The Efficacy of a Rapid-Acting Intramuscular Formulation of Olanzapine for Positive Symptoms

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Rapid tranquilization of acutely psychotic patients with schizophrenia is usually carried out using typical antipsychotic agents. The objective of such treatment is to control agitation, not to treat psychosis, which usually responds only after a few weeks of treatment. An intramuscular formulation of the atypical antipsychotic olanzapine was developed for treatment of agitation in acutely psychotic patients. Studies conducted to assess control of agitation in schizophrenia also investigated the positive symptom efficacy of olanzapine when used to provide rapid tranquilization. This article summarizes the results of 3 clinical trials with intramuscular olanzapine with regard to positive symptom efficacy as measured by the Brief Psychiatric Rating Scale (BPRS; 0–6 scale) positive subscale. In 2 open-label trials, patients treated with intramuscular olanzapine experienced a mean decrease from baseline in BPRS positive subscale score. In 1 double-blind clinical trial of intramuscular olanzapine versus intramuscular haloperidol and intramuscular placebo, the mean decrease from baseline in BPRS positive subscale score for patients treated with intramuscular olanzapine was statistically significant ($p < .05$). In all 3 studies, positive symptom improvement continued following transition to oral olanzapine. These results suggest that intramuscular olanzapine has positive symptom efficacy early in the course of treatment and may provide a smooth transition to maintenance therapy with oral olanzapine.

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No atypical antipsychotic drug is currently licensed for parenteral administration, with the exception of clozapine in Hungary and Israel. Most acutely psychotic and/or agitated patients in need of rapid tranquilization therefore receive intramuscular (i.m.) or intravenous (i.v.) formulations of typical antipsychotics and/or benzodiazepines. Patients treated in this manner are exposed to the adverse effects of such drugs, which may include acute dystonia, respiratory depression, and cardiovascular instability, especially prolongation of the QTc interval. In addition, intramuscular and intravenous typical antipsychotics may not provide early efficacy against positive psychotic symptoms, an essential property, since most violent behavior by acutely agitated patients occurs during psychotic episodes.[1,2]

The oral formulation of olanzapine is effective in treating the positive,[3] negative,[4] and affective[5] symptoms of schizophrenia and related disorders. Oral olanzapine also has demonstrated safety advantages over oral haloperidol, a typical antipsychotic agent.[3,6] A rapid-acting intramuscular formulation of olanzapine that has qualitatively similar clinical effects to oral olanzapine but a faster onset and shorter duration of action has recently been developed.[7] Thus, patients with acute agitation may experience the benefits of an atypical antipsychotic agent. In addition, patients with acute agitation treated with an atypical antipsychotic may have a decreased risk of recurrence of agitation on transition from intramuscular to oral maintenance antipsychotic therapy. This article summarizes the positive symptom efficacy in clinical trials conducted to date with intramuscular olanzapine in acutely agitated patients with schizophrenia. The results from 2 open-label clinical trials[8,9] and 1 double-blind, placebo-controlled study[10] of intramuscular olanzapine versus intramuscular haloperidol are presented.

OPEN-LABEL TRIALS OF THE EFFICACY AND SAFETY OF INTRAMUSCULAR OLANZAPINE

The efficacy and safety of intramuscular olanzapine in patients meeting DSM-IV criteria for acute nonorganic psychosis have been investigated in 2 open-label, single-blind (patient was blinded) clinical trials.[8,9] Patients were required to have a minimum mean baseline Brief Psychiatric Rating Scale (BPRS)[11] score of 36.5 and a Clinical Glo-

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Table 1. Mean Baseline to Endpoint Change on the BPRS Positive Subscale With Intramuscular Olanzapine[a]

	Baseline Score		Mean Change From Baseline		
Study	Mean	SD	Endpoint 1[b]	Endpoint 2[c]	Endpoint 3[d]
LOAR (N = 26)[8]	11.4	2.7	–2.4	—	–5.3
LOAT (N = 82)[9]	14.0	2.6	–5.2	—	–6.5
HGHB (N = 122)[10]	10.7	3.8	–2.9	–2.8	–3.6

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, i.m. = intramuscular.
[b]Day 3 for LOAR and LOAT; 2 hours after first i.m. injection for HGHB.
[c]Twenty-four hours after first i.m. injection; applies to HGHB only.
[d]Day 5, following 2 days (LOAR and LOAT) or 4 days (HGHB) of oral olanzapine (5–20 mg/day).

bal Impressions-Severity of Illness scale[12] rating of moderate, marked, or severe illness.

In the first trial (Study LOAR),[8] 26 male inpatients (24 black, 1 white, 1 multiracial; mean ± SD age = 29.5 ± 8.7 years) received i.m. injections of 2.5, 5.0, 7.5, or 10.0 mg (fixed doses) of olanzapine (1–4 injections/day for 3 days) followed by oral olanzapine (10–20 mg/day for 2 days). In the second trial (Study LOAT),[9] 82 inpatients (55 men, 27 women; 15 white, 49 black, 18 multiracial; mean ± SD age = 33.2 ± 9.2 years) received i.m. injections of 2.5, 5.0, 7.5, or 10.0 mg (variable doses) of olanzapine (1–4 injections/day for up to 3 days) followed by oral olanzapine (10–20 mg/day for 2 days).

