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 in both groups ($p < .0001$) 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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Acute agitation is a common presentation in emergency departments and is often secondary to an underlying psychotic condition.[1,2] In many emergency settings, treatment consists of parenteral administration of 2 classes of psychotropic drugs: high-potency antipsychotics and benzodiazepines.[3,4] Lorazepam has become the benzodiazepine of choice because it is reliably absorbed by intramuscular (IM) administration and has a relatively short half-life (10–20 hours), no active metabolites, and virtually no drug-drug interactions.[5] The first-generation agent haloperidol is preferred over the lower potency drugs such as chlorpromazine because it is associated with a less extensive side effect burden.[6]

Parenteral treatment with haloperidol and lorazepam is associated with several potential drawbacks. Patients perceive IM administration as coercive and abusive, and therefore prefer oral medication over forced injections.[7] Intramuscular drug administration also carries the risk to the staff of accidental needle sticks and associated exposure to blood-borne pathogens.[8] Furthermore, the standard IM treatment of psychotic agitation can result in adverse physical effects such as confusion, disinhibition,

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.[1,10] A recent expert consensus guideline recommended risperidone as a first-line treatment option in this setting when oral treatment is possible.[7] 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 psychotically agitated patients.[11] Placebo-controlled prospective studies suggest that risperidone is efficacious in controlling psychosis, aggression, and agitation associated with dementia[12] and is superior to haloperidol in controlling hostility associated with schizophrenia.[13] This advantage over haloperidol may be related to differences in serotonergic and other central nervous system receptor activity between the atypical and conventional antipsychotic drugs.[14,15]

Results from a recent prospective, naturalistic pilot study at an urban emergency department suggest that oral treatment is an important alternative to IM injection.[16] In that study, agitated patients were offered oral risperidone liquid concentrate plus oral lorazepam or IM haloperidol plus IM lorazepam. Both treatments reduced agitation and were well tolerated. While the study was suggestive, it had significant limitations, including inadequate statistical power and nonrandom assignment to treatment condition.

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.

METHOD

This is 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 telephone-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.

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)[17]; and (4) a score ≥ 3 on the Clinical Global Impressions-Severity of Illness scale (CGI-S).[18] Eligible women were required to use an acceptable method of birth control (if of childbearing potential) or were postmenopausal or had 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.

Treatment

Patients were randomly assigned to receive a single oral dose of 2 mg of risperidone solution (1 mg/mL) plus 2 mg of oral lorazepam or an IM injection of 5 mg of haloperidol (5 mg/mL) plus 2 mg of IM lorazepam. Additional doses of 2 mg of oral lorazepam could be administered every 2 hours as needed after the initial dosing if indicated; the total dose was not to exceed 8 mg over the 24-hour treatment period.

The following concomitant medications were not permitted: antipsychotics other than risperidone or haloperidol, anxiolytics (except for lorazepam), psychoactive drugs, and continuous use of an anticholinergic. Antiparkinsonian drugs could be given at the lowest effective dose if movement disorders emerged or worsened during the trial. Patients were not allowed to take mood stabilizers or antidepressants unless they were receiving a stable

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).[19] 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.[16] Other measures included the PANSS total score and the PANSS factors (positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression).[20] 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 0–5; 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)[21] and the Simpson-Angus Scale (SAS)[22] (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).

Table 1. Baseline Patient Characteristics and Clinical Data

Variable	Oral Treatment	IM Treatment	p[a]
Safety population[b]	(N = 83)	(N = 79)	
Age, mean (SD), y	39.7 (10.1)	38.7 (12.3)	.37
Age range, y	19–63	18–65	
Men/women, N (%)	56 (67)/27 (33)	49 (62)/30 (38)	.52
Race, N (%)			.35
White	39 (47)	30 (38)	
African American	33 (40)	33 (42)	
Hispanic	10 (12)	12 (15)	
Other	1 (1)	4 (5)	
Diagnosis,[c] N (%)			.61
Paranoid schizophrenia	26 (31)	28 (35)	
Schizoaffective disorder	18 (22)	18 (23)	
Bipolar I disorder, manic severe with psychotic features	7 (8)	6 (8)	
Psychotic disorder not otherwise specified	14 (17)	17 (22)	
Other	18 (22)	10 (13)	
Efficacy population[b]	(N = 80)	(N = 67)	
Acute agitation cluster score, mean (SD)	19.0 (3.0)	19.1 (3.0)	.85
OAS scores, mean (SD)			
Total score	3.6 (4.2)	3.4 (4.2)	.44
Aggression score	2.8 (3.5)	2.5 (3.4)	.35
CGI-S disease severity, N (%)			.90
Mild	3 (4)	1 (1)	
Moderate	35 (44)	30 (45)	
Marked	31 (39)	29 (43)	
Severe	11 (14)	7 (10)	

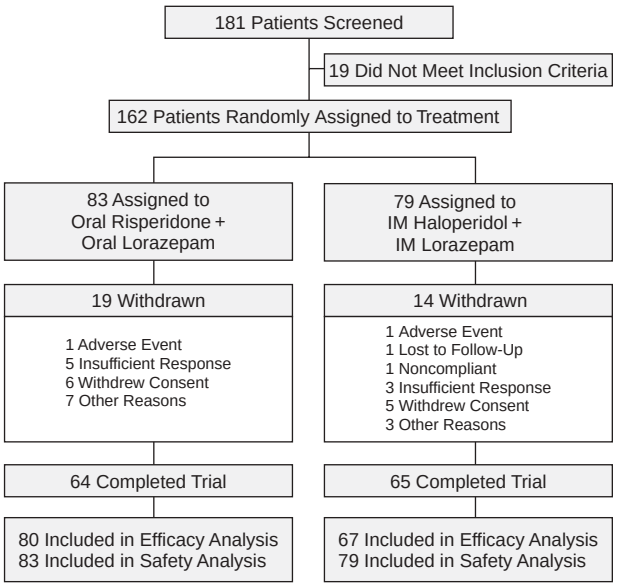
[a]The categorical variables were analyzed for treatment group differences using the Cochran-Mantel-Haenszel test controlling for investigator, and the continuous variables were analyzed using analysis of variance with treatment and investigator as factors.
[b]The safety population includes all randomized patients who received medication. The efficacy population includes all randomized patients who received at least 1 postbaseline assessment.
[c]All patients were agitated.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, IM = intramuscular, OAS = Overt Aggression Scale.

Table 2. Patients Who Completed the Trial and Reasons for Discontinuation, N (%)

Patient Disposition	Oral Treatment (N = 83)	IM Treatment (N = 79)	Total (N = 162)
Completed trial	64 (77)	65 (82)	129 (80)
Reason for discontinuation			
Adverse events	1 (1)	1 (1)	2 (1)
Insufficient response	5 (6)	3 (4)	8 (5)
Lost to follow-up	0 (0)	1 (1)	1 (1)
Withdrawn consent	6 (7)	5 (6)	11 (7)
Noncompliance	0 (0)	1 (1)	1 (1)
Other	7 (8)	3 (4)	10 (6)

Abbreviation: IM = intramuscular.

Figure 1. Patient Flow



Abbreviation: IM = intramuscular.

Study patients were experiencing behavioral emergencies at study entry, as reflected in mean baseline scores of ≥ 19.0 on the acute-agitation cluster and ≥ 14.0 on the PANSS factor of uncontrolled hostility/excitement; 78 (53%) had a baseline CGI-S score of ≥ 5 (marked symptoms). Patients' mean baseline OAS scores were ≥ 3.4 (total aggression) and ≥ 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 ± SD additional dose of lorazepam (2.6 ± 1.2 mg and 2.5 ± 1.2 mg in the oral group and the IM group, respectively) and the mean ± SD time to the first additional dose (20.1 ± 7.2 hours and 20.3 ± 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.

