Acute Treatment of Psychotic Agitation: A Randomized Comparison of Oral Treatment With Risperidone and Lorazepam Versus Intramuscular Treatment With Haloperidol and Lorazepam

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Background: Standard treatment for acute psychotic agitation often involves intramuscular administration of the benzodiazepine lorazepam and the antipsychotic haloperidol. This study compared the efficacy and safety of oral treatment with the atypical antipsychotic risperidone plus lorazepam with those of standard intramuscular treatment. We hypothesized that the efficacy and speed of action of both treatments would be similar.

Method: In a prospective, parallel-group, randomized, rater-blinded noninferiority study conducted at 24 sites in the United States, 162 patients exhibiting agitation associated with active psychosis were randomly assigned to receive either oral treatment with 2 mg of risperidone plus 2 mg of lorazepam (N = 83) or intramuscular treatment with 5 mg of haloperidol plus 2 mg of lorazepam (N = 79). The change scores on a 5-item acute-agitation cluster from the Positive and Negative Syndrome Scale (hallucinatory behavior, excitement, hostility, uncooperativeness, and poor impulse control) were the main outcome measure. The study was conducted from January 8 to August 8, 2001.

Results: Mean acute-agitation cluster scores were similar in the 2 groups at baseline. Mean score improvements at 30, 60, and 120 minutes after dosing were significant at each timepoint (p < .0001) and were similar in both groups (p > .05). Both treatments were well tolerated.

Conclusion: A single oral dose of risperidone plus lorazepam was as effective as parenterally administered haloperidol plus lorazepam for the rapid control of agitation and psychosis. These findings suggest that this oral regimen is an acceptable alternative to the current intramuscular treatment for acute psychotic agitation.

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ataxia, and prolonged sedation. Sedative effects of drug treatment can be particularly problematic as they may delay further diagnostic assessment and the initiation of definitive treatment of the underlying disorder.9

A variety of expert treatment guidelines recommend oral therapy before parenteral treatment for behavioral emergencies.14,15 A recent expert consensus guideline recommended risperidone as a first-line treatment option in this setting when oral treatment is possible.1 However, published data supporting and guiding physicians on the use of oral atypical antipsychotics in the acute setting are limited, and the treatment guidelines have had limited effect on clinical practice. Nonetheless, data are accumulating to support a shift toward oral treatment using newer agents.

A recent case series demonstrates that oral olanzapine can be used effectively to produce rapid tranquilization of psychotic agitation.16 The current study compares oral risperidone plus oral lorazepam with IM haloperidol and IM lorazepam in a prospective, randomized, rater-blinded study of patients with psychotic agitation.

This is a prospective, parallel-group, randomized, rater-blinded study of emergency department patients or inpatients exhibiting both psychosis and agitation judged to be in a condition.

Patients

Inclusion criteria included (1) men or women aged 18 to 65 years; (2) DSM-IV diagnosis of acute exacerbation of schizophrenia or schizoaffective disorder, mania with psychotic features, acute paranoid reaction, or delusional disorders; (3) a score of ≥14 on a 5-item acute-agitation cluster derived from the Positive and Negative Syndrome Scale (PANSS); and (4) a score ≥3 on the Clinical Global Impressions-Severity of Illness scale (CGI-S).18 Eligible patients were required to use an acceptable method of birth control (if of childbearing potential) or to have undergone a total hysterectomy at least 3 months before they enrolled in the study.

Exclusion criteria included delirium, epilepsy, or mental retardation; intoxication or symptoms of withdrawal from alcohol or other psychoactive substances; clinical laboratory values indicating serious medical illness; treatment with any antipsychotic or benzodiazepine within 6 hours of screening; a history of neuroleptic malignant syndrome or known hypersensitivity to any of the trial medications; treatment with a depot antipsychotic within 1 treatment cycle of screening; and use of disallowed medication.

Method

This was a prospective, parallel-group, randomized, rater-blinded study of emergency department patients or inpatients exhibiting both psychosis and agitation judged by clinicians to require pharmacologic intervention. It was conducted from January 8 to August 8, 2001, at 24 sites in the United States. Study personnel received central training on study-related procedures and assessments, including evaluation of patient capacity to consent. All efficacy raters were trained on the primary and secondary outcome parameters, with subsequent evaluation of interrater reliability. Throughout the study, independent raters blinded to treatment arm conducted efficacy assessments.

