Intramuscular B52

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As psychiatry residents, we necessarily encounter aggressive patients. Often, these patients respond to nonpharmacologic measures such as verbal de-escalation or to a less invasive pharmacologic measure such as an oral medication. Sometimes these measures fail, and a patient's aggression is so severe that it necessitates use of an intramuscular agent. Across several training sites, we are often taught to order intramuscular (IM) haloperidol with IM lorazepam with IM diphenhydramine. This recommendation is so common that it even has its own name: B52 or Benadryl (diphenhydramine), haloperidol 5 mg, and lorazepam 2 mg.

This article stems from the widespread use of this cocktail. On the basis of many psychiatrists' personal anecdotes, it seems to work well. But, does its teaching harm an approach to psychiatry that is evidence based?

Methods

We conducted a systematic literature review consistent with Preferred Reporting Items for Systematic Review Protocols guidelines. Inclusion criteria were adults with or without psychiatric conditions who were treated with an intramuscular agent for aggression. Only randomized controlled trials were included. We excluded children and adults with a primary neurologic disorder such as dementia. We excluded all studies that were not randomized controlled trials. PubMed was searched with the following MeSH terms: *aggression* AND *randomized controlled trial*. The initial search resulted in 1,481 articles. Duplicates were removed. A screening of the titles and abstracts with inclusion/exclusion criteria resulted in a total of 11 articles.[1–11] Four articles were excluded because they analyzed medications not available in the United States (zuclupenthixol, levomepromazine, and flunitrazepam), resulting in 7 final articles for this review.[1–4,7,8,11]

Results

We were unable to identify any randomized controlled trials that have utilized intramuscular B52 for aggression. Table 1 summarizes the findings from randomized controlled trials that have investigated intramuscular agents for aggression. Intramuscular haloperidol, administered with or without midazolam, promethazine, or lorazepam demonstrates efficacy in the reduction of aggression. Other identified intramuscular agents that also demonstrate efficacy include lorazepam alone, midazolam alone, and droperidol with or without midazolam. Further, this review identifies available data on the use of second-generation antipsychotics as intramuscular agents for aggression in adults, primarily olanzapine and ziprasidone.

Discussion

There are many practices in psychiatry that do not necessarily warrant need for the quality of evidence afforded by randomized controlled trials. Intramuscular B52 may well be one such practice. We do not provide evidence, if such evidence even exists, that the addition of intramuscular diphenhydramine exposes patients to undue harm.

But we do question the utility of adding diphenhydramine to an intramuscular cocktail of medications that are already supported by data from randomized controlled trials. Perhaps diphenhydramine is added to prophylactically treat for acute dystonia? If so, its explicit use for this purpose should be clear.

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Table 1. Randomized Controlled Trials That Investigated Intramuscular Agents for Aggression

