Olanzapine was more effective than lorazepam at 2 hours but not at 24 hours in bipolar mania with acute agitation


**QUESTION:** In patients with bipolar mania who are acutely agitated, how effective are olanzapine, lorazepam, and placebo for rapidly calming patients?

**Main outcome measures**
Agitation (PANSS-EC scale; Agitated Behavior Scale (ABS) total score; Agitation-Calmness Evaluation Scale (ACES)) at 2 and 24 hours after the first injection.

**Main results**
Analysis was by intention to treat with last observation carried forward. Olanzapine decreased agitation more than lorazepam at 2 hours ($p<0.006$), but groups did not differ at 24 hours ($p>0.8$) (table). Olanzapine decreased agitation more than placebo at 2 and 24 hours ($p<0.025$) (table). A greater change in ABS and ACES scores (decreased agitation) occurred in the lorazepam group than in placebo at 2 and 24 hours ($p<0.01$), but groups had a similar change in PANSS-EC score ($p>0.05$) (table).

**Conclusions**
Olanzapine was more effective than lorazepam at 2 hours, but was as effective at 24 hours for rapidly calming patients with bipolar mania who were acutely agitated. Olanzapine was more effective than placebo. Lorazepam was more effective than placebo on 2 of 3 agitation scales.

*See glossary.

**Olanzapine (Olan) v lorazepam (Lor) v placebo (Pl) in bipolar mania with acute agitation**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Difference in mean score change from baseline (95% CI)†</th>
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<tbody>
<tr>
<td><strong>Decrease in PANSS-EC score</strong></td>
<td>2.85 (1.18 to 4.52) 0.13 (−1.54 to 1.80) 4.76 (3.14 to 6.38) 1.84 (0.26 to 3.42) 1.91 (−0.04 to 3.86) 1.71 (−0.18 to 3.60)</td>
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<tr>
<td><strong>Decrease in ABS score</strong></td>
<td>2.91 (0.81 to 5.02) 0.12 (−1.93 to 2.17) 6.52 (4.50 to 8.54) 3.16 (1.18 to 5.14) 3.61 (1.27 to 5.95) 3.04 (0.86 to 5.22)</td>
</tr>
<tr>
<td><strong>Increase in ACES score</strong></td>
<td>1.02 (0.41 to 1.63) 0.02 (−0.26 to 0.30) 2.08 (1.50 to 2.66) 0.48 (0.17 to 0.79) 1.06 (0.43 to 1.69) 0.50 (0.15 to 0.85)</td>
</tr>
</tbody>
</table>

†PANSS-EC = Positive and Negative Syndrome Scale-Excited Component (decrease=decreased agitation); ABS = Agitated Behaviour Scale (decrease=decreased agitation); ACES = Agitation-Calmness Evaluation Scale (increase=decreased agitation). ‡CI calculated from data in article.

**COMMENTARY**

The study by Meehan et al looks at the role of olanzapine in the resolution of acute agitation in bipolar mania and therefore strays into a number of grey areas. The introduction of acute injectable atypical antipsychotics has been eagerly awaited in several quarters—somewhat wrongly in my view. The therapeutic aim in acutely agitated manic patients who have been admitted to my psychiatric intensive care unit being able to participate in this trial.

Olanzapine was more effective than lorazepam at 2 hours but not at 24 hours in bipolar mania with acute agitation. However, close reading of the recent draft of the Helsinki declaration, the European directive on clinical trials, and the Nuffield council documents on bioethics reveals that trials in non-consenting patients are permitted on 2 conditions: (1) no other context exists in which to answer the question, and (2) all trial participants get clear therapeutic benefit from whichever arm they are randomised to. So placebo cannot be used in these studies. More importantly, this extreme end of psychiatric practice where randomised controlled trials are difficult is an example where observational and naturalistic studies can guide practice and utility.

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**Design**
Randomised (unclear allocation concealment*), blinded (unclear)*, placebo-controlled trial.

**Setting**
USA and Romania.

**Patients**
201 patients ≥18 years of age (mean age 40 y, 53% men) who had bipolar disorder, mania, or a mixed diagnosis confirmed with the Structured Clinical Interview for DSM-III-R considered by the site physician to have severe agitation requiring injections and who had a total score ≥14 on the 5 item Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) scale with ≥1 individual score of ≥4. Two patients were not included in the analysis.

**Intervention**
Patients were allocated to 1 of 3 groups. Patients received 1–3 intramuscular injections. First and second injections ≥2 hours apart were olanzapine (n=99), 10 mg each; lorazepam (n=51), 2 mg each; and placebo (n=51). Third injections ≥1 hour after the second were olanzapine, 5 mg; lorazepam, 1 mg; and olanzapine (placebo group), 10 mg. All were given <20 hours after the first injection.

**Conclusion**
Olanzapine was more effective than lorazepam at 2 hours, but not at 24 hours in bipolar mania with acute agitation. However, close reading of the recent draft of the Helsinki declaration, the European directive on clinical trials, and the Nuffield council documents on bioethics reveals that trials in non-consenting patients are permitted on 2 conditions: (1) no other context exists in which to answer the question, and (2) all trial participants get clear therapeutic benefit from whichever arm they are randomised to. So placebo cannot be used in these studies. More importantly, this extreme end of psychiatric practice where randomised controlled trials are difficult is an example where observational and naturalistic studies can guide practice and utility.

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