The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–8, 2022

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2022.01.009

Pharmacology in Emergency Medicine

Efficacy of Combination Haloperidol, Lorazepam, and Diphenhydramine vs. Combination Haloperidol and Lorazepam in the Treatment of Acute Agitation: A Multicenter Retrospective Cohort Study

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□ **Abstract—Background: Antipsychotic and sedative combinations are commonly used for treating agitation in the emergency department despite limited evidence regarding their comparative safety and efficacy. Objectives: To compare the efficacy and safety of combination haloperidol, lorazepam, and diphenhydramine (B52) to combination haloperidol and lorazepam (52) in treating acute agitation. Methods: This multicenter, retrospective cohort study included adult patients ≥ 18 years of age who received either B52 or 52 at a Banner Health facility between August 2017 and September 2020. Patients were excluded if they had a pre-existing movement disorder or were withdrawing from alcohol. The primary outcome was administration of additional agitation medication(s) within 2 h of B52 or 52. Secondary outcomes included incidence of extrapyramidal symptoms, length of stay, and additional safety measures. Results: There was no difference in administration frequency of additional agitation medication(s) (B52: n = 28 [14%] vs. 52: n = 40 [20%]; $p = 0.11$). Patients who received 52 were more likely to require an antimuscarinic medication within 2 days (15 vs. 6 patients, $p = 0.04$). Of the patients who received an antimuscarinic medication, none had documented extrapyramidal symptoms. The 52 group had shorter length of stay (13.8 vs. 17 h; $p = 0.03$), lower incidence of hypotension (7 vs. 32 patients; $p < 0.001$), and oxygen desaturation (0 vs. 6 patients; $p = 0.01$), and fewer physical restraints (53 vs. 86 patients; $p = 0.001$) compared with the B52 group. Conclusions: Both the B52 and 52 combinations infrequently required repeat agitation medication; however, the B52 combination resulted in more oxygen desaturation, hypotension, physical restraint use, and longer length of stay. © 2022 Published by Elsevier Inc.**

□ **Keywords—agitation; emergency department; pharmacotherapy; antipsychotic; benzodiazepine; B52; 52; extrapyramidal symptoms; safety; efficacy**

Introduction

Antipsychotic and sedative combinations are commonly used for treating acute agitation in the emergency department (ED), though there is little evidence to support which combinations have superior efficacy or safety (1–3). Combination haloperidol, lorazepam, and diphenhydramine (B52) and combination haloperidol and lorazepam (52) are two examples of commonly used combination regimens (4,5). Proposed rationale for adding lorazepam to haloperidol for treating agitation is to provide additional sedation, because haloperidol is not as sedating as other antipsychotics (4). However, a Cochrane review of four clinical trials published in 2017 comparing the use of haloperidol alone vs. in combination with other

Received: 4 September 2021; Final submission received: 20 December 2021;
Accepted: 16 January 2022

Please cite this article as: T. Jeffers et al., Efficacy of Combination Haloperidol, Lorazepam, and Diphenhydramine vs. Combination Haloperidol and Lorazepam in the Treatment of Acute Agitation: A Multicenter Retrospective Cohort Study, Journal of Emergency Medicine, https://doi.org/10.1016/j.jemermed.2022.01.009

agents found that adding lorazepam did not significantly improve agitation, but did increase the incidence of sedation (6). Despite the author's conclusion that adding a benzodiazepine to haloperidol does not have strong evidence of benefit, this combination continues to be used for agitation.

Although the cited rationale for adding diphenhydramine to haloperidol is for extrapyramidal symptom (EPS) prevention, it is likely that the B52 combination is used due to provider familiarity and long history of use (7). Co-administration of diphenhydramine may, in theory, prevent the development of EPS, however, there is currently no strong evidence regarding how effective it is in doing so. One 2001 study by Vinson and Drotts found that the addition of diphenhydramine to prochlorperazine reduced the incidence of akathisia by 22% compared with placebo; however, there were numerous limitations to this study, such as small sample size and not using the gold-standard rating scale for assessing akathisia (8). Therefore, additional studies investigating the impact of co-administered diphenhydramine for agitation are needed.

Unfortunately, this is difficult to study because the incidence of EPS after haloperidol administration for acute agitation seems to be very low. Klein et al. observed that, out of 302 patients who received haloperidol monotherapy for acute agitation in the ED setting, only 2 patients (1%) developed dystonic reactions (9). Furthermore, reliably determining the true incidence of EPS is difficult given that studies assessing the treatment of agitation in the ED setting are often prone to bias, as demonstrated by Schneider and colleagues in 2021 (10). The low incidence of EPS does, however, support the need to question whether coadministration of diphenhydramine with haloperidol and lorazepam is even necessary when treating agitation. This is important considering that using multiple medications to treat agitation may increase the risk of drug–drug interactions and over-sedation (5).