Study	Study Design	Subjects Completing Intervention, n	Intervention (mg); Distribution of Subjects	Main Findings
Thomas et al, 1992[11]	Double-blind, randomized	68	IM haloperidol (5 mg); 21 IM droperidol (5 mg); 26 IV haloperidol (5 mg); 12 IV droperidol (5 mg); 9	IM droperidol resulted in statistically significant reductions in combativeness compared to IM haloperidol at 10 minutes ($P < .01$), at 15 minutes ($P < .05$), and at 30 minutes ($P < .05$). No statistically significant differences between IV haloperidol and IV droperidol in reducing combativeness. No statistically significant differences between medications in terms of alterations in heart rate and blood pressure within 60 minutes.
Bieniek et al, 1998[3]	Double-blind, randomized	20	IM lorazepam (2 mg); 11 IM lorazepam (2 mg) plus IM haloperidol (5 mg); 9	At 60 minutes, IM lorazepam plus IM haloperidol resulted in statistically significant improvements in OAS scores compared to IM lorazepam alone ($P < .05$). At 60 minutes, IM lorazepam plus IM haloperidol resulted in statistically significant improvements in visual analog scale scores compared to IM lorazepam alone ($P < .05$). No statistically significant differences in CGI-S scores between the interventions at 60 minutes. Statistically significant improvements in OAS scores over time with IM lorazepam plus IM haloperidol compared to IM lorazepam alone ($P < .05$). No statistically significant differences in visual analog scale scores or in CGI-S scores between the interventions after 60 minutes.
TREC Collaborative Group, 2003[1]	Single-blind, randomized	301	IM midazolam (15 mg); 151 IM haloperidol (5–10 mg) plus promethazine (25–50 mg); 150	IM midazolam had a statistically significant relative advantage compared to IM haloperidol plus promethazine in terms of achieving tranquilization or sedation by 20 minutes ($RR = 1.32$; 95% CI, 1.16–1.49) and by 40 minutes ($RR = 1.13$, 99% CI, 1.01–1.26). After 60 minutes, approximately 90% of subjects in both groups were tranquilized or asleep. No statistically significant differences in tranquilization or sedation outcomes between the interventions after 120 minutes, requirement of additional tranquilizing medications, need for physical restraints, episodes of aggression after 24 hours, requirement for doctor to see the patient, or discharge by 2 weeks.
Huf et al, 2007[7]	Randomized, open-label	316	IM haloperidol (5–10 mg); 156 IM haloperidol (5–10 mg) plus promethazine (25–50 mg); 160	By 20 minutes, more subjects treated with IM haloperidol plus promethazine were tranquil or asleep compared to those treated with IM haloperidol alone ($RR = 1.30$; 95% CI, 1.10–1.55). No statistically significant differences between treatments in terms of number of subjects tranquil or asleep after 20 minutes, another episode of aggression or agitation, additional visit from doctor during the first 24 hours, overall antipsychotic load in the first 24 hours, or continued presence in hospital after 2 weeks. Adverse effects in patients treated with IM haloperidol plus promethazine were lower compared to those treated with IM haloperidol alone ($RR = 0.07$; 95% CI, 0.01–0.75).
Isbister et al, 2010[8]	Double-blind, randomized	91	IM droperidol (10 mg); 33 IM midazolam (10 mg); 29 IM droperidol (5 mg) plus IM midazolam (5 mg); 29	No statistically significant differences in the duration of the episode between the interventions. Significantly more subjects treated with IM midazolam alone required additional sedation compared to those treated with IM droperidol alone. No significant differences in patient and staff injuries or calls to security for assistance. IM droperidol produced more consistent moderate sedation compared to IM midazolam or IM droperidol plus IM midazolam as assessed by AMSS scores. Two adverse effects reported in subjects treated with IM droperidol (6%, 95% CI, 1%–22%), 8 reported for subjects treated with IM midazolam (28%, 95% CI, 13%–23%), 2 reported for subjects treated with IM droperidol plus IM midazolam (7%, 95%, 1%–24%). No significant differences in QT prolongation among the different interventions.
Baldaçara et al, 2011[2]	Double-blind, randomized	150	IM haloperidol (5 mg); 30 IM haloperidol (5 mg) plus midazolam (15 mg); 30 IM haloperidol (5 mg) plus promethazine (50 mg); 30 IM olanzapine (10 mg); 30 IM ziprasidone (20 mg); 30	All interventions produced a calming effect within 1 hour of administration. Within 1 hour, IM olanzapine and IM haloperidol resulted in statistically significant reduced mean OASS scores ($P < .05$) and IM olanzapine resulted in statistically significant reduced OAS mean scores ($P < .05$). IM ziprasidone, IM olanzapine, and IM haloperidol were similarly effective in lowering mean OASS scores and were more effective compared to IM haloperidol plus promethazine and IM haloperidol plus IM midazolam ($P < .05$). IM ziprasidone and IM haloperidol plus promethazine were similarly effective in lowering mean OAS scores and were more effective compared to IM olanzapine, IM haloperidol alone, or IM haloperidol plus IM midazolam ($P < .05$). After 12 hours, mean OASS and OAS scores remained significantly higher in subjects receiving IM haloperidol plus IM midazolam compared to those receiving IM haloperidol, IM haloperidol plus promethazine, IM olanzapine, or IM ziprasidone ($P < .05$). No statistically significant differences in mean RSS scores among the different interventions.
Calver et al, 2015[4]	Double-blind, randomized	228	IM droperidol (10 mg); 118 IM haloperidol (10 mg); 110	Ninety-two percent of subjects treated with either medication were sedated within 120 minutes. No statistically significant differences in median time to sedation, use of additional sedation, or adverse effects between the interventions ($P > .05$). Eight staff injuries, most documented just prior to or during injection administration.

Abbreviations: AMSS = Altered Mental Status Scale, CGI-S = Clinical Global Impressions Severity, IM = intramuscular, IV = intravenous, OAS = Overt Aggressive Scale, OASS = Overt Agitation Severity Scale.

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