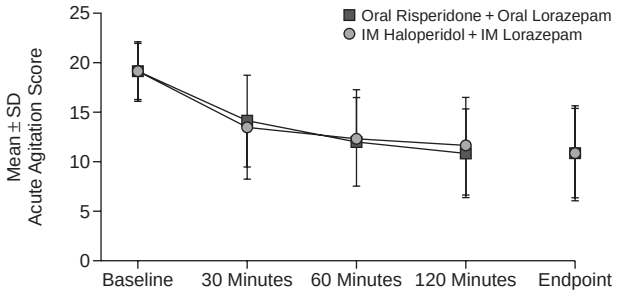
Treatment effects were assessed on 2 of the 5 behaviors (acute-agitation cluster items) that are of special concern in the emergency department: hostility and excitement. Mean ± SD scores on these items were similar in the 2 groups at baseline (hostility, 3.6 ± 1.2 in the oral group and 3.7 ± 1.3 in the IM group; excitement, 4.0 ± 0.9 and 4.1 ± 1.0, respectively), as were the least-squares mean ± SE reductions in scores at 60 minutes (hostility, –1.6 ± 0.1 and –1.6 ± 0.2; excitement, –1.3 ± 0.1 and

Table 3. Baseline Scores and Changes From Baseline on the 5-Item Acute-Agitation Cluster Score[a,b]

	Oral Treatment		IM Treatment		Analysis[c]			
Timepoint	N	Score[d]	N	Score[d]	95% CI[e]	F	df	p
Baseline	80	19.0 ± 3.0	67	19.1 ± 3.0		0.04	1,133	.85
30 min[f]	75	–4.9 ± 0.4	53	–5.8 ± 0.5	–0.4 to 2.2	2.06	1,113	.15
60 min[f]	61	–6.9 ± 0.5	38	–7.2 ± 0.6	–1.3 to 1.8	0.11	1,84	.74
120 min[f]	44	–7.8 ± 0.7	26	–8.2 ± 0.9	–1.8 to 2.7	0.19	1,55	.67
Endpoint[f]	80	–8.0 ± 0.4	67	–8.4 ± 0.5	–0.8 to 1.6	0.35	1,132	.55

[a]Hallucinatory behavior, excitement, hostility, poor impulse control, and uncooperativeness. Possible scale scores range from 5 to 35.
[b]Sleeping patients were not awakened for assessments.
[c]Analysis of covariance model with factors for treatment, baseline values, and investigator for postbaseline assessments and without the factor baseline values for baseline assessment.
[d]Baseline scores expressed as mean ± SD, change scores at other timepoints expressed as least-squares mean ± SE.
[e]Difference between oral and IM treatment in mean change from baseline.
[f]Significant change from baseline in both treatment groups ($p < .0001$ by paired t tests).
Abbreviation: IM = intramuscular.

Figure 2. Acute-Agitation Cluster Scores From Baseline to Endpoint in Patients Receiving Oral or Intramuscular (IM) Treatment[a,b]



[a]Each of the 5 items is scored on a scale from 1 (absent) to 7 (extreme); range of possible scores is 5 to 35.
[b]$p < .0001$ vs. baseline at each timepoint for both groups.

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

	Oral Treatment		IM Treatment		Analysis[a]			
Score	N	Score[b]	N	Score[b]	95% CI[c]	F	df	p
Total								
Baseline	78	95.7 ± 17.5	58	97.0 ± 18.5		0.23	1,122	.63
Endpoint[d]	78	–19.0 ± 1.6	58	–18.4 ± 1.9	–5.5 to 4.3	0.06	1,121	.81
Positive symptoms								
Baseline	78	28.3 ± 5.8	58	27.6 ± 6.8		0.33	1,122	.57
Endpoint[d]	78	–5.2 ± 0.6	58	–5.0 ± 0.7	–1.9 to 1.5	0.04	1,121	.84
Negative symptoms								
Baseline	78	19.0 ± 6.5	58	20.8 ± 7.6		2.92	1,122	.09
Endpoint[d]	78	–2.4 ± 0.5	58	–2.2 ± 0.6	–1.7 to 1.3	0.07	1,121	.79
Disorganized thoughts								
Baseline	78	20.9 ± 5.9	58	21.3 ± 6.1		0.18	1,122	.68
Endpoint[d]	78	–3.1 ± 0.4	58	–3.2 ± 0.5	–1.2 to 1.4	0.02	1,121	.88
Hostility/excitement								
Baseline	78	14.3 ± 2.7	58	14.0 ± 3.4		0.27	1,122	.61
Endpoint[d]	78	–5.3 ± 0.4	58	–4.9 ± 0.5	–1.6 to 0.9	0.31	1,121	.58
Anxiety/depression								
Baseline	71	13.2 ± 3.9	58	13.3 ± 4.1		0.01	1,122	.91
Endpoint[d]	78	–3.0 ± 0.3	58	–2.8 ± 0.4	–1.1 to 0.8	0.13	1,121	.72

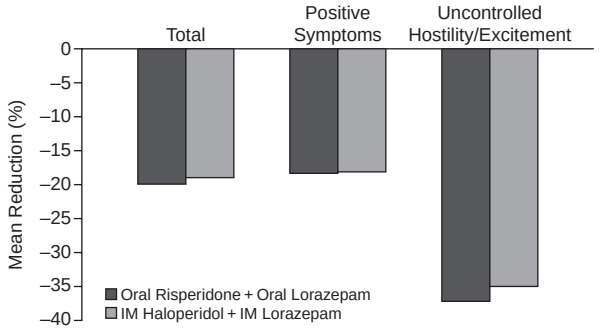
[a]Analysis of covariance model with factors for treatment, baseline values, and investigator for postbaseline assessments and without the factor baseline values for baseline assessment.
[b]Baseline scores expressed as mean ± SD, change scores at other timepoints expressed as least-squares mean ± SE.
[c]Difference between oral and IM treatment in mean change from baseline.
[d]Significant change from baseline in both treatment groups ($p < .001$).
Abbreviation: IM = intramuscular.

–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 ($p > .6$).

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.

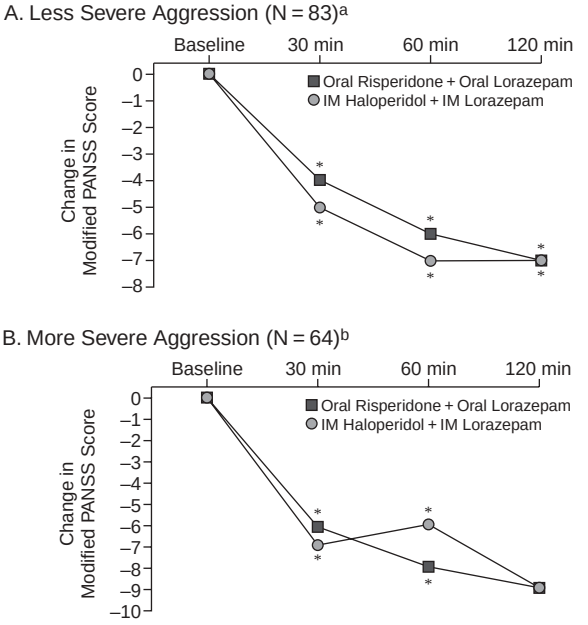
Both treatment groups demonstrated reduced verbal and physical aggression (OAS scores) with no significant between-treatment differences (Table 5). Acute-agitation cluster scores and OAS total aggression scores were determined in the 82 patients with schizophrenia or schizoaffective disorder. As in the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

Figure 3. Reduction in PANSS Total and Positive Symptoms and Uncontrolled Hostility/Excitement Factors at Endpoint in Patients Receiving Oral or Intramuscular (IM) Treatment



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 4. Modified Positive and Negative Syndrome Scale Score Change From Baseline by Aggression Severity (observed cases)



[a]Aggression item score < 3.524 at baseline.
[b]Aggression item score ≥ 3.524 at baseline.
*p < .05 vs. baseline.

