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Differential Effects Of Lorazepam Dosages On Manic Symptoms In Bipolar Disorder: Observations On Agitation, Aggression, And Sedation Outcomes

Khaled Hamed,
MSN
USA/ CA

Abstract
Objective:
This study evaluates the differential effectiveness of two lorazepam dosages (1 mg and 2 mg) on managing acute manic symptoms in patients with bipolar disorder. The research focuses on the impact of these dosages on sedation, agitation, and aggression and examines the need for emergency interventions.
Methods:
An observational cohort study was conducted in two inpatient psychiatric facilities, involving 284 patients with bipolar disorder in acute manic phases. Participants were divided into two groups based on prescribed lorazepam dosages: 1 mg every 6 hours (4 mg/day) and 2 mg every 8 hours (6 mg/day). Primary outcomes included sedation effectiveness (measured using the Ramsay Sedation Scale), changes in agitation and aggression (using the Modified Overt Aggression Scale), and the frequency of emergency interventions. Data were analyzed using chi-square tests and t-tests to compare outcomes between dosage groups.
Results:
Patients receiving 2 mg of lorazepam showed slightly higher sedation and reduced aggression compared to the 1 mg group. However, both dosages required frequent emergency interventions to manage persistent agitation and psychological restlessness. Specifically, 84.52% of females and 75.64% of males in the 1 mg group required additional emergency medication, compared to 69.23% of females and 72.29% of males in the 2 mg group. As measured by the Ramsay Sedation Scale, Sedation levels did not differ significantly between the groups ($p > 0.05$).
Conclusions:
While the 2 mg dosage offers marginally improved sedation and aggression control, neither dosage alone is sufficient to manage the comprehensive symptoms of acute mania. These findings highlight the necessity of adjunctive therapy with antipsychotics or mood stabilizers for optimal symptom management.

Keywords: *Lorazepam, bipolar disorder, manic symptoms, agitation, aggression, sedation, emergency intervention.*

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I. Introduction

While much progress has been made in the pharmacological treatment of bipolar disorder, the management of acute manic episodes continues to represent a major therapeutic dilemma in contemporary psychiatry, necessitating the use of rapid-acting agents for patients' pronounced psychopathological features, including agitation, aggression, or insomnia. Lorazepam is a benzodiazepine with significant anxiolytic and sedative effects that is used in the setting of these episodes only on a short-term basis for stabilization. Research has shown that lorazepam has efficacy in decreasing severe behavioral manifestations. However, the optimal dosage, which will balance positive impacts on behavior, and possible side effects are still under discussion (Faden et al., 2023; Ward & Citrome, 2020).

Clinical significance of the existence of differential effects of different doses of lorazepam especially 1 mg and 2 mg for reducing manic symptoms, has been demonstrated. A dose of 2 mg has been found to measure more severe sedation, which may reduce the need for other emergency medications (Howard et al., 2014). However, side effects of 2 mg include resulting in dementia and dependence, which are risky for longer use of this medication. In contrast, there is evidence of a possibility of a safer profile in the side effect profile relating to the 1 mg dose. However, its effectiveness in managing severe aspects of agitation and aggression is still obscure, Faden and colleagues also seem to agree with this conclusion as the lower dose may not be effective enough to manage acute records of mania seen in patients.

Moreover, research on the usage of benzodiazepines including lorazepam revealed that people should be prescribed those with an individual approach to reach the best outcomes. Since the patients with bipolar disorder demonstrate varying sensitivity to sedatives, generalization of dosage for effective symptom management and free of side effects is challenging. Current study evidence indicates that to address the comprehensiveness of symptoms that characterizes manic episodes, a synergistic combination of lorazepam, along with adjunct antipsychotic or mood-stabilizing drugs, is needed.

The present study therefore seeks to establish the differences between 1 mg and 2 mg of lorazepam regarding their efficiency in the areas of agitation, aggression and sedation in bipolar disorder in acute mania. In particular, the question arises whether these dosages are sufficient in and of themselves or whether other measures are needed in order to achieve the ideal level of symptom management. Thus, by demonstrating these outcomes in a naturalistic clinical setting for the investigated medication, this study enriches the ongoing discussion about the dose and combination regimens that can effectively alleviate manic symptoms.

