**Critical Review Form**

 **Therapy**

[Klein LR, Driver BE, Horton G, Scharber S, Martel ML, Cole JB. Rescue Sedation When Treating Acute Agitation in the Emergency Department With Intramuscular Antipsychotics. J Emerg Med. 2019 May;56(5):484-490.](http://pmid.us/30745194)

PGY-2

**Objectives: "to compare the use of intramuscular [IM] droperidol, olanzapine, and haloperidol for treatment of acute agitation in the ED." (p. 484)**

**Methods: This retrospective, observational study was conducted at Hennepin County Medical Center, a large urban tertiary care hospital in Minneapolis, MN, from 2012 to 2016. Adult patients (aged 18 or older) receiving IM droperidol, olanzapine, or haloperidol for an encounter with "Altered Mental Status" as the chief complaint were eligible for enrollment. Cases were identified from an electronic medical record query and all data was collected by blinded data abstractors using standardized collection methods.**

**The primary outcome of the study was need for rescue sedation within one hour of initial medication administration, defined as administration of an additional dose of an antipsychotic, a benzodiazepine, or ketamine. Secondary outcomes included need for rescue sedation at any time, serious adverse events (tachydysrhythmias, endotracheal intubation, or cardiac arrest), and extrapyramidal side effects (EPS). The occurrence of serious adverse events was determined solely by review of inpatient records for those admitted to the hospital. EPS cases were determined by assessing for administration of diphenhydramine (assuming it was not given concomitantly with the sedative).**

**There were 15,918 eligible encounters, with 4947 patients receiving droperidol (median dose 5 mg), 8825 receiving olanzapine (median dose 10 mg), and 2147 receiving haloperidol (median dose 5 mg). The median age was 37 years and around 12,000 were male. The cause of agitation was alcohol intoxication in 92% of patients.**