Each center’s institutional review board approved the protocol, and all patients provided written informed consent before enrollment. A formal assessment of decisional capacity was conducted on patients and documented by clinicians unaffiliated with the protocol and also by members of the research team. Patients who met the inclusion criteria, were judged to be capable of making health care decisions, and gave their written informed consent were randomly assigned to treatment. A telephoner-based central service was used to randomly assign eligible patients to receive a single dose of oral treatment or IM injection. Patients were followed up for up to 24 hours after dosing.

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dose before study entry. Concurrent use of sedatives was not allowed.

Assessment of Efficacy and Safety

Patients were rated at 30 minutes and 1, 2, 3, 6, and 24 hours after receiving the initial dose of study medication, although sleeping patients were not awakened for assessments. Efficacy was assessed using 3 validated instruments: the PANSS, the CGI-S, and the Overt Aggression Scale (OAS). The primary measure of efficacy was change in scores on an acute-agitation cluster, composed of 5 items from the PANSS (excitement, hostility, uncooperativeness, hallucinatory behavior, and poor impulse control). Each item is scored on a 7-point scale (1 = absent to 7 = extreme). The same 5-item acute-agitation scale was used in a prior study of oral risperidone for agitation. Other measures included the PANSS total score and the PANSS factors (positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression). The 30-item PANSS total baseline evaluation was completed when patients became cooperative and could be assessed.

Overall improvement was assessed with the CGI-S (ranging from 1 = no symptoms to 7 = extremely severe symptoms). The 16-item OAS consists of 4 categories: verbal aggression (items scored from 1–4), physical aggression against objects (2–5), physical aggression against self (3–6), and physical aggression against others (3–6). Two scores are derived from the OAS. The aggression score is the sum of the weighted scores for the most severe behavior in each of the 4 categories (maximum score is 21), and the total aggression score is the aggression score plus the score for the most restrictive intervention required (scored from 0 to 5; the maximum score is 26). Patients with no aggressive incidents, as recorded on their case report forms, had their total aggression and aggression scores set equal to zero in the analysis.

Also recorded was the time that elapsed before additional lorazepam was administered and before sleep occurred. Investigators monitored and collected spontaneous reports of adverse events and assessed the severity and relationship to the study drug. Physical and neurologic examinations were performed at baseline or as soon as feasible within 24 hours of study entry. Movement disorders were evaluated using the Barnes Akathisia Scale (BAS) and the Simpson-Angus Scale (SAS) (for parkinsonian symptoms). Sedation was assessed by means of a 4-point scale (0 = no signs, 1 = slightly sedated, 2 = moderately sedated, and 3 = asleep).

Data Analyses

According to the definition of treatment noninferiority used (a difference of < 4 between oral and IM treatments in mean changes from baseline at 1 hour on the acute-agitation cluster score), 80 patients per treatment were necessary for 80% power and a 2-sided type I error of 5% (assuming a standard deviation of 9.0).

Efficacy in all randomized patients with at least 1 postbaseline assessment was assessed by means of the acute-agitation cluster. The primary timepoint was 60 minutes after dosing. Safety was assessed in all randomized patients who received medication. Observed-case data and last-observation-carried-forward (endpoint) data are presented.

On the primary measure of efficacy (acute-agitation cluster) and on the PANSS total and factor scores, treatment groups were compared using an analysis of covariance (ANCOVA) with treatment, investigator, and baseline score as the covariates and the treatment-by-covariate interaction term as factor. If the interaction term was not significant at the .10 level, it was dropped from the model and the analyses were based on the reduced model. A 95% confidence interval for the difference in treatment least-squares means was computed, and tests for noninferiority were performed using a confidence-interval approach. The CGI-S data were analyzed using the Cochran-Mantel-Haenszel (CMH) test for row mean scores, controlling for investigator.

Time to sleep during the first 24 hours after dosing and time to the first additional lorazepam dose were analyzed using Kaplan-Meier product-limit survival curve estimates. The log-rank test was used to compare treatment groups. Patients who did not sleep during the first risperidone/haloperidol dosing cycle were censored at the time they received additional study medication. Patients who did not receive additional lorazepam were censored at 24 hours. The additional average total daily dose of lorazepam administered was analyzed using an analysis of variance with treatment and investigator as factors.

The BAS and SAS scores were evaluated in all patients with at least 1 postbaseline PANSS assessment and analyzed using the same ANCOVA model as in the PANSS analyses, except that the covariate in the model was the baseline value of the variable being examined. Between-group differences in adverse events were compared using the Fisher exact test.

RESULTS

Of the 181 patients screened, 162 were randomly assigned to treatment: 83 to a single oral dose of risperidone plus lorazepam and 79 to a single IM injection of haloperidol plus lorazepam. The patients’ ages spanned a broad range from 18 to 65 years, and the most frequent diagnoses were paranoid schizophrenia (33%) and schizoaffective disorder (22%) (Table 1). Between-group differences in baseline characteristics were not statistically significant. A similar proportion of patients in both groups completed the study: 77% in the oral group and 82% in the IM group (Table 2; Figure 1).
Study patients were experiencing behavioral emergencies at study entry, as reflected in mean baseline scores of \( \geq 19.0 \) on the acute-agitation cluster and \( \geq 14.0 \) on the PANSS factor of uncontrolled hostility/excitement; 78 (53\%) had a baseline CGI-S score of \( \geq 5 \) (marked symptoms). Patients’ mean baseline OAS scores were \( \geq 3.4 \) (total aggression) and \( \geq 2.5 \) (aggression), and an aggressive incident was observed in 82 (56\%) of the 147 patients within the week preceding enrollment.

Additional lorazepam was received by similar proportions of patients in the 2 groups: 28 (35\%) of the 80 patients in the oral group and 21 (31\%) of the 67 patients in the IM group. The mean \( \pm \) SD additional dose of lorazepam (2.6 \( \pm \) 1.2 mg and 2.5 \( \pm \) 1.2 mg in the oral group and the IM group, respectively) and the mean \( \pm \) SD time to the first additional dose (20.1 \( \pm \) 7.2 hours and 20.3 \( \pm \) 7.4 hours, respectively) were not significantly different between the 2 groups.

### Efficacy

The efficacy population included all randomized patients who received at least 1 postbaseline acute-agitation cluster assessment. The upper limit of the 95\% confidence interval was well below 4 at each timepoint after dosing, demonstrating noninferiority of oral treatment (Table 3). In both treatment groups, significant improvements on the acute-agitation cluster score were seen at 30, 60, and 120 minutes after dosing and at treatment endpoint (\( p < .0001 \) at each timepoint) (Table 3, Figure 2). Between-treatment differences in mean change scores on the acute-agitation cluster and on the 5 individual items were not significant.

Treatment effects were assessed on 2 of the 5 behaviors (acute-agitation cluster items) that are of special concern in the emergency department: hostility and excitement. Mean \( \pm \) SD scores on these items were similar in the 2 groups at baseline (hostility, 3.6 \( \pm \) 1.2 in the oral group and 3.7 \( \pm \) 1.3 in the IM group; excitement, 4.0 \( \pm \) 0.9 and 4.1 \( \pm \) 1.0, respectively), as were the least-squares mean \( \pm \) SE reductions in scores at 60 minutes (hostility, \(-1.6 \pm 0.1 \) and \(-1.6 \pm 0.2 \); excitement, \(-1.3 \pm 0.1 \) and \(-1.3 \pm 0.1 \).
The baseline PANSS total scores reflect each patient’s condition at the time the patient could be fully assessed (Table 4). Significant improvements were seen in both the oral and IM treatment groups, and the between-treatment differences were not significant. At 24 hours, 40% of the oral treatment group and 34% of the IM treatment group had at least a 20% improvement in PANSS total scores (Figure 3). Since informed consent was obtained from enrolled subjects, subanalyses were conducted to assess generalizability to patients with severe agitation. The study population was divided according to the upper (> 3.524) and lower halves of the scores on the aggression item in the baseline PANSS score. As shown in Figure 4, both treatments were equivalently efficacious in reducing acute-agitation cluster scores in the higher and lower aggression severity groups.