II. Methods

Study Design and Setting

This observational cohort study was conducted at two inpatient psychiatric facilities from December 2023 to September 2024. The study aimed to assess the differential effects of 1 mg oral lorazepam administered every 6 hours and 2 mg oral lorazepam administered every 8 hours, on acute manic symptoms in patients with bipolar disorder.

Participants

This research enrolled 284 patients with bipolar disorder in an acute manic phase. Criteria for patient selection included Age between 18 and 65 years; confirmed DSM-5 bipolar disorder; admission level manic symptoms moderate to severe. Patient exclusion criteria were any history of SUD in the last 3 months, pregnancy and breastfeeding, concomitant use of other sedative medications, and a known contraindication to benzodiazepines.

Participants were stratified into two groups: 1 mg or 2 mg oral lorazepam. Randomization was not used because this was a cohort study; however, the plan was done according to clinical judgement of the treating physician regarding the severity of the patient's symptoms.

Dosage Administration

Patients in each group were given lorazepam orally at 6 and 8 hourly intervals. The 1 mg group received a total daily dose of 4 mg, while the 2 mg group received 6 mg per day. Treatment duration varied depending on the patient's clinical needs but was evaluated consistently for a period of 72 hours following initial administration.

Outcome Measures

The primary outcomes were:

1. Sedation Effectiveness – Evaluated using the Ramsay Sedation Scale (RSS), with sedation success defined as a RSS score of -1 to -2 within the first 24 hours.
2. Agitation and Aggression Levels – Measured using the Modified Overt Aggression Scale (MOAS), assessing both frequency and intensity of aggressive behaviors.
3. Emergency Intervention Requirement – Defined as the need for additional antipsychotic medications or other sedatives (e.g., IM Chlorpromazine, IM Haloperidol, or IM Olanzapine) in addition to (IM Diphenhydramine and IM Lorazepam) due to inadequate response to the assigned oral lorazepam dosage.

Data Collection and Statistical Analysis

Data were collected at baseline, 24 hours, and 72 hours post-administration, focusing on changes in RSS and MOAS scores, along with the frequency of emergency interventions. Descriptive statistics were used to summarize demographic and baseline clinical characteristics. Chi-square tests were conducted to compare categorical outcomes (e.g., proportion of patients requiring emergency interventions) between groups. Continuous outcomes, such as changes in RSS scores, were analyzed using t-tests to determine statistically significant differences between the 1 mg and 2 mg groups. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

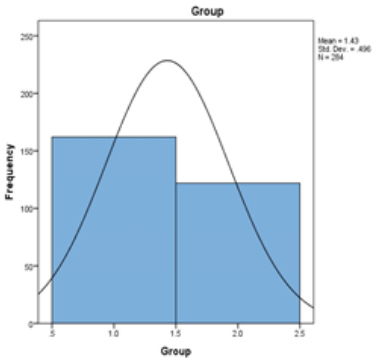
This study was conducted in accordance with the Declaration of Helsinki

III. Observations/Results

Group

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1 mg oral lorazepam	162	57.0	57.0	57.0
	2 mg oral lorazepam	122	43.0	43.0	100.0
	Total	284	100.0	100.0	

Of the total 284 participants, 162 (57%) received 1 mg of oral lorazepam, while 122 (43%) received 2 mg of oral lorazepam. This distribution is further illustrated by the histogram below;



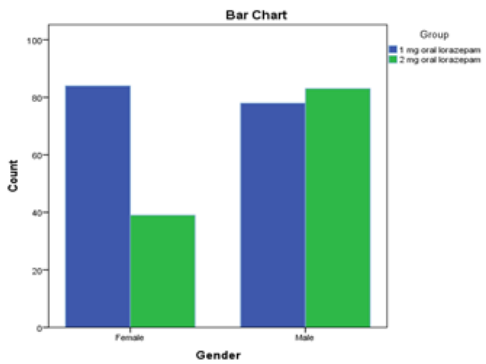
The histogram above illustrates the frequency distribution of participants across two dosage groups of oral lorazepam, with a superimposed normal distribution curve. The 1 mg dosage group shows a higher frequency, approximately 162 participants, compared to the 2 mg dosage group with 122 participants. The mean dosage level is reported as 1.43, with a standard deviation of 0.496, based on a total sample size of 284. The curve suggests a slight skew toward the lower dosage group, consistent with the larger proportion of participants in this category.

