Randomized Double-Blind Trial of Intramuscular Droperidol, Ziprasidone and Lorazepam for Acute Undifferentiated Agitation in the Emergency Department

Running Title: Droperidol, Ziprasidone or Lorazepam for Agitation

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Randomized Double-Blind Trial of Intramuscular Droperidol, Ziprasidone and Lorazepam for Acute Undifferentiated Agitation in the Emergency Department

Background: The optimal agent to treat acute agitation in the emergency department (ED) has not been determined. The objective of this study was to compare the effectiveness and safety of intramuscular droperidol, ziprasidone, and lorazepam for acute agitation in the emergency department.

Methods: This was a randomized, double-blind trial of ED patients with acute agitation requiring parenteral sedation. The study was conducted under exception from informed consent (21 CFR 50.24) from July 2004 to March 2005. Patients were randomized to receive droperidol 5mg, ziprasidone 10mg, ziprasidone 20mg, or lorazepam 2mg intramuscularly. We recorded Altered Mental Status Scale (AMSS) scores, nasal end-tidal carbon dioxide (ETCO2), and pulse oximetry (SpO2) at 0, 15, 30, 45, 60, 90, and 120 minutes, as well as QTc durations and dysrhythmias. Respiratory depression was defined as a change in ETCO2 consistent with respiratory depression or SpO2 <90%. The primary outcome was the proportion of patients adequately sedated (AMSS≤0) at 15 minutes.

Results: We enrolled 115 patients. Baseline AMSS scores were similar between groups. For the primary outcome, adequate sedation at 15 minutes, droperidol administration was effective in

16/25(64%) patients, compared to 7/28 (25%) for ziprasidone 10mg, 11/31 (35%) for ziprasidone 20mg, and 9/31 (29%) for lorazepam. Pairwise comparisons revealed that droperidol was more effective that the other medications, with 39% (95% CI 3-54$) more compared to ziprasidone 20mg, and 33# (95% CI 8-58%) more compared to lorzaepam. There was no significant difference between groups in need of additional rescue sedation. Numerically, respiratory depression was lower with droperidol (3/25; [12%]) compared to ziprasidone 10mg (10/28; [36%]), ziprasidone 20mg (12/31; [39%]), or lorazepam (15/31; [48%]). One patient receiving ziprasidone 20mg required intubation to manage an acute subdural hematoma. No patients had ventricular dysrhythmias. QTc durations were similar in all groups.

Conclusions: Droperidol was more effective than lorazepam or either dose of ziprasidone for the treatment of acute agitation in the emergency department and caused fewer episodes of respiratory depression.

INTRODUCTION:

Agitation is a common presentation in emergency medicine, ranging from a state of restlessness to overtly violent behavior. It may be a component of up to 2.6% of emergency department (ED) encounters,[1] and can result in injury to both patients and their caregivers.[2] Agitation in the ED is frequently undifferentiated and multifactorial, but commonly results from ethanol or drug intoxication, decompensated mental illness, or a subset of medical conditions.

If verbal de-escalation fails, physical restraints are commonly used;[3] however they are frequently ineffective as monotherapy, and restraint without sