20) has suggested that neuroleptic-induced extrapyramidal symptoms "are among the most troublesome side effects." They are seen in 50%–75% of patients receiving neuroleptic drugs and are a common reason why patients discontinue their drug treatment. Extrapyramidal symptoms are the result of the nonselective antagonism of brain dopamine receptors (i.e., those of the basal ganglia or A9 dopaminergic pathway). While these symptoms were once assumed to be a necessary consequence of a therapeutically effective dose (the "neuroleptic-threshold"), experience with clozapine has disproved the concept (21).

Efficacy

Both the BPRS and the Positive and Negative Syndrome Scale are widely accepted psychometric instruments for the assessment of antipsychotic efficacy. The BPRS score, defined a priori as the primary outcome measure, was "extracted" from items on the Positive and Negative Syndrome Scale. These items do not fully correspond to traditional BPRS definitions; however, both scales were consistent in that the last-observation-carried-forward analysis of acute treatment revealed a significantly greater effect among olanzapine-treated than among haloperidol-treated patients. Given the long course of schizophrenic illness and the previous treatment histories of this study group, one might speculate that a selection bias against haloperidol explains this difference. However, since lack of response to or tolerance of a last course of treatment with haloperidol was an exclusion criterion, this confounding factor should have been minimized.

While the present study was not a systematized effort (22) to evaluate olanzapine versus haloperidol among treatment-resistant patients, these data provide a signal that olanzapine offers potential in the treatment of nonresponders or partial responders to previous antipsychotic therapy. In turn, it is plausible that the olanzapine treatment effect might have been even greater in a less chronically ill group.

As noted earlier, an overall treatment response is composed of changes in at least three elements: positive, negative, and depressive symptoms. Haloperidol has been repeatedly shown to be an effective treatment for the positive features of schizophrenia (23). However, the present trial favored olanzapine over haloperidol on improvement in Positive and Negative Syndrome Scale positive symptom scores in the last-observation-carried-forward analysis. In a classic work, Creese et al. (24) demonstrated a strong correlation between a neuroleptic's D_2 receptor affinity and its potency as an antipsychotic. Thus, possible interpretations of olanzapine's superior positive symptom effect over that of haloperidol include its unique dopamine receptor profile (D_1–D_4), greater regional specificity (e.g., mesolimbic), or effects on other neurotransmitters modulating dopamine (e.g., 5-HT, acetylcholine, glutamate).

An even more robust contribution to the improvement in total Positive and Negative Syndrome Scale and total BPRS scores favoring olanzapine was the response of negative symptoms. In the last-observation-carried-forward analysis of change in negative symptoms (Positive and Negative Syndrome Scale), the improvement associated with olanzapine was significantly superior to that seen among the haloperidol-treated patients. An observed case analysis further demonstrated that the superior benefit of olanzapine for negative symptoms was evident early in the course of pharmacotherapy (by week 2) and sustained at least through week 6.

The effect of olanzapine on negative symptoms has been predicted on the basis of several preclinical studies, including the induction of social isolation in rodents by the *N*-methyl-D-aspartic acid receptor antagonist phencyclidine. This model has been suggested by Corbett et al. (7) as a preclinical screen to identify novel agents in the treatment of negative schizophrenic symptoms.

The significantly superior treatment benefits of olanzapine relative to haloperidol for negative symptoms among patients with schizophrenia have been pre-

viously demonstrated. In a study of 335 patients (25), olanzapine (mean daily dose=15 mg, SD=2.5) was associated with a mean baseline-to-endpoint improvement of –4.1 (SD=5.2) in summary score on the Scale for the Assessment of Negative Symptoms versus a mean change of –2.0 (SD=4.6) with haloperidol ($p<0.05$).

An unexpected difference in efficacy in the present study was the olanzapine group's superior improvement on the Montgomery-Åsberg Depression Rating Scale. The effect size difference favoring olanzapine (3 points on the Montgomery-Åsberg Depression Rating Scale, effect size=–0.33) is meaningful in scope for this population and actually approximates that seen in several placebo-controlled antidepressant trials (Montgomery, personal communication). In the present study a more conservative analysis of responders (≥50% improvement from baseline) corroborated an antidepressant-like effect of olanzapine, in which significantly more olanzapine-treated patients (46%) than haloperidol-treated patients (35%) achieved a response ($\chi^2=12.0$, df=1, $p=0.001$).

The broad receptor profile of olanzapine may again contribute to this treatment difference. The density of 5-HT_{2A} receptors, for example, has been reported to be increased among patients with major depression. Accordingly, olanzapine, as a potent 5-HT_{2A} antagonist, may have acted at these sites, similar to the action of the recently approved antidepressant nefazodone (26). The importance of these mood-related findings is clinically relevant regardless of whether they are primary or secondary therapeutic effects and should become a better-recognized efficacy target in the development of novel antipsychotics.

In a review of these results, the dose of haloperidol merits comment. In this study, a 5-, 10-, 15-, or 20-mg daily dose of haloperidol was permitted, and adjustments were made at the investigators' discretion. This dose range for haloperidol represents an optimal balance between safety and efficacy (27). Even so, one might argue that within this range, the adverse event profile of haloperidol limits optimal dose titration for some patients. However, offsetting this potential confounding factor was the protocol option to use a concomitant benzodiazepine and/or anticholinergic agent. Both concomitant drugs were used more often among the haloperidol-treated patients and should have minimized any limitation on efficacy for positive symptoms because of adverse events.