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| **Critical Review Form: Therapy** |
| Guide | Comments |
| **Are the results valid?** |
| **Did experimental and control groups being the study with a similar prognosis?** |
| Were patients randomized? | No. This was a retrospective chart review. Drug selection was made by the treating clinicians, putting the results at high risk of [selection bias](http://pmid.us/21491415). There was a period in late 2013 in which droperidol was on shortage and was not available. |
| Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be “randomized” to a particular group? | N/A. |
| Were patients analyzed in the groups to which they were randomized? | Yes. The study was not randomized and all patients were analyzed according to which initial sedative medication was administered. |
| Were patients in the treatment and control groups similar with respect to known prognostic factors? | Yes, for those factors for which information was provided. Patients in the three groups were similar with respect to age, gender, etiology of agitation (alcohol, drug intoxication, psychiatric, medical), alcohol concentration, need for hospital admission, and need for ICU admission. The authors did not provide any information regarding medical history, psychiatric history, and specific drugs ingested. |
| **Did experimental and control groups retain a similar prognosis after the study started?** |
| Were patients aware of group allocation? | In theory they could be, but were unlikely to be given their agitation. Either way, it is unlikely that [performance bias](http://bmg.cochrane.org/assessing-risk-bias-included-studies) on the part of patients would have influenced outcomes. |
| Were clinicians aware of group allocation? | Yes. It is possible that [performance bias](http://bmg.cochrane.org/assessing-risk-bias-included-studies) on the part of the patients would have affected outcomes. |
| Were outcome assessors aware of group allocation? | Yes. Although the authors specifically mention that blinded data abstractors collected all data (which would have included the outcomes), they were likely blinded to study protocol but would have been aware of which medication was initially administered. It seems unlikely that [observer bias](http://pmid.us/23359047) would have affected outcome interpretation. |
| Was follow-up complete? | Purportedly yes. All outcomes were assessed by medical record review and medical records were available for all patients. The use of surrogate markers for the reported outcomes and review of admission records alone for evaluation of serious adverse outcomes likely resulted in omission of key outcomes for some patients, though the extent of omission cannot be determined from the paper alone. |
| **What are the results?** |
| How large was the treatment effect? | * Rescue sedation within 1 hour was required in 11% (95% CI 10-12%) of droperidol cases, 11% (95% CI 10-12%) of olanzapine cases, and 18% (95% CI 17-20%) of haloperidol cases.
	+ The rescue medication was olanzapine in 9% of droperidol cases, 67% of olanzapine cases, and 18% of haloperidol cases.
	+ The rescue medication was droperidol in 88% of droperidol cases, 2% of olanzapine cases, and 0% of haloperidol cases.
	+ The rescue medication was haloperidol in 0.2% of droperidol cases, 28% of olanzapine cases, and 65% of haloperidol cases.
	+ Benzodiazepines and ketamine were used in a small number of cases.
* Rescue sedation during the entire ED stay was required in 17% (95% CI 16-18%) of droperidol cases, 19% (95% CI 18-20%) of olanzapine cases, and 26% (95% CI 24-28%) of haloperidol cases.
* Respiratory adverse events occurred in 0.2% of droperidol patients, 0.4% of olanzapine cases, and 0.2% of haloperidol patients. There were no cardiac events (cardiac arrest, torsades) in droperidol or haloperidol patients, and 1 episode (0.01%) in olanzapine patients.
* EPS or allergic reaction only occurred in 13 total cases, with no statistically significant difference in incidence between the groups.
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| How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?) | See above. For the primary outcome, the 95% CIs for the incidence of need for rescue sedation within one hour and need for rescue sedation at any time during the ED stay for the haloperidol group did not cross the intervals for the other 2 groups. Patients receiving haloperidol were therefore statistically significantly more likely than those receiving droperidol or olanzapine to need rescue sedation. |
| **How can I apply the results to patient care?** |
| Were the study patients similar to my patient? | No. While this study was conducted in the ED of a large, US, tertiary care center, it enrolled predominantly patients with alcohol intoxication (92%). While a large number of patients present to our ED with alcohol intoxication, I suspect that a significant proportion of our patients requiring sedation for acute agitation have primary psychiatric disorders or intoxication with a substance other than ethanol (i.e. cocaine, amphetamines, and PCP), raising the issue of [external validity](http://www.epmonthly.com/archives/features/understanding-external-validity/). |
| Were all clinically important outcomes considered? | No. While the primary outcome in this study is a reasonable one (need for rescue sedation), other important [patient-centered outcomes](http://omerad.msu.edu/ebm/Intro/Intro6.html) such as need for physical restraint (e.g. seclusion, locked limb restraints), time to sedation, and development of rhabdomyolysis. |
| Are the likely treatment benefits worth the potential harm and costs? | Uncertain. Rescue sedation was required with significantly higher frequency among patients receiving haloperidol than those receiving olanzapine or droperidol. While this suggests that haloperidol should not be used in favor of the alternatives for management of acute agitation in the ED, patients in this study did not appear to receive concomitant benzodiazepines (which are frequently administered in our ED). Additionally, the vast majority of patients in this study presented with alcohol intoxication and these results do not necessarily apply to those with primary psychiatric issues or intoxication with other agents. The authors also did not consider other important outcomes, such as need for physical restraint or the development of rhabdomyolysis. |

**Limitations:**

1. **This was a retrospective chart review rather than a randomized controlled trial with a high risk of** [**selection bias**](http://pmid.us/21491415)**.**
2. **The authors make several assumptions to allow for enrollment and interpretation of outcomes based on retrospective chart review. Specifically:**
	1. **Use of "Altered Mental Status" chief complaint as the sole means of identifying patients assumes that all cases of agitation are admitted to the ED with this complaint.**
	2. **Review of admitted cases alone to identify serious adverse events assumes that all patients with such events were admitted and that none were discharged or expired.**
	3. **The use of diphenhydramine administration alone as a surrogate for EPS events has not been validated, assumes all cases were treated in the ED, assumed no other medication (e.g. benztropine) was used to treat these cases, and assumes all cases in which diphenhydramine was administered were for EPS.**
3. **The cause of agitation was alcohol intoxication in 92% of patients (**[**external validity**](http://www.epmonthly.com/archives/features/understanding-external-validity/)**).**
4. **A low median dose of haloperidol and droperidol was used** [**compared to other studies**](pmid.us/25395689)**.**
5. **No mention of whether concomitant benzodiazepines were administered**

**Bottom Line:**

**This retrospective, observational study found that rescue sedation was needed more frequently among patients who received IM haloperidol for acute sedation when compared with those who received IM droperidol or olanzapine. Lack of randomization, inclusion of population almost entirely comprised of patients with alcohol intoxication, and the use of several non-validated assumptions to identify patients and outcomes put these results at very high risk of bias.**