Effective Resolution With Olanzapine of Acute Presentation of Behavioral Agitation and Positive Psychotic Symptoms in Schizophrenia

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Behavioral agitation and prominent positive psychotic symptoms often characterize the acute presentation of schizophrenia. The clinical treatment goal is a rapid control of these symptoms. The relative efficacy of olanzapine, a novel antipsychotic drug, was compared with that of the conventional antipsychotic drug haloperidol. A post hoc analysis conducted on a large multicenter, double-blind, 6-week study of acute-phase patients with DSM-III-R schizophrenia or schizophreniform or schizoaffective disorders treated with olanzapine (5–20 mg/day) or haloperidol (5–20 mg/day) assessed the treatment effects on agitation (Brief Psychiatric Rating Scale [BPRS] agitation score) and positive symptoms (BPRS positive symptom score). Overall, olanzapine-treated patients experienced significantly greater improvement in behavioral agitation than did haloperidol-treated patients (last observation carried forward [LOCF]; $p < .0002$). Both groups showed similar reductions in agitation scores during the first 3 weeks of therapy; olanzapine was associated with significantly greater improvements at weeks 4, 5, and 6 (observed cases [OC]). Similarly, patients with predominantly positive psychotic symptoms experienced significantly greater improvement in BPRS positive symptom scores with olanzapine compared with haloperidol (LOCF; $p = .013$). In olanzapine-treated patients, improvement in BPRS agitation and positive symptom scores was significantly greater at weeks 4, 5, and 6 (agitation scores, $p \leq .01$; positive symptom scores, $p < .05$) (OC). These data suggest that olanzapine may be considered a first-line treatment for the patient in an acute episode of schizophrenia.

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Schizophrenia is characterized by a complex psychopathology consisting of the core features of positive and negative symptoms associated with marked social or occupational dysfunction (DSM-IV). While the disease is not characterized by clearly defined stages, it is helpful to clinicians to consider 3 phases of the illness: an acute phase lasting 4 to 6 weeks, a resolving phase lasting 4 to 6 months, and a stable phase that lasts as long as the patient is in remission.[1] Most patients with schizophrenia come to the clinic in the acute phase, resulting from relapse of a previously stable condition, or during the first episode of psychotic illness. The acute phase is often characterized by extreme agitation and/or hostility and an increase in positive symptoms including delusions, hallucinations, thought disorders, changing mood, and catatonic phenomena. The goal of therapy is a rapid reduction in the agitation and aggression that are often seen in acute-phase patients.[2,3] The acute phase is also a critical juncture at which to begin a definitive therapeutic strategy that can allow a seamless progression from acute to long-term treatment.

Conventional antipsychotics have been the mainstay of therapy in the acute schizophrenic patient. While they are effective in relieving acute positive symptoms, their efficacy in treating negative, depressive, and cognitive symptoms is very limited, or nonexistent, and they are associated with a high prevalence of side effects.[4–7] Expert Consensus Guidelines now strongly recommend the newer atypical antipsychotics as the first line of treatment for schizophrenia in most clinical situations.[8] These drugs have been shown to be as effective as the typical antipsychotic haloperidol in improving overall psychopathology and superior in treating negative symptoms.[9,10] Additionally, the atypical antipsychotics have a much better safety profile, particularly with respect to extrapyramidal symptoms.[9–13]

Among the atypicals, olanzapine has all of the abovementioned attributes; in addition, olanzapine has been shown to be superior to haloperidol on other efficacy measures such as improvement of depressive and cognitive symptoms in schizophrenic patients, enhanced quality of life, and prevention of relapse.[14–19] Olanzapine has a supe-

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Table 1. Population Characteristics[a]

Variable	Agitation		Positive Symptoms	
	Olanzapine (N = 1336)	Haloperidol (N = 660)	Olanzapine (N = 257)	Haloperidol (N = 131)
Age, mean ± SD, y	38.7 ± 11.6	38.3 ± 11.1	38.7 ± 11.5	37.4 ± 10.7
Sex, N (%)				
Male	869 (65.0)	427 (64.7)	169 (65.8)	95 (72.5)
Female	467 (35.0)	233 (35.3)	88 (34.2)	36 (27.5)
Duration of illness, mean ± SD, y	14.5 ± 10.5	14.9 ± 10.1	14.8 ± 10.2	14.9 ± 10.1
Daily dose, mean ± SD, mg	10.47 ± 3.54	9.38 ± 3.48	10.55 ± 3.47	9.36 ± 3.46

[a]Data from Tollefson et al.[11]

rior safety profile compared with haloperidol with respect to tardive dyskinesia[12] and hyperprolactinemia.[20] Despite this superior efficacy and safety profile and the expert consensus opinion that atypical antipsychotics should be considered first-line therapy for acute schizophrenia, there is an unfortunate clinical impression that these novel drugs may not be very effective in the acutely agitated and psychotic patient.

