Flexible oral olanzapine dosing in acutely agitated people is immediately effective in reducing symptoms

Baker RW, Kinon BJ, Maguire GA, *et al.* Effectiveness of rapid initial dose escalation of up to forty milligrams per day of oral olanzapine in acute agitation. *J Clin Psychopharmacol* 2003;**23**:342–8.

Q What is the efficacy and safety of rapid initial dose escalation of oral olanzapine compared with usual clinical practice in people with acute agitation?

METHODS

	Design: Multicentre randomised controlled trial.
	Allocation: Unclear.
	Blinding: Blinded (participants, clinicians, and assessors).
	Follow up period: Four days.
	Setting: 18 centres across the USA; timeframe not specified.
	Patients: 148 people aged 18 to 55 years (mean age 39 years) diagnosed with schizophrenia, schizoaffective disorder, schizophreniform disorder, or bipolar I disorder (manic or mixed episode) according to DSM-IV criteria. Main inclusion criteria were: agitated at baseline (as defined by a score of >20 points according to the Positive and Negative Syndrome Scale-Excited Component test (PANSS-EC; see below)). Exclusions: serious, unstable medical illness, substance-induced psychoses, or hospitalisation less than 1 week before study enrolment.
	Intervention: Participants were randomised to rapid initial dose escalation (RIDE, n=72) group or to usual clinical practice (UCP, n=62). On days 1–4, oral olanzapine at either 20 mg (RIDE) or 10 mg (UCP) was administered in addition to flexible dosing of either olanzapine (RIDE; to a maximum of 2×10 mg for days 1–2 and a maximum of 1×10 mg for days 3–4) or lorazepam (UCP; maximum of 2×2mg for days 1–2 and a maximum of 1×2 mg for days 3–4) as required for treatment of persistent or re-emergent agitation.
	Outcomes: PANSS-EC test, which scores the following 5 items: poor impulse control, tension, hostility, uncooperativeness and excitement, on a scale from 1 (not present) to 7 (extremely severe).
	Patient follow up: 86%

MAIN RESULTS

After 24 hours, people in both the RIDE and UCP groups achieved a significant mean reduction of PANSS-EC score from baseline (mean

reduction from baseline: RIDE 7.0 v UCP 5.5, $p<0.0001$ for both groups). However, people in the RIDE treatment group experienced significantly greater improvement in agitation scores than those in the UCP group on study days 1 ($p = 0.006$), 2 ($p = 0.03$), 3 ($p = 0.08$), and 4 ($p = 0.001$). There were no clinically significant differences in safety measures between groups.

CONCLUSIONS

RIDE was more effective than usual clinical practice within the first 4 days of treatment for acutely agitated people with schizophrenia, schizoaffective disorder, schizophreniform disorder, or bipolar I disorder.

Commentary

This is a report of a multicentre, double blind, randomised clinical trial of olanzapine conducted by its manufacturer. It is important for two reasons: (1) it confirms the clinical utility of an aggressive dosing strategy that is employed by many practitioners involved in the acute management of schizophrenia and bipolar disorder, and (2) it also brings to light the fact that the suggested dose of a medication at product launch may be quite different from what is actually used once sufficient clinical experience has accumulated.¹

The superiority of RIDE dosing in reducing agitation is particularly impressive as the comparator was not placebo, but a therapeutic dose (10 mg) of the same agent (olanzapine) combined with a commonly used sedating agent (lorazepam) given on an as needed basis. Also demonstrated was that the higher doses of olanzapine were reasonably well tolerated.

Second generation antipsychotics have generally replaced the older neuroleptics as first line treatment for schizophrenia. Their advantages include a lower propensity for extrapyramidal side effects, including akathisia and tardive dyskinesia, and perhaps a specific anti-aggressive effect over time.² Intramuscular formulations have their place,³ but for the most part oral medication is offered first, and having a well tolerated efficacious oral strategy is highly desirable.

Generalisability of this study is limited to people with schizophrenia, schizoaffective disorder, schizophreniform disorder, or bipolar I disorder, manic or mixed episode. People with substance induced psychosis were excluded, as were those under the age of 18 years or older than 55 years. These groups may have different dosing needs. Future research should address additional clinical questions such as how the different second generation antipsychotics compare against each other in controlling agitation, and the differences seen with the different oral formulations such as regular tablets, rapidly disintegrating tablets, and liquids.

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