Both treatment groups demonstrated reduced verbal and physical aggression (OAS scores) with no significant between-treatment differences (Table 5). Acute-agitation cluster scores and OAS total aggression scores were determined in the 82 patients with schizophrenia or schizoaffective disorder. As in the total population, significant

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### Table 3. Baseline Scores and Changes From Baseline on the 5-Item Acute-Agitation Cluster Score

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Oral Treatment Mean Score</th>
<th>SD</th>
<th>IM Treatment Mean Score</th>
<th>SD</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>19.0 ± 3.0</td>
<td></td>
<td>19.1 ± 3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>–4.9 ± 0.4</td>
<td>55</td>
<td>–5.8 ± 0.5</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>–6.9 ± 0.5</td>
<td>38</td>
<td>–7.2 ± 0.6</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>120 min</td>
<td>–7.8 ± 0.7</td>
<td>26</td>
<td>–8.2 ± 0.9</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Positive and Negative Syndrome Scale Total and Factor Scores at Baseline and Changes at Endpoint

<table>
<thead>
<tr>
<th>Score</th>
<th>Oral Treatment Mean Score</th>
<th>SD</th>
<th>IM Treatment Mean Score</th>
<th>SD</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Baseline</td>
<td>5.7 ± 1.7</td>
<td></td>
<td>19.0 ± 1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint</td>
<td>27.6 ± 6.8</td>
<td></td>
<td>–14.0 ± 1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive symptoms Baseline</td>
<td>28.3 ± 5.8</td>
<td></td>
<td>27.6 ± 6.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint</td>
<td>–5.2 ± 0.6</td>
<td></td>
<td>–5.0 ± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative symptoms Baseline</td>
<td>19.0 ± 6.5</td>
<td></td>
<td>20.8 ± 7.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint</td>
<td>–2.4 ± 0.5</td>
<td></td>
<td>–2.2 ± 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorganized thoughts Baseline</td>
<td>20.9 ± 5.9</td>
<td></td>
<td>21.3 ± 6.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint</td>
<td>–3.1 ± 0.4</td>
<td></td>
<td>–3.2 ± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hostility/excitement Baseline</td>
<td>14.3 ± 2.7</td>
<td></td>
<td>14.0 ± 3.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint</td>
<td>–5.3 ± 0.4</td>
<td></td>
<td>–4.9 ± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety/depression Baseline</td>
<td>13.2 ± 3.9</td>
<td></td>
<td>13.3 ± 4.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint</td>
<td>–3.0 ± 0.3</td>
<td></td>
<td>–2.8 ± 0.4</td>
<td></td>
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</tr>
</tbody>
</table>

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-1.4 ± 0.2) and at 120 minutes (hostility, -1.7 ± 0.2 and -1.8 ± 0.2; excitement, -1.8 ± 0.2 and -1.8 ± 0.2). The between-treatment differences in each of these comparisons were not significant (p > .6).

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**Abbreviation:** IM = intramuscular.
improvements (p < .01 vs. baseline, paired t test) on both scores were seen in this subgroup, with no significant between-group differences.

The CGI assessments of disease severity at baseline and at 24 hours after dosing were similarly distributed in the 2 treatment groups (Figure 5). The proportions of patients whose disease severity was rated as marked to severe decreased from 53% (oral treatment [N = 80]) and 54% (IM treatment [N = 67]) at baseline to 24% and 21%, respectively, at 24 hours.

Thirty minutes after receiving treatment, only 5 patients (6%) in the oral group could not be evaluated with the acute-agitation cluster because they were sleeping, while 14 (21%) in the IM group could not be evaluated due to sleep. A difference was also observed at 60 minutes postdose, when 18 (23%) and 29 (43%) of the patients assigned to oral and IM treatment, respectively, could not be evaluated due to sleep. This difference persisted at 120 minutes, when 35 (44%) and 40 (60%), respectively, could not be evaluated. The cumulative frequency distribution of the patients’ first time to sleep was twice as great in the first 60 minutes after treatment in the IM group as in the oral treatment group (55% [35/64] vs. 24% [19/79]; Fisher exact $\chi^2 = 14.12$, df = 1, $p < .001$; total group Ns differ from efficacy Ns due to missing data) (Figure 6). The same pattern was seen at 120 minutes (Fisher exact $\chi^2 = 4.59$, df = 1, $p = .04$) and 180 minutes after dosing.