Given the limited evidence available to support the addition of diphenhydramine to haloperidol and lorazepam, the purpose of this study was to compare the efficacy and safety of combination haloperidol, lorazepam, and diphenhydramine vs. combination haloperidol and lorazepam in treating acute agitation.

Materials and Methods

This study was an investigator-initiated, multicenter, retrospective noninferiority cohort study comparing intramuscular (i.m.) B52 and 52 in the treatment of acute agitation in the ED setting. The investigators were responsible for the trial design, data collection, and data analysis.

The trial was approved by the Banner Health institutional review board. The trial was conducted with waived informed consent from patients within the study, as this was a retrospective chart review. Primary data were pulled systemwide for all patients receiving i.m. haloperidol, lorazepam, or diphenhydramine from August 1, 2017 to September 1, 2020. These data were then randomized utilizing Microsoft Excel's (Microsoft Corporation, Redmond, WA) random number generator and the first 400 patient charts resulting from the randomization process were reviewed. If a patient met exclusion criteria, the next patient's chart was reviewed and included in the study, if appropriate. Investigators reviewed a total of 403 patient charts. Patients included in this study were treated in 21 EDs in six states, with sites ranging from large academic medical centers to smaller community hospitals. Chart review included evaluation of medication administration records, progress notes, admission and discharge notes, and laboratory results. A standardized data collection form was utilized by investigators to extract data. A standard workflow was also established by investigators prior to chart review to ensure that data were collected in the same manner. If discrepancies occurred, the investigators independently reviewed the chart then met to discuss findings and reach a consensus. A final data conference was held between the two reviewers who performed data collection to confirm observations and determine findings. If there were missing data, the patient was excluded from the study.

Eligibility Criteria

Patients were eligible for inclusion if they were $\geq$ 18 years of age and received either a combination of i.m. 52 (haloperidol 5 mg along with lorazepam 2 mg), or a combination of i.m. B52 (haloperidol 5 mg, lorazepam 2 mg, and diphenhydramine 50 mg) at a Banner Health ED during the study period. Only those receiving these medication combinations at the same time, defined within 15 min of one another, were included. Patients were excluded if they had a pre-existing movement disorder or were in active alcohol withdrawal. Pre-existing movement disorders were identified by reviewing the past medical history of the patient and any accompanying diagnosis codes in the patient's chart. Alcohol withdrawal was identified by reviewing the differential diagnosis and assessment portions of the ED providers' notes.

Outcomes

To compare the efficacy of B52 vs. 52, the primary endpoint was administration of additional agitation medications within a 2-h period after administration of the initial regimen. Additional medications for agitation were

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defined as repeat doses of haloperidol, benzodiazepines, and alternative first- or second-generation antipsychotic medication, including olanzapine, and ziprasidone. Additionally, order indications from the medication administration record were evaluated to confirm whether the medication was being used for agitation. The primary end point was chosen as an indirect indication that the original regimen was not effective in resolving acute agitation.

Secondary objectives were to assess the incidence of EPS after the administration of i.m. B52 or 52 along with additional safety measures: incidence of hypotension (blood pressure < 90/60 mm Hg), bradycardia (heart rate < 60 beats/min) hypoxia (oxygen saturation < 90%), need for respiratory support (requiring nasal cannula, nonrebreather mask, oropharyngeal airway, nasopharyngeal airway, or intubation), or documented use of physical restraints. Due to the retrospective design of this study, EPS was defined as the administration of an antimuscarinic medication (e.g., diphenhydramine, benztropine, trihexyphenidyl) up to 2 days after administration of the original i.m. B52 or 52. This 2-day window was chosen because most cases of acute dystonia occur within this time frame, whereas other types of EPS typically take longer to develop (8–10). For example, akathisia typically develops after a few days to weeks of initiating an antipsychotic (11). Additionally, we chose common pharmacologic treatment options for EPS caused by neuroleptic medications to serve as a surrogate endpoint to account for the potential lack of adverse effect documentation (12). Demographic data including age, weight, gender, and race were also collected, along with ED length of stay and suspected causes of agitation.

Statistical Analysis

It was estimated that 400 patients meeting eligibility criteria were required to ensure an adequate sample size to detect a 10% difference in the need for additional sedative use between groups with an alpha of 0.05 and beta of 0.2.