This study therefore looked at the efficacy of olanzapine versus haloperidol in treating schizophrenic patients who are acutely agitated and have predominantly positive symptoms during the acute phase of schizophrenic illness decompensation.

METHOD

This subanalysis was performed on data from the 6-week acute phase of a large, prospective, international, multicenter, double-blind, randomized, controlled trial conducted on patients with schizophrenia or schizoaffective or schizophreniform disorders that have been previously reported.[11] After a 2- to 9-day screening and washout period, patients were randomly assigned to study drug in a 2:1 ratio of olanzapine to haloperidol. All patients began therapy with 5 mg/day of study drug; after each 7-day period, the study drug could be adjusted in increments or decrements within the allowed dose range of 5 to 20 mg/day. Benztropine in doses of up to 6 mg/day was allowed for treatment-emergent extrapyramidal symptoms. Limited use of benzodiazepines as concomitant medications was also allowed.

Eligible subjects included both male and female patients 18 years and older who met the DSM-III-R criteria for schizophrenia or schizophreniform or schizoaffective disorder. Patients had to score at least 18 on the Brief Psychiatric Rating Scale (BPRS; items scored 0–6) and/or be intolerant of current antipsychotic therapy (excluding haloperidol) (Table 1).

Outcome measures included the BPRS agitation score and the BPRS positive symptom score. Agitation was assessed weekly in all patients using the BPRS agitation score, which comprised 5 nonpsychosis items: anxiety, tension, hostility, uncooperativeness, and excitement. The BPRS positive symptom score, consisting of conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content, was assessed weekly in a subpopulation of study patients (N = 388) who demonstrated predominantly positive psychotic symptoms at baseline. To be included in the predominantly positive symptoms subgroup, patients had to score ≥ 4 on 3 or more items on the Positive and Negative Syndrome Scale (PANSS) positive subscale and ≥ 4 on no more than 2 PANSS negative subscale items (see Table 1 for population characteristics).

Mean change from baseline to endpoint (last observation carried forward [LOCF]) and from baseline to each week (observed cases [OC]) was assessed using analysis of variance.

Table 2. Change in BPRS Agitation Score (LOCF)[a]

Treatment Group	Baseline		Change	
	Mean	SD	Mean	SD
Olanzapine (N = 1313)	10.15	4.23	–2.59*	5.12
Haloperidol (N = 635)	10.39	4.34	–1.70	4.75

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, LOCF = last observation carried forward.
*p = .0002.

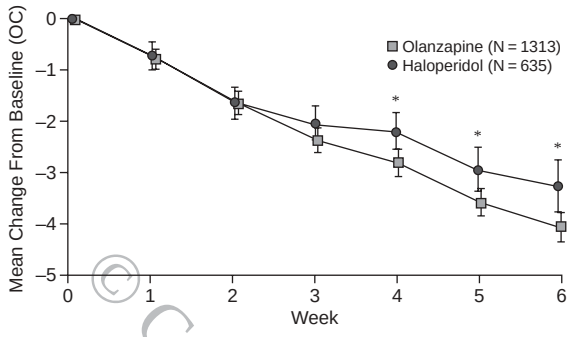
RESULTS

Of the original database consisting of 1996 patients, 1336 were randomly assigned to receive olanzapine, while 660 were randomly assigned to receive haloperidol. All patients were assessed for treatment effect on agitation. A subgroup of patients demonstrating predominantly positive symptoms (olanzapine, N = 257; haloperidol, N = 131) was assessed for response to treatment of positive symptoms. There were no significant differences between treatment groups for age, gender, and duration of disease. Disease duration averaged approximately 14 years; thus, most patients had chronic disease. The mean ± SD daily dose of olanzapine was 10.47 ± 3.54 mg in the agitation group (the total group) and 10.55 ± 3.47 mg in the positive symptom subgroup, while the mean ± SD daily dose of haloperidol was 9.38 ± 3.48 mg in the agitation group and 9.36 ± 3.46 mg in the positive symptom subgroup (See Table 1 for population characteristics).