Gender * Group Crosstabulation

Count

		Group		Total
		1 mg oral lorazepam	2 mg oral lorazepam	
Gender	Female	84	39	123
	Male	78	83	161
Total		162	122	284

The cross-tabulation table illustrates the distribution of participants by gender across two lorazepam dosage groups. Out of the total 284 participants, 123 were female and 161 were male. Among females, 84 (68.3%) were in the 1 mg oral lorazepam group, while 39 (31.7%) were in the 2 mg group. Among males, 78 (48.4%) were in the 1 mg group, and 83 (51.6%) were in the 2 mg group.



The bar chart above indicates a higher proportion of females in the 1 mg group, whereas males were more evenly distributed between the two dosage groups.

1 mg Oral Lorazepam Group (162 patients; 78 male, 84 female)

In the 1 mg oral lorazepam group out of 84 female patients only 13 (15.48%) had mild improvement which allowed avoiding emergency intervention. Such patients exhibited some measure of relaxation of their psychological disturbed status and could therefore independently cope with their symptoms without the need for further drugs. But, 71 of women patients (84.52%) needed emergent medications which consist of injections of antipsychotics such as Thorazine, Haldol, Olanzapine along with Benadryl and 2 mg IM lorazepam. This group complained of continued symptoms like hyperactivity, being over talkative and sleepless, which shows that the 1 mg dose was several times inadequate to manage the newbie and definite symptoms of mania.

The same pattern was observed in the male subgroup of 78 patients, in whom 19 patients (24.36%) regained improvement with decreased agitation and could be saved from further emergency treatments. However, 59 of male patients (75.64%) needed additional emergency medication after the sedation effect of lorazepam had been observed. These patients were still so symptomatic as to become hyperactive, talkative and insomnia much of the time requiring more than occasional brief emergency antipsychotic and sedative treatments for their psychological restlessness. From this data it can be inferred that although some male patients had moderate positive results prescribed with 1 mg lorazepam the dosage is less optimal for treating all aspects of the symptoms in the majority of cases for this type of patient.

2 mg Oral Lorazepam Group (122 patients; 83 male, 39 female)

Out of 39 female patients of 2 mg oral lorazepam group, 12 (30.77 %) recorded significant improvement and were able to avert emergency procedures. This group of patients noted some improvement in the manic symptoms they were presenting with; thus they did not require even more drug intervention. But 27 female patients (69.23%) of them still had to take an emergency medication because of the symptoms. These patients persisted in having hyperactivity, talkativeness, and insomnia, suggesting that with a higher concentration of the drug, lorazepam alone could not fully control the patients' symptoms.

Out of the 83 patients in the male subgroup, only 23 (27/71%) showed improvement, which means no emergencies occurred due to agitation, and no medication was given. But an equal number of male patients, 60 (72.29%) required more intense emergency care to address their incompletely treated symptoms. Even after the first 2 mg dose that made these patients sedated, they continued to be hyperactive, speaking excessively and could not sleep, and they received multiple doses of antipsychotics and CDVs to manage their symptoms. This indicates that, indeed, the higher dose of lorazepam offered significant relief to a proportion of the male patients, but a vast majority needs other emergency medications for optimal symptom control.

The above outcome is as summarized in the table and graphs below;

	Female	
Row Labels	**Percentage Showing Improvement (%)**	**Percentage Requiring Emergency Medication (%)**
1 mg Lorazepam	15.48	84.52
2 mg Lorazepam	30.77	69.23
Grand Total	**46.25**	**153.75**

	Male	
Row Labels	**Percentage Showing Improvement (%)**	**Percentage Requiring Emergency Medication (%)**
1 mg Lorazepam	24.36	75.64
2 mg Lorazepam	27.71	72.29
Grand Total	**52.07**	**147.93**

	Row Labels	Percentage Showing Improvement (%)	Percentage Requiring Emergency Medication (%)
	1 mg Lorazepam	39.84	160.16
	2 mg Lorazepam	58.48	141.52
	Grand Total	**98.32**	**301.68**

In total, the 1 mg dosage was given to 57.04% of patients and 2 mg was given to 42.96% of patients in both dosages groups. Lorazepam treatment program in both groups, emergency interventions were often required in situations when patients were oppressive and agitated, especially the targeted patients with schizophrenia who did not show reasonable response to the initial course of oral lorazepam.