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] slept; 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

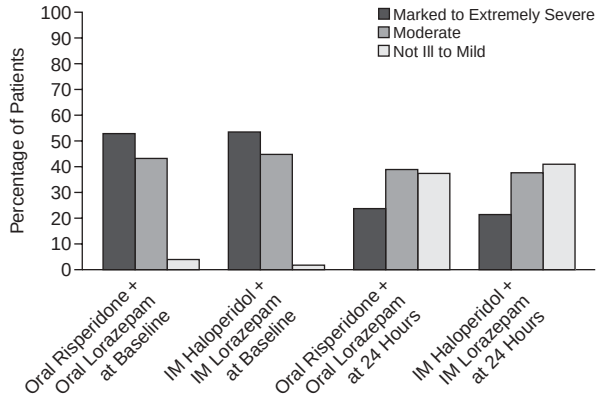
The safety population includes all randomized patients who received medication. The incidence of treatment-related adverse events was not significantly different between the 2 treatment groups (24% and 25%, respectively). Adverse events reported in 5% or more of patients in either group included headache (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

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

	Oral Treatment		IM Treatment		Analysis[a]			
OAS Component	N	Score[b]	N	Score[b]	95% CI[c]	F	df	p
Total aggression[d]								
Baseline	80	3.6 ± 4.2	67	3.4 ± 4.2		0.59	1,133	.443
30 min[e]	80	–2.5 ± 0.2	67	–3.0 ± 0.3	–0.2 to 1.2	2.03	1,132	.156
60 min[e]	79	–3.0 ± 0.2	67	–3.2 ± 0.2	–0.3 to 0.7	0.48	1,131	.491
120 min[e]	79	–3.4 ± 0.1	66	–3.5 ± 0.1	–0.2 to 0.4	0.33	1,130	.567
Aggression[f]								
Baseline	80	2.8 ± 3.5	67	2.5 ± 3.4		0.89	1 133	.346
30 min[e]	80	–1.8 ± 0.2	67	–2.2 ± 0.2	–0.2 to 1.0	1.56	1,132	.213
60 min[e]	79	–2.3 ± 0.2	67	–2.4 ± 0.2	–0.3 to 0.7	0.15	1,131	.695
120 min[e]	79	–2.6 ± 0.1	66	–2.6 ± 0.1	–0.2 to 0.2	0.08	1,130	.779

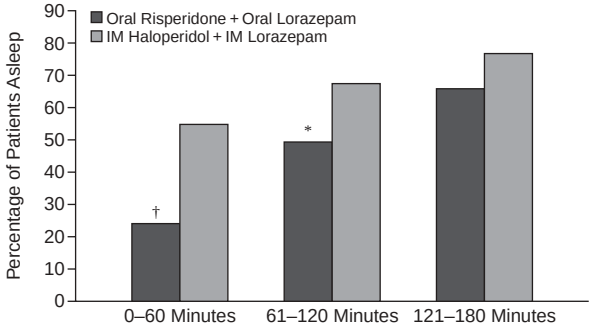
[a]Analysis of covariance model with factors for treatment, baseline values, and investigator for postbaseline assessments and without the factor baseline values for baseline assessment.
[b]Baseline scores expressed as mean ± SD, change scores at other timepoints expressed as least-squares mean ± SE.
[c]Difference between oral and IM treatment in mean change from baseline.
[d]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.
[e]Significant change from baseline in both groups ($p < .0001$).
[f]Sum of the weighted scores for the most severe behavior in each of the 4 categories.
Abbreviation: IM = intramuscular.

Figure 5. Severity of Illness on the Basis of CGI-S Rating at Baseline and 24 Hours in Patients Receiving Oral or Intramuscular (IM) Treatment



Abbreviation: CGI-S = Clinical Global Impressions-Severity of Illness scale.

Figure 6. Percentage of Patients Receiving Oral or Intramuscular (IM) Treatment Who Were Sleeping for the First Time at 0 to 60, 61 to 120, and 121 to 180 Minutes After Admission



*$p < .05$ vs. IM treatment.
†$p < .001$ vs. IM treatment.

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.[7]

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.[23,24] 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.[13] reported that risperidone was more efficacious than haloperidol in controlling hostility in patients with schizophrenia. Katz et al.[25] and De Deyn et al.[26] 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[27] and in children with pervasive developmental disorder.[28]

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/lorazepam 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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