Categorical variables such as need for additional sedation, antimuscarinic use, and incidence of adverse drug events between groups were compared using Chi-squared or Fisher's exact testing, as appropriate. ED length of stay was analyzed using a Shapiro–Wilk test to determine parametric assumptions, followed by a Wilcoxon rank sum, given the data were not normally distributed. A p-value of < 0.05 was considered statistically significant.

Results

An original 8357 patient charts were identified for analysis during the study period. The data were randomized using a random number generator to avoid bias in practice style between institutions. A total of 403 patient charts were reviewed. Three patients were excluded, two of which were in active alcohol withdrawal and one who did not receive the combination of medications within the 15-min time frame (Figure 1). Of the remaining 400 patients included for analysis, 200 received the B52 combination and 200 received the 52 combination.

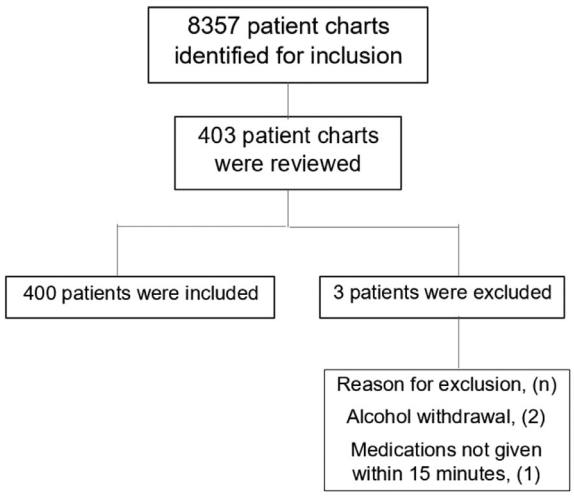

Figure 1. Patient Enrollement.

Baseline characteristics were similar between groups (Table 1). The mean age was 39 years, 60% were men, and 81.3% were white; 35.5% had psychiatric illness identified as a suspected cause for acute agitation, 26% had documented alcohol intoxication, and 30.8% tested positive for an illicit substance on urine drug screen. Patients with psychiatric illness as their suspected cause for acute agitation were more likely to receive the B52 combination compared with the 52 (42.5% vs. 28.5, $p = 0.003$). A similar number of patients in each group presented with positive blood alcohol levels and positive urine drug screen results, with cannabinoids and amphetamines being the most commonly detected substances.

Primary and secondary outcome data are reported in Table 2. There was no difference in the need for additional agitation medication(s) between the two groups (B52: n = 28 [14%] vs. 52: n = 40 [20%]; $p = 0.11$). Patients who received the 52 combination were more likely to require an additional antimuscarinic medication within 2 days compared with those who received the B52 combination (15 vs. 6 patients; $p = 0.04$). Indications documented for the use of additional antimuscarinic medications within this time period included insomnia, itching or allergy symptoms, and continuation of home medications (Table 3). Of the 21 patients who received an additional antimuscarinic medication during this period, none were documented to have experienced EPS.

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Table 1. Baseline Characteristics.

	52 (n = 200)	B52 (n = 200)	*p*-Value
Age, years			
Mean (SD)	39.1 (15.7)	39.5 (15)	0.819
Sex, n (%)			
Female	72 (36)	89 (44.5)	
Male	128 (64)	111 (55.5)	
Race, n (%)			
American Indian/Alaska Native	3 (1.5)	7 (3.5)	
Asian	2 (1)	0 (0)	
African American	17 (8.5)	22 (11)	
White	162 (81)	163 (81.5)	
Other	16 (8)	8 (4)	
Weight, kg			
Mean (SD)	80 (21.1)	79.8 (21.7)	0.968
Suspected cause of agitation, n (%)			
Alcohol intoxication	54 (27)	51 (25.5)	0 .733
Illicit substance	59 (29.5)	64 (32)	0.588
Psychiatric illness	57 (28.5)	85 (42.5)	0.003
Other	46 (23)	19 (9.5)	< 0.001
Blood alcohol level, n (%)			
Positive	52 (26)	49 (24.5)	0.646
Urine drug screen (UDS) results, n (%)			
Amphetamine	63 (31.5)	53 (26.5)	0.271
Opiate	9 (4.5)	13 (6.5)	0.38
Oxycodone	1 (0.5)	4 (2)	0.177
Benzodiazepine	11 (5.5)	26 (13)	0.01
Cannabinoid	71 (35.5)	62 (31)	0.339
Barbiturate	1 (0.5)	1 (0.5)	1
Methadone	1 (0.5)	0 (0)	0.317
Cocaine	9 (4.5)	6 (3)	0.43
Phencyclidine	0 (0)	1 (0.5)	0.317
None or UDS unavailable	58 (29)	66 (33)	0.387