T-Test
RSS scores

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Ramsay Sedation Scale	Equal variances assumed	11.959	.001	-1.759	282	.080	-.089	.051	-.189	.011
	Equal variances not assumed			-1.728	241.424	.085	-.089	.052	-.191	.013

Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
Ramsay Sedation Scale	1 mg oral lorazepam	162	1.20	.399	.031
	2 mg oral lorazepam	122	1.29	.454	.041

An independent samples t-test was conducted to compare Ramsay Sedation Scale scores between the 1 mg oral lorazepam group (M = 1.20, SD = 0.399) and the 2 mg oral lorazepam group (M = 1.29, SD = 0.454). The assumption of equal variances was tested using Levene's Test, which indicated a significant difference in variances between the groups (F = 11.959, p = .001). The t-test results showed that, assuming equal variances, there was no statistically significant difference in Ramsay Sedation Scale scores between the two groups (t(282) = -1.759, p = .080, 95% CI [-0.189, 0.011]). When equal variances were not assumed, the results also indicated no significant difference (t(241.424) = -1.728, p = .085, 95% CI [-0.191, 0.013]). Therefore, we fail to reject the null hypothesis, concluding that there is insufficient evidence to suggest that sedation levels differ significantly between the two lorazepam dosage groups. These findings indicate that the dosage of lorazepam does not significantly impact Ramsay Sedation Scale scores.

Measured using the Modified Overt Aggression Scale (MOAS)

Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
Measured using the Modified Overt Aggression Scale	1 mg oral lorazepam	162	20.86	9.428	.741
	2 mg oral lorazepam	122	18.28	10.704	.969

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Measured using the Modified Overt Aggression Scale	Equal variances assumed	3.299	.070	2.159	282	.032	2.586	1.198	.227	4.944
	Equal variances not assumed			2.120	241.695	.035	2.586	1.220	.183	4.988

An independent samples t-test was conducted to compare scores on the Modified Overt Aggression Scale between the 1 mg oral lorazepam group (M = 20.86, SD = 9.428) and the 2 mg oral lorazepam group (M = 18.28, SD = 10.704). The assumption of equal variances was tested using Levene's Test, which indicated no significant difference in variances between the groups (F = 3.299, p = .070). Assuming equal variances, the t-test revealed a statistically significant difference in aggression scores between the two groups (t(282) = 2.159, p = .032, 95% CI [0.227, 4.944]). When equal variances were not assumed, the results also showed a significant difference (t(241.695) = 2.120, p = .035, 95% CI [0.183, 4.988]). These findings suggest that participants in the 1 mg group exhibited significantly higher aggression levels compared to those in the 2 mg group, as measured by the Modified Overt Aggression Scale.

Chi-square tests
Gender Gender * RSS Ramsay Sedation Scale

Crosstab

Count

		Ramsay Sedation Scale		
		1	2	Total
Gender	Female	98	25	123
	Male	119	42	161
Total		217	67	284

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.284[a]	1	.257		
Continuity Correction[b]	.984	1	.321		
Likelihood Ratio	1.297	1	.255		
Fisher's Exact Test				.324	.161
Linear-by-Linear Association	1.280	1	.258		
N of Valid Cases	284				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 29.02.

b. Computed only for a 2x2 table

A chi-square test was conducted to examine the relationship between gender and Ramsay Sedation Scale (RSS) scores. The cross tabulation revealed that, among females, 98 had an RSS score of 1 and 25 had an RSS score of 2. Among males, 119 had an RSS score of 1 and 42 had an RSS score of 2. The chi-square test did not reveal a statistically significant association between gender and RSS scores, $\chi^2(1, N = 284) = 1.284$, $p = .257$. The present results imply that gender is not a potential predictor of sedation effectiveness based on the RSSscores.

Group Group * RSS Ramsay Sedation Scale

Crosstab

Count

		Ramsay Sedation Scale		
		1	2	Total
Group	1 mg oral lorazepam	130	32	162
	2 mg oral lorazepam	87	35	122
Total		217	67	284

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.082[a]	1	.079		
Continuity Correction[b]	2.607	1	.106		
Likelihood Ratio	3.059	1	.080		
Fisher's Exact Test				.091	.054
Linear-by-Linear Association	3.072	1	.080		
N of Valid Cases	284				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 28.78.

b. Computed only for a 2x2 table

Hypothesis analysis for the relationship between lorazepam dosage of 1 mg and 2 mg and its effect on RSS was determined using a chi-square test. Structured cross tabulation showed that in the 1 mg group 130 participants had an RSS score of 1 and 32 had an RSS score of 2. From the 2 mg group, there was 87 participants with an RSS score of 1 and 35 with an RSS score of 2. When conducted the chi-square test for independent samples it has shown no significant relationship between the lorazepam dosage and RSS scores χ^2 (1, N = 284) = 3.082, p = 0.079. From these results, the authors found no evidence of a positive correlation between the amount of lorazepam taken and the degree of sedation required as indicated by RSS scores.