Sedation scale scores in the 2 groups were similar at baseline (all patients scored ≤ 1), but significant differences were noted at later timepoints. The proportions of patients scoring 1 or above at 30 minutes were 37% (N = 83) of oral patients and 72% (N = 78) of IM patients (CMH $\chi^2 = 19.37$, df = 1, $p < .0001$); at 60 minutes, 61% (N = 82) and 85% (N = 79), respectively (CMH $\chi^2 = 13.39$, df = 1, $p = .003$); and at 120 minutes, 85% (N = 82) and 94% (N = 78) (CMH $\chi^2 = 4.86$, df = 1, p = .0027) (Ns represent the number of patients for whom data were obtained at each timepoint).

**Safety**

The safety population includes all randomized patients who received medication. The incidence of treatment-related adverse events was not significantly different between the 2 treatment groups (24% and 25%, respectively). Adverse events reported in 5% or more of patients in either group included headache (in 4 patients [4.8%] receiving oral treatment and 5 [6.3%] receiving IM treatment), hyperkinesia (in 1 [1.2%] and 4 [5.1%] of the patients, respectively), agitation (in 4 patients in each group [4.8% and 5.1%, respectively]), and somnolence (in 11 [13.3%] and 10 [12.7%] of the patients, respectively). There were no significant between-group differences in the incidence of any adverse event. Adverse events resolved spontaneously in most patients by the time of their last assessment (in 74% of patients in the oral group and 73% in the IM group). The only adverse events assessed as severe were agitation (in 1 patient in the oral group and 2 in the IM group), anxiety (in 1 patient in the IM group), insomnia (in 1 patient in the oral group), psychosis (in 4 patients in the oral group), and somnolence (in 1 patient in the IM group). One patient assigned to each treatment group discontinued study medication because of adverse events. The patient assigned to oral treatment experienced...
a worsening of psychotic symptoms, and the patient assigned to IM treatment experienced somnolence that resolved the day after treatment discontinuation.

Specific movement disorders were reported as adverse events by 4 patients in the oral group (dystonia in 2, hyperkinesia in 1, and hypertonia in 1) and 8 patients in the IM group (dyskinesia in 1, dystonia in 1, hyperkinesia in 4, and tremor in 2). Severity of akathisia and parkinsonism was low at baseline in both groups (mean ± SD BAS total scores, 1.5 ± 2.6 and 1.6 ± 2.8; SAS total scores, 1.7 ± 2.7 and 2.2 ± 3.2, respectively) and was further reduced or remained unchanged during treatment (BAS change, −0.6 ± 0.2 and −0.3 ± 0.2; SAS change, −0.3 ± 0.2 and 0.1 ± 0.2, respectively, at endpoint).

Vascular stability as assessed by mean blood pressure and mean heart rate was similar in the 2 groups at baseline. Changes in mean blood pressure did not differ between the 2 treatment groups; however, 2 patients assigned to IM treatment experienced orthostatic hypotension. No episodes of syncope were reported. Mean changes in heart rate were generally the same in the 2 groups except at 2 timepoints. It differed at 1 hour postdose (6.5 ± 1.7 beats per minute with oral treatment vs. −2.9 ± 2.1 beats per minute with IM treatment) and at 8 hours after treatment (1.6 ± 2.4 vs. −7.2 ± 3.6 beats per minute, respectively).

**DISCUSSION**

Agitation remains a common management problem that frequently necessitates urgent pharmacologic intervention. Many clinicians perceive intramuscular treatments as having faster onset and greater efficacy and hence are more likely to prescribe injections for even moderately agitated patients.

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### Table 5. Overt Aggression Scale (OAS) Scores at Baseline and Changes at 30, 60, and 120 Minutes

| OAS Component | Oral Treatment | IM Treatment | Analysis
<table>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Score b</td>
<td>N</td>
</tr>
<tr>
<td>Total aggression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>80</td>
<td>3.6 ± 4.2</td>
<td>67</td>
</tr>
<tr>
<td>30 min c</td>
<td>80</td>
<td>−2.5 ± 0.2</td>
<td>67</td>
</tr>
<tr>
<td>60 min c</td>
<td>79</td>
<td>−3.0 ± 0.2</td>
<td>67</td>
</tr>
<tr>
<td>120 min c</td>
<td>79</td>
<td>−3.4 ± 0.1</td>
<td>66</td>
</tr>
<tr>
<td>Aggression  d</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>80</td>
<td>2.8 ± 3.5</td>
<td>67</td>
</tr>
<tr>
<td>30 min c</td>
<td>80</td>
<td>−1.8 ± 0.2</td>
<td>67</td>
</tr>
<tr>
<td>60 min c</td>
<td>79</td>
<td>−2.3 ± 0.2</td>
<td>67</td>
</tr>
<tr>
<td>120 min c</td>
<td>79</td>
<td>−2.6 ± 0.1</td>
<td>66</td>
</tr>
</tbody>
</table>

