

10 mg intramuscular olanzapine reduces acute agitation in schizophrenia more effectively than lower doses

Brier A, Meehan K, Birkett M *et al*. A double-blind, placebo-controlled dose-response comparison of intramuscular olanzapine and haloperidol in the treatment of acute agitation in schizophrenia. *Archives of General Psychiatry* 2002 May; 59: 441–8.

QUESTION: What is the efficacy and safety of intramuscular olanzapine for acute agitation in schizophrenia? Is there a dose-response relationship?

Design

Allocation concealed placebo-controlled trial. Investigators, patients, clinical carers and raters were blinded.

Setting

4 sites in Croatia, 1 site in Italy, 3 sites in Romania and 6 sites in South Africa.

Participants

270 adults diagnosed with schizophrenia, schizophreniform disorder or schizoaffective disorder (DSM-IV criteria) recently hospitalised with acute agitation; 66% white; 46% women; mean age 36 years (range 18–73 years). All had a score of 14 or higher (out of 35) on the PANSS-EC; a score of 4 or higher (out of 7) on at least 1 item, and were agitated enough to warrant parenteral antipsychotic therapy. Exclusion criteria were alcohol or drug dependency; violence towards other individuals; need for physical restraint, and significant medical disorders.

Intervention

Following a 2 hour screening period, participants received intramuscular treatment with 2.5mg, 5mg, 7.5mg or 10mg per injection of olanzapine; 7.5mg per injection of haloperidol, or placebo. A maximum of 3 injections were administered over 24 hours, at the discretion of the clinician. Concomitant alprazolam, anoretics, antiemetics, antiarrhythmics, carbamazepine, methyl dopa, neuroleptics, phenobarbital, reserpine and zolpidem tartrate were prohibited during treatment.

Main outcome measures

Agitation was measured using PANSS-excitement factor scores (PANSS-EC), the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions-Severity (CGI-S), Agitated Behavior Scale (ABS) and the Agitation Calmness Evaluation Scale (ACES) 2, 4, 6, 12 and 24 hours after initial injection. Safety was measured using adverse event profiles and electrocardiograms 24 hours after the initial injection.

Mean reduction in PANSS-EC score 2 hours after initial injection

Drug and dose	Mean PANSS-EC reductions 2 hours after first injection (standard deviation in parenthesis)
Placebo (n=45)	2.9 (4.7)
2.5mg olanzapine (n=48)	5.5 (4.6) *
5.0mg olanzapine (n=45)	8.1 (5.3) **
7.5mg olanzapine (n=46)	8.7 (5.0) **
10mg olanzapine (n=46)	9.4 (4.9) **
7.5mg haloperidol (n=40)	7.5 (5.9)

* placebo < olanzapine < haloperidol (p<0.05)

** placebo < olanzapine and haloperidol (p<0.05)

Main results

All doses of olanzapine reduced excitement and agitation compared to placebo. There was a dose-response relationship. Olanzapine doses of 5mg, 7.5mg or higher had similar effects to 7.5mg haloperidol on most clinical scales. There were no significant differences in hypotension, the most commonly reported adverse effect, or clinically relevant changes in the QTc interval. Treatment emergent parkinsonism was more common in the haloperidol group (16.7% v 0%–2.9% olanzapine and 0% placebo).

Conclusions

Olanzapine was as effective as haloperidol in reducing excitement and agitation among adults with schizophrenia.

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COMMENTARY

Atypical antipsychotics such as olanzapine and risperidone are increasingly used as first line therapy for schizophrenia and related disorders. Oral atypical antipsychotics have equal or superior efficacy to conventional antipsychotics, but conventional antipsychotics are still used extensively for two purposes: controlling agitation in acute treatment and long-term maintenance with depot preparations when there are adherence problems. Atypical antipsychotics have fewer adverse motor effects than most conventional antipsychotics. If safe and effective intramuscular preparations are developed, atypical antipsychotics are likely to supplant conventional antipsychotics for controlling agitation and depot maintenance therapy.

Brier *et al* examine olanzapine versus haloperidol for acute agitation in people with schizophrenia or schizoaffective disorder. The authors used a sufficient sample and objective rating scale measures. Olanzapine doses of 5mg, 7.5mg or higher had similar clinical benefits to 7.5mg haloperidol and fewer adverse effects. Intramuscular olanzapine has also been found to reduce agitation in people with dementia and bipolar disorder.¹⁻² A similar study is being conducted in the United States, but results are not yet available.

Participants did not receive treatment with their standard antipsychotic drugs during the one day study period. This affords a cleaner design, but is at variance with standard clinical practice. Another limit is the exclusion of violent patients who might not meet ethical consent criteria.

Short-acting intramuscular olanzapine is not available for use in the United States. It awaits FDA approval after minor technical problems, presumably related to the injection vehicle substance. The next stage of development may be a depot form of olanzapine for long-term maintenance when adherence to treatment is unreliable. Several clinical trials have been completed with a depot form of risperidone, another atypical antipsychotic. This has yet to be approved for use in the United States by the FDA, although preliminary unpublished results suggest clinical efficacy and patient acceptance.

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- 1 Meehan KM, Wang H, Davis S *et al*. Comparison of rapidly acting intramuscular olanzapine, lorazepam and placebo: a double-blind, randomized study in acutely agitated patient with dementia. *Neuropsychopharmacology* 2002; 26: 494–504.
- 2 Meehan K, Zhang F, Davis S *et al*. A double-blind randomized comparison of the efficacy and safety of intramuscular injections of olanzapine, lorazepam, or placebo in treating acutely agitated patients diagnosed with bipolar mania. *J. Clin Psychopharmacology* 2001; 21: 389–97.

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