For both open-label studies and across all dose groups, mean BPRS positive subscale score decreased from baseline to endpoint for the 3-day period of intramuscular injections for patients treated with intramuscular olanzapine (Table 1). There was a further decrease in BPRS positive subscale scores from baseline to the day 5 endpoint, which was 2 days after the transition from intramuscular olanzapine to oral olanzapine (LOAR, mean modal dose = 10.4 mg/day; LOAT, mean modal dose = 13.4 mg/day).

DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF INTRAMUSCULAR OLANZAPINE VERSUS INTRAMUSCULAR HALOPERIDOL

This study (Study HGHB)[10] was a double-blind, multicenter, intramuscular placebo-controlled clinical trial of intramuscular olanzapine versus intramuscular haloperidol in the treatment of acute agitation in hospitalized patients with schizophrenia. A total of 311 acutely agitated patients (66% male; 73% white, 19% black, 5% Hispanic, 1% Asian, 2% other; mean ± SD age = 38.2 ± 11.6 years) with DSM-IV schizophrenia, schizophreniform disorder, or schizoaffective disorder were randomly assigned in a 2:2:1 ratio to receive up to 3 injections of intramuscular olanzapine (10 mg/injection; N = 131), intramuscular haloperidol (7.5 mg/injection; N = 126), or intramuscular placebo (N = 54) within 24 hours. All patients were required to have a minimum total score of 14 on the Positive and Negative Syndrome Scale[13] excited component with a score of 4 or more on at least 1 item (based on a 1–7 scoring system for each item). Following the 24-hour intramuscular injection phase, 285 patients entered a 4-day oral treatment phase (patients previously receiving intramuscular olanzapine received oral olanzapine, 5–20 mg/day [N = 122]; patients previously receiving i.m. haloperidol received oral haloperidol, 5–20 mg/day [N = 116]; patients previously receiving i.m. placebo received oral olanzapine, 5–20 mg/day [N = 47]).

A significantly greater mean improvement from baseline in BPRS positive subscale score was found with intramuscular olanzapine and intramuscular haloperidol compared with intramuscular placebo at both 2 hours and 24 hours after the first injection; however, improvements with intramuscular olanzapine and intramuscular haloperidol did not differ significantly from each other (repeated-measures analysis of variance with a significance level of $p < .05$). Patients treated with intramuscular olanzapine experienced a further decrease in mean baseline to endpoint BPRS positive subscale scores by day 5, which was 4 days after the transition from intramuscular olanzapine to oral olanzapine therapy (mean modal dose = 13.2 mg/day) (see Table 1). No significant difference was found between intramuscular olanzapine and intramuscular haloperidol from baseline to day 5 endpoint in mean BPRS positive subscale score.

CONCLUSIONS

The results of these clinical trials support the positive symptom efficacy of intramuscular olanzapine in acutely agitated patients with schizophrenia. Intramuscular olanzapine was shown to be superior to intramuscular placebo in treating positive symptoms as early as 2 hours after injection, and this significant difference was sustained through 24 hours. Although intramuscular olanzapine did not differ from intramuscular haloperidol, this finding suggests that positive symptoms can be rapidly improved with atypical antipsychotics if they are used in a manner that is similar to rapid tranquilization using typical antipsychotics. In addition, in all studies, it appeared that a successful transition was made from intramuscular olanzapine to oral olanzapine, with continued positive symptom improvement for at least 2 days and up to 4 days after the switch. This consistent and progressive improvement in positive symptoms supports the reliability of positive symptom improvement early in the course of treatment. Thus, acutely agitated patients with schizophrenia who are displaying positive symptoms may be effectively treated with intramuscular olanzapine for rapid tranquilization and successfully switched to oral olanzapine maintenance therapy.

Of interest was the 10-mg i.m. dose of olanzapine in the double-blind study that was effective in treating positive symptoms early in the course of treatment. This dose

might be expected to correspond, in terms of peak plasma level, to an oral dose of approximately 20 mg. Thus, in agitated, acutely psychotic patients with schizophrenia who are compliant with oral therapy, an oral dose of olanzapine, 20 mg, given in the first few hours of treatment may be highly effective. The dose could then be lowered for maintenance therapy, as suggested by the mean modal doses of oral olanzapine in all 3 studies following the transition to oral therapy.

Although it can be argued that positive symptom improvement early in the use of atypical antipsychotics may be due to nonspecific improvement in behavioral agitation, a rapid decrease in positive symptom intensity would be clinically relevant no matter what mechanism produces it. Given that atypical antipsychotics as a class have not been used frequently in rapid tranquilization paradigms, early treatment of positive symptoms using atypical antipsychotics such as olanzapine should be studied further.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa).

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