Agitation

Olanzapine-treated patients experienced a significantly greater improvement in behavioral agitation (mean ± SD = –2.59 ± 5.12; N = 1313) than did haloperidol-treated patients (mean ± SD = –1.70 ± 4.75, LOCF; N = 635; p = .0002) (Table 2). Both groups showed similar reductions in overall agitation scores during the first 3 weeks of therapy. However, olanzapine was associated with significantly greater improvements at weeks 4, 5, and 6 (OC) (Figure 1). Of the components of the agitation score, anxi-

Figure 1. Change in BPRS Agitation Score[a]



[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, OC = observed cases. BPRS agitation score includes anxiety, tension, hostility, uncooperativeness, and excitement components.
*p ≤ .01 (visitwise).

Table 3. Change in Individual BPRS Agitation Score Items (LOCF)[a]

	Olanzapine (N = 1313)		Haloperidol (N = 635)		
Agitation Symptom	Mean	SD	Mean	SD	p Value
Anxiety	–0.92	1.47	–0.62	1.41	< .001
Tension	–0.79	1.38	–0.49	1.38	< .001
Hostility	–0.29	1.37	–0.27	1.34	.769
Uncooperativeness	–0.10	1.31	–0.10	1.25	.983
Excitement	–0.49	1.42	–0.23	1.36	< .001

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, LOCF = last observation carried forward.

Table 4. Change in BPRS Positive Symptom Score (LOCF)[a]

	Baseline		Change	
Treatment Group	Mean	SD	Mean	SD
Olanzapine (N = 252)	11.47	2.90	–4.04*	4.47
Haloperidol (N = 130)	11.07	3.11	–2.90	3.80

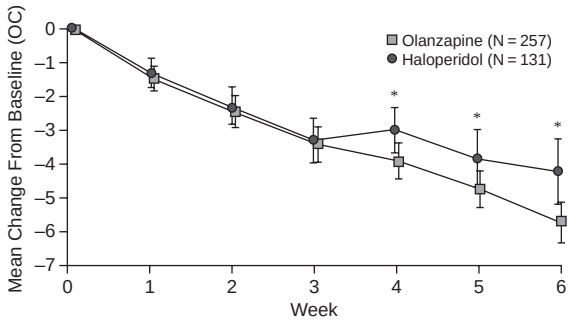
[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, LOCF = last observation carried forward.
*p = .013.

ety, tension, and excitement were decreased significantly more by olanzapine than by haloperidol (LOCF; p < .001) (Table 3).

Positive Symptoms

Patients with predominantly positive symptoms showed a significant improvement in their BPRS positive symptom scores with olanzapine treatment (mean ± SD = –4.04 ± 4.47; N = 252) as compared with haloperidol treatment (mean ± SD = –2.90 ± 3.80, LOCF; N = 130; p = .013) (Table 4). Both groups showed similar reductions in overall positive symptom scores during the first 3 weeks of treatment. Again, olanzapine treatment was associated with a statistically significant improvement at weeks 4, 5, and 6 (OC) (Figure 2). Among the positive symptom items, olanzapine was more effective than haloperidol in reducing unusual thought content (LOCF; p = .006), with conceptual disorganization and hallucinatory behavior showing a trend toward greater improvement (Table 5).

Figure 2. Change in BPRS Positive Symptom Score (patients with predominantly positive symptoms at baseline)[a]



[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, OC = observed cases. Patients included in this group had a score of ≥ 4 on 3 or more Positive and Negative Syndrome Scale (PANSS) positive subscale items and a score of ≥ 4 on no more than 2 PANSS negative subscale items.
*p < .05 (visitwise).

Table 5. Change in Individual BPRS Positive Symptom Score Items (LOCF)[a]

	Olanzapine (N = 257)		Haloperidol (N = 131)		
Positive Symptom	Mean	SD	Mean	SD	p Value
Conceptual disorganization	–0.84	1.37	–0.58	1.28	.074
Hallucinatory behavior	–1.08	1.54	–0.80	1.55	.074
Suspiciousness	–1.07	1.57	–0.88	1.31	.319
Unusual thought content	–1.05	1.42	–0.65	1.26	.006

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, LOCF = last observation carried forward.

DISCUSSION

This subanalysis conducted on the results of a large, international, randomized double-blind trial indicates that olanzapine is superior to haloperidol in reducing agitation and positive symptoms in patients in the acute phase of schizophrenia. The initial rate of improvement of both behavioral agitation and positive symptoms was found to be comparable for olanzapine and haloperidol. With continued therapy, though, olanzapine demonstrated significantly greater improvement in agitation and positive symptoms than did haloperidol. These results are supportive of the beneficial effects of olanzapine in rapidly controlling behavioral agitation and positive psychotic symptoms associated with schizophrenic decompensation and indicate that olanzapine may be considered a first-line treatment for an acute episode of schizophrenia.