* Analysis of covariance model with factors for treatment, baseline values, and investigator for postbaseline assessments and without the factor baseline values for baseline assessment.
* Difference between oral and IM treatment in mean change from baseline.
* Sum of the weighted scores for the most severe behavior in each of the 4 categories plus the score for the most restrictive intervention required.
* Significant change from baseline in both groups (p < .0001).
* Sum of the weighted scores for the most severe behavior in each of the 4 categories.

Abbreviation: IM = intramuscular.
This randomized single-blind study found that both oral treatment with risperidone, 2 mg, plus lorazepam, 2 mg, and intramuscular treatment with haloperidol, 5 mg, plus lorazepam, 2 mg, were similarly efficacious in treating acute agitation. Both treatment combinations worked rapidly and produced a clinical response comparable with that of IM atypical antipsychotics in placebo-controlled trials of acute agitation. Clinical response was seen across a broad range of symptoms, including hostility and excitement.

The efficacy results of this study are consistent with studies that have demonstrated the efficacy of risperidone in the treatment of agitation in varied patient populations. In 1995, Czobor et al. reported that risperidone was more efficacious than haloperidol in controlling hostility in patients with schizophrenia. Katz et al. and De Deyn et al. demonstrated in randomized, double-blind, placebo-controlled trials involving elderly patients with dementia that risperidone reduced aggression without causing sedation. In double-blind, placebo-controlled studies, risperidone reduced aggressive behavior in adults with autistic disorder and in children with pervasive developmental disorder.

It was interesting to note substantially less sedation and sleep observed from 30 to 120 minutes in the oral treatment arm. The cumulative time to sleep for patients in each treatment group, a measure never before reported, strongly favors oral treatment in this study. Because comparable doses of lorazepam were used in both treatment groups, this difference may derive from either the route of administration or the use of a different antipsychotic. Risperidone is one of the least sedating antipsychotic medications, and it is more likely that this difference in antipsychotics explains the observed effect. A clinically important improvement in quality of care may be associated with this ability to achieve targeted control of problem symptoms without producing unnecessary sedation, which may impair proper patient evaluation during an acute episode and be perceived negatively as an imposition of “chemical restraints.”

The study has several limitations, including the absence of a placebo group; the use of only 1 dose of each antipsychotic; the administration of lorazepam to all patients, which confounded the interpretation of pure antipsychotic response; the comparison of oral and intramuscular lorazepam, which may have differential efficacy; and the inclusion of only consenting agitated patients. While including only patients capable of giving informed consent may have excluded those with the most severe illness, this group may well represent the patients appropriate for this regimen: those who are willing and able to accept an oral medication. Furthermore, this limitation is common to nearly all controlled studies of agitation that have been published recently. The study design precludes separating antipsychotic effects from those of adjunctive lorazepam; however, antipsychotic/oralazine combinations are widely used in the emergency setting to control agitation, making a comparison of these combination regimens relevant to current clinical practice. These data do suggest that an oral combination of atypical antipsychotic and benzodiazepine may be an alternative to the popular intramuscular “agitation cocktail” of haloperidol, 5 mg, and lorazepam, 2 mg. Future research comparing antipsychotic monotherapies at different doses would produce useful information about the specific response associated with each dose.

**CONCLUSION**

Single-dose oral treatment with risperidone plus lorazepam safely and rapidly controlled agitation and aggression and produced less potentially undesirable sedation than did IM haloperidol plus lorazepam. These results challenge the reliance on intramuscular treatment of acute agitation and suggest that this oral regimen may be an effective alternative therapeutic option.

**Drug names:** chlorpromazine (Thorazine and others), haloperidol (Haldol and others), lorazepam (Ativan), olanzapine (Zyprexa), risperidone (Risperdal), zolpidem (Ambien).


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