Patients who received the 52 combination had a shorter median ED length of stay compared with those who received the B52 combination (13.8 vs. 17 h; $p = 0.03$). Additionally, restraints were used less often in patients who received the 52 combination (53 vs. 86 patients; $p = 0.001$). More patients who received the B52 combination developed hypotension (32 vs. 7 patients, $p < 0.001$) and required respiratory support via nasal cannula due to oxygen desaturation (6 vs. 0 patients; $p = 0.01$). No difference in the incidence of new-onset bradycardia was found between groups.

Discussion

To the best of our knowledge, this is the first study to compare the efficacy and safety of B52 and 52 combinations despite their common use in clinical practice. Our findings suggest that both regimens are similarly effective in managing acute agitation in the ED. However, the B52 combination was associated with an increased incidence of oxygen desaturation, hypotension, physical restraint use, and longer length of stay. Although patients who received the 52 combination were more likely to require additional antimuscarinic medication, documented indications suggest this was not for EPS resulting from haloperidol administration. These findings raise the question of whether diphenhydramine is an appropriate adjunct agent for the treatment of acute agitation in the ED setting.

Only 20% of patients who received the 52 combination and 14% of those who received the B52 combination required additional medication(s) for agitation. Results

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Table 2. Primary and Secondary End Points

	52	B52	*p*-Value
Administration of additional agitation medication within 2 h, n (%)	40 (20)	28 (14)	0.11
Anticholinergic use within 2 days, n (%)	15 (7.5)	6 (3%)	0.04
ED length of stay, hours			
Median (IQR)	13.8 (9, 21)	17 (10, 26.5)	0.03
Use of restraints, n (%)	53 (26.5)	86 (43)	0.001
Hypoxia, n (%)	14 (7)	10 (5)	0.4
Use of respiratory support			
Nasal canula	0 (0)	6 (3)	0.01
Non-rebreather mask	0 (0)	1 (0.5)	0.32
Intubation	0 (0)	3 (1.5)	0.08
Hypotension, n (%)	7 (3.5)	32 (16)	< 0.001
Bradycardia, n (%)	9 (4.5)	5 (2.5)	0.28

Hypoxia is defined as oxygen saturation < 90% or the required use of interventions including nasal cannula, non-rebreather mask, oropharyngeal airway/nasopharyngeal airway, or intubation; bradycardia is defined as heart rate < 60 beats/min; hypotension is defined as blood pressure < 90/60 mm Hg.
52 = combination haloperidol and lorazepam; B52 = combination haloperidol, lorazepam, and diphenhydramine; ED = emergency department; IQR = interquartile range.

Table 3. Documented indications for anticholinergic medication use

Indication	52 (n = 200)	B52 (n = 200)
Itching or allergy symptoms, n (%)	1 (0.5)	1(0.5)
Home benztropine, n (%)	2 (1)	4 (2)
Insomnia, n (%)	4 (2)	0 (0)
Unclear, n (%)	8 (4)	1 (0.5)

52 = combination haloperidol and lorazepam; B52 = combination haloperidol, lorazepam, and diphenhydramine.

from this retrospective study are similar to other studies evaluating combination therapy for acute agitation. For example, Hui et al. and Battaglia et al. similarly found that the 52 regimen was effective in reducing the need for additional neuroleptic medication compared with placebo (15,16). Our study further supports the efficacy of the 52 combination for treating agitation while demonstrating that additional sedative/anticholinergic medication will not necessarily improve efficacy or safety outcomes. This is important for providers to consider because rapid assembly and administration in the event of acute agitation is also crucial, and lorazepam and haloperidol can be combined in one syringe and given simultaneously (17).

None of the 21 patients who received an additional antimuscarinic medication were found to have any documentation of EPS. Indications recorded for the use of additional antimuscarinic medications included insomnia, itching or allergic symptoms, and continuation of home medications. Similar to findings by Klein et al., the incidence of EPS was very low (9). Although it is possible that in some cases patients may have received additional medication due to akathisia symptoms being interpreted as agitation, the literature suggests that anticholinergic administration is not as effective for treating akathisia compared with dystonia (14,18,19). Therefore, it would not be expected that the B52 combination would be superior for preventing akathisia compared with the 52 combination. Additionally, akathisia typically takes more than a couple days to develop (13). Future research with even larger sample sizes is needed to determine whether diphenhydramine helps prevent EPS.