Early and effective control of agitation is very important in the acute patient, and haloperidol has been widely

used for this purpose. All patients in the olanzapine treatment arm were initially started at 5 mg/day of olanzapine; even this low dose of olanzapine was as effective as haloperidol in the first 3 weeks of therapy. Olanzapine-treated patients then separated significantly from the haloperidol-treated patients in weeks 4, 5, and 6, indicating a therapeutic superiority of olanzapine. Of the components of the agitation score, anxiety, tension, and excitement were decreased significantly more by olanzapine than by haloperidol, while decreases in hostility and aggression were comparable with those for haloperidol.

Similarly, olanzapine demonstrated comparable efficacy with haloperidol in reducing positive psychotic symptoms in the first 3 weeks of therapy, even at the low initiating dose of 5 mg/day. These results are consistent with the parent study. However, in the subpopulation of patients with predominantly positive psychotic symptoms, the olanzapine-treated group separated significantly from the haloperidol-treated group in terms of positive symptoms in weeks 4, 5, and 6. This separation was driven mainly by a decrease in unusual thought content, with a trend seen toward a decrease in conceptual disorganization and hallucinatory behavior. Unusual thought content forms one of the core symptoms of schizophrenic psychopathology, and the results from this analysis suggest that the therapeutic effectiveness of olanzapine is not a nonspecific calming effect but rather a true action on core schizophrenic symptoms. The original study demonstrated that olanzapine was superior to haloperidol in improving global psychopathology and negative symptoms on the BPRS and PANSS scales, while showing a trend toward improvement in positive symptoms ($p = .06$). A post hoc analysis conducted by Gomez and Crawford[21] that included only schizophrenic patients also demonstrated a statistically significantly greater improvement in the olanzapine treatment group compared with the haloperidol treatment group on the BPRS positive symptom subscale and the PANSS positive symptom subscale.

Why the effects of olanzapine do not separate from those of haloperidol in the first 3 weeks of therapy is unclear. It has been suggested that the acute calming effect seen with antipsychotics is different from their true antipsychotic effect: it may take at least 4 to 6 weeks before they begin to exert a true therapeutic effect.[22,23] However, data from placebo-controlled pivotal clinical trials suggest that olanzapine may, in some cases, begin exerting a therapeutic effect on core schizophrenic psychopathologic symptoms at an earlier point in therapy.[10] Positive symptoms in the haloperidol treatment group were also significantly improved by 1 week. However, this improvement may have, in part, been due to drowsiness and hypokinesia, which can motorically reduce the manifestations of agitation and perhaps positive symptoms soon after treatment initiation. In fact, the original study showed that patients treated with haloperidol experienced a significantly greater incidence of these adverse events (hypokinesia: 13.5% with haloperidol vs. 5.1% with olanzapine; drowsiness: 31.3% with haloperidol vs. 26% with olanzapine; LOCF; $p < .05$).[11] Therefore, the treatment effect of olanzapine on acute-phase illness symptoms is clearly manifest even in the relative absence of acute extrapyramidal motor symptoms.

The treatment of agitation can often be confounded by the concomitant presence of akathisia. There is often a failure to differentiate illness-induced agitation from neuroleptic-induced akathisia.[24–26] Often, treatment-emergent akathisia is misdiagnosed as agitation, resulting in an increase of the antipsychotic dosage, thus compounding the problem. The incidence of akathisia is low in patients treated with olanzapine; in the original study, patients treated with haloperidol had a higher incidence of akathisia as compared with patients treated with olanzapine (22.6% with haloperidol vs. 7.8% with olanzapine, $p < .0001$).[11] It could be argued that the difference between the olanzapine and haloperidol groups was a result of the confounding presence of akathisia in the haloperidol group. On the other hand, the significantly greater improvement with olanzapine versus haloperidol on specific components of the BPRS scale such as anxiety, tension, and excitement shows a true therapeutic effect with olanzapine versus haloperidol that was probably not confounded by akathisia, which would have contributed to the persistence of such behaviors.

Atypical antipsychotics have been underutilized as first-line therapy despite expert consensus recommendations that they be considered the treatment of choice in schizophrenia. Atypical antipsychotics are an effective and safer alternative to typical antipsychotics. Starting therapy with an atypical antipsychotic would make it easier to achieve long-term control of symptoms with the same drug, with a much improved safety profile. This study suggests the effectiveness of olanzapine in treating agitation and positive symptoms, 2 of the most troublesome presentations of schizophrenic patients in the acute setting, and suggests that physicians should consider using olanzapine as the first line of therapy in acute schizophrenia.

Drug names: benztropine (Cogentin and others), haloperidol (Haldol and others), olanzapine (Zyprexa).

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