Safety

In this study a significant advantage of olanzapine was evident in the incidence of premature study discontinuations due to an adverse event; fewer olanzapine-treated patients discontinued therapy (4.5%) than did their haloperidol-treated counterparts (7.3%). This difference corresponds to a superior 6-week completion rate for olanzapine treatment (66.5%) versus haloperidol treatment (46.8%).

The magnitude of treatment noncompliance in schizophrenia is profound (4). Adverse event experiences, especially extrapyramidal symptoms and anticholinergic events, contribute substantially to this problem (20). In the extensive safety analyses, perhaps the most dramatic between-treatment difference was the comparative incidence of treatment-associated extrapyramidal symptoms. Olanzapine-treated patients manifested baseline-to-endpoint improvement in extrapyramidal symptoms, whereas haloperidol-treated patients on average worsened despite significantly greater anticholinergic use. This robust olanzapine-haloperidol difference in extrapyramidal symptoms was reflected by both spontaneous and clinician-solicited (AMDP-5) adverse event reporting. This improvement from baseline scores is consistent with the results of three other olanzapine trials (25, 28, 29) where the rate of extrapyramidal symptoms was similar to that with placebo or a minimally effective dose of olanzapine (1 mg/day).

The atypical extrapyramidal symptom profile of olanzapine is a predicted advantage based on a series of preclinical studies. Stockton and Rasmussen (30) reported that the chronic administration of olanzapine did not reduce spontaneous dopamine neuronal firing rates within striatal A9 pathways, in contrast to haloperidol. Furthermore, the dose of olanzapine necessary to inhibit a conditioned avoidance response (suggestive of antipsychotic potential) is severalfold less than that required to induce catalepsy, a model for liability to extrapyramidal symptoms.

In vivo human neuroimaging studies also corroborate this extrapyramidal symptom profile. Nyberg and colleagues (31), using positron emission tomography (with raclopride), reported a higher percentage of 5-HT_2 ligand displacement (84%) than D_2 ligand displacement (61%) following a single 10-mg dose of olanzapine. This level of D_2 receptor displacement is similar to clozapine's and below a critical extrapyramidal symptom threshold. Pilowsky et al. (32) recently reported similar conclusions based on single photon emission computerized tomography results from 32 schizophrenic patients. Both olanzapine and clozapine responders demonstrated significantly lower rates of D_2 occupancy than either haloperidol or risperidone responders.

The significantly lower incidence and magnitude of elevated prolactin levels among olanzapine-treated patients may have important long-term relevance for safety. Hyperprolactinemia has been implicated in galactorrhea, amenorrhea, and sexual dysfunction and may play a yet-to-be-clarified role in osteoporosis (33). A review of other laboratory analytes reveals that olanzapine is associated with a higher categorical incidence of transaminasemia (SGPT/ALT) than is haloperidol. Modest elevations of transaminase among olanzapine-treated patients are typically early and transient and without apparent clinical sequelae. The absence of a baseline-to-endpoint difference between acute olanzapine and haloperidol treatment underscores the transient nature of these elevations. The elevation of liver enzyme levels by antipsychotic drugs has been described

in the literature (34). Dujovne and Zimmerman (35) showed that phenothiazines release both AST and ALT from hepatocytes in vitro. Olanzapine may operate through a similar mechanism. In the absence of clinical sequelae or evidence of progression, as seen in this study, mild transaminasemia does not appear to represent a major safety issue.

No case of agranulocytosis was observed among the 1,996 patients in this study. Moreover, among a subgroup of 32 patients with previously reported clozapine-related hematotoxicity, no recurrence accompanied their treatment with olanzapine. Several explanations for the benign hematologic profile of olanzapine are possible. In contrast to clozapine, olanzapine is without a chlorine substitution. This halogen can be implicated in the generation of the toxic free radical metabolite from clozapine (36). Also unlike clozapine, olanzapine has not shown reactive metabolites (e.g., a neutrophil-derived nitrenium ion) (37). Experience to date appears to differentiate these two compounds on this important safety parameter.

Results of the review of vital signs were unremarkable, although olanzapine-treated patients did experience more weight gain and haloperidol-treated patients more weight loss. Further exploration of olanzapine-related weight gain demonstrated that it was significantly more common among patients with a low baseline body mass index. Thus, overall weight gain occurred most often among individuals who were below their ideal body weight, perhaps reflecting their disease process. None of 1,336 olanzapine-treated patients discontinued early because of weight gain. Some degree of weight gain is associated with a number of the newer antipsychotic compounds. In trials with clozapine (38), acute weight gain averaged approximately 6 kg over 16 weeks. Weight gain also has characterized the experience with the serotonin-dopamine antagonists (e.g., risperidone) (39).

CONCLUSIONS

The introduction of chlorpromazine in the early 1950s heralded an important advance in the treatment of schizophrenia and related disorders. However, over the subsequent 40 years, further advances had been discouragingly sparse. The renaissance triggered by clozapine ushered in a new era in the development of drugs for psychoses. Such progress is welcome in light of the therapeutic limitations, in both efficacy and safety, that characterize conventional neuroleptic drugs. In the present multinational trial that included 1,996 patients, olanzapine treatment demonstrated significant advantages for overall psychosis, negative symptoms, associated mood impairment, pseudo-parkinsonism, akathisia, and elevation of prolactin levels. Furthermore, it was associated with significantly fewer early discontinuations of therapy, including those due to adverse events.

On the basis of this study, olanzapine meets a number of the criteria for a novel atypical antipsychotic. While the robustness of these advantages should be replicated in a usual-care (naturalistic) setting, these data represent an encouraging advance for the victims of psychotic disorders.

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