IV. Discussion

The results of the present study also give insight into the following understanding about the effect of Lorazepam in bipolar disorder manic symptoms in concentrate with acute phase with respect to dosage levels: Taken together, our findings indicate that the therapeutic efficacy of lorazepam is higher at the dosage of 2.0 mg as compared to 1.0 mg of the drug in attenuating physical signs of sedation and decreasing aggression score mildly. However, only the first dose had a modest effect in reducing agitation and aggression, which supports multi-modal interventions.

Comparison with Existing Literature

These findings are consistent with prior investigations showing the fast onset of sedation with lorazepam but also suggest that it is inadequate for manic signs when given alone. As similarly noted by Amore et al (2021), this paper establishes that, while lorazepam is very useful in managing physical movement disorder, it has very little to offer in managing anxiety most of which requires combination with antipsychotic or mood stabilizers. The higher dose of 2 mg yielded a slight incremental increase in the decrease of aggression rates compared to the 1 mg dose consistent with the hypothesis of Howard et al. (2014) that higher doses may reduce the number of rescue interventions. However, the higher frequency of emergency intervention in both groups suggests the ineffective of lorazepam in dealing with multiple symptoms in acute mania.

Clinical Implications

The results show that the use of lorazepam is beneficial in physically controlling the patients but does not encompass the full psychological disturbances associated with mania including psychological restlessness and aggression. From this limitation, it can be recommended that for the usage of lorazepam, one may be used together with antipsychotic or mood stabilizing. The choice between 1 mg and 2 mg dose should be made with caution, taking into consideration the need for sedation versus risk of side effects, as well as dependency and cognitive impairment risks, while the dose of 2 mg should be used in patients who need to be sedated rapidly while the lower doses may be preferable for the patients, who require long-term treatment.

Limitations

There are some limitations in this study that should be borne in mind regarding the various findings derived from the analysis of the results. First, there is an inherent weakness of observing patients in this study because it diminishes the possibility of causality since patients were allocated to dosage groups according to clinical conveniences rather than random assignment. Second, intention to treat analysis and not having a placebo group, and limited usage of EMI data to a primary outcome may also decrease generalisability of results. Additionally, we didn't look into the effects of lorazepam usage with regard to the long-term side effects of the drug for treatment of the manic episode.

Future Research Directions

Future studies should look into RCTs with larger sample sizes to look into causality regarding lorazepam dosage and symptom control. Furthermore, the evaluation of the effectiveness of combined treatment with lorazepam and individual antipsychotic or mood-stabilizing drugs could contribute to further understanding of better global management of manic symptoms. Additional useful information for the clinician can be obtained from studies that were aimed at exploring long-term consequences of lorazepam use on the crucial domains such as cognitive thorough and dependency potential.

V. Conclusion

This study emphasizes the impact of dosage of lorazepam on the degrees of sedation and irritability in bipolar attendees during acute mania. In the study, 2 mg provides better sedative activity and slightly improved outcome regarding the aspect of aggression, but no significant benefit for other symptoms as an independent regimen besides 1 mg. Thus, these results raise the question of the role of lorazepam in treatment of the psychological symptoms of mania, and recommends may be used more effectively as an adjunct treatment rather than as a sole treatment.

In clinically, this study validates with the previous recommendation that lorazepam is most appropriate in acute mania to gain rapid physical restrainment particularly in patients who require prompt behavioral containment. However, given the high rate of emergency interventions needed, adjunctive treatments with antipsychotic or mood-stabilizing agents are likely necessary for optimal symptom management. Future randomized controlled trials are recommended to explore the effectiveness of lorazepam in combination with other agents, as well as to assess long-term outcomes related to cognitive impact and dependency risks associated with prolonged benzodiazepine use.

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