Patients who received the B52 combination were more likely to require respiratory support with nasal cannula than those who received the 52 combination and were also more likely to develop hypotension. Given the study's retrospective design, it is difficult to ascertain whether new-onset respiratory depression or hypotension was the direct result of study medication(s). However, it is not unreasonable to consider this may have been the case because previous study findings have reported oxygen de-

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saturation to be the most common adverse event during the pharmacologic management of acute agitation (20). Additionally, hypotension is a well-known adverse effect of each component of the B52 combination (21). Therefore, patients who receive combinations of these agents or require multiple doses may be at higher risk of developing hypotension or oxygen desaturation.

Patients who received the B52 combination were also more likely to require physical restraint placement compared with those who received the 52 combination. Previous studies have demonstrated high incidence of restraint use with this medication combination (22). However, this finding may not be due to the specific medication combination, rather, this may be attributed to differences in provider practice styles or patient-specific characteristics not adequately captured through chart review. Additionally, patients with psychiatric illness identified as their suspected cause for acute agitation were more likely to receive the B52 combination compared with the 52 combination. This is likely due to routine practice differences between institutions or providers rather than a predetermined need for diphenhydramine. This may also explain why more patients in the B52 group required physical restraints (association between physical restraints and agitation secondary to psychiatric illness exacerbation rather than B52 administration). Additionally, it has previously been reported that the B52 combination is a preferred pharmacologic treatment option for acute agitation among some psychiatrists, psychiatry residents, and psychiatric nurses (23).

Lastly, patients who received the 52 combination had a significantly shorter length of stay compared with those who received the B52 combination. This may be due to the higher incidence of adverse effects leading to longer monitoring times for patients who received the B52 combination. Additionally, because patients with a documented psychiatric illness as the suspected cause of acute agitation were more like to receive the B52 combination, the increased length of stay may have been due to additional time needed to arrange transfer to another care facility.

Limitations

Limitations of this trial include its retrospective design and use of surrogate clinical endpoints. Documentation regarding medications administered by emergency medical services en route were unavailable, which may have impacted efficacy and safety outcomes. Urine drug screen results were utilized to identify illicit substance use as a potential cause of agitation, which are often prone to false positive or negative results and may not accurately reflect a patient's cause of acute agitation (24). The use of additional sedative and antimuscarinic agents were used as surrogate markers for the study outcomes of interest, due to absence of a standardized agitation scale in addition to challenges in identifying/documenting EPS in the emergency setting. In patients who received antimuscarinic medication, the indication was not always documented; therefore, we were not always able to determine whether the use may have been for EPS, sedation, or otherwise. To address this, the electronic medical record was reviewed for EPS documentation, although reporting may not have occurred or specified the type of EPS (e.g., dystonia vs. akathisia). The medication administration record was also reviewed for each participant in a 2-week period to ensure capturing readmissions due to EPS development, although, if the participant sought care at an outside facility, this could not be determined. Lastly, confounding factors such as differences in culture between practice sites and heterogeneity between patient populations should be taken into consideration.

Conclusions

Both the B52 and 52 combinations resulted in a relatively low frequency of subsequent medication administration for acute agitation in the ED setting. However, the 52 combination was associated with a shorter ED length of stay and fewer incidents of hypotension, oxygen desaturation, and physical restraint use compared with the B52 combination. Further prospective studies are needed to support the exclusion of diphenhydramine from the 52 combination.

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ARTICLE SUMMARY

1. Why is this topic important?

The B52 (combination haloperidol, lorazepam, and diphenhydramine) and 52 (combination haloperidol and lorazepam) are commonly utilized medication regimens to treat acute agitation. Despite a lack of data supporting the use of diphenhydramine, it is routinely added to medication regimens in this clinical context.

2. What does this study attempt to show?

This study aims to demonstrate the comparative efficacy and safety of B52 and 52 combinations in the treatment of acute agitation.

3. What are the key findings?

The B52 and 52 combinations are equally effective in the treatment of acute agitation in the emergency department (ED) setting. Utilizing 52 for acute agitation was associated with a shorter ED length of stay and lesser incidence of hypotension compared with the use of B52. Patients receiving repeat dosing of medications for agitation should be monitored closely, as they are more likely to experience adverse effects including hypotension and hypoxia.

4. How is patient care impacted?

To our knowledge, this is the first study evaluating the efficacy of B52 compared with 52 in the treatment of acute agitation. Given our results demonstrating equal efficacy between groups, the exclusion of diphenhydramine from combination therapy may be considered as it does not seem to confer additional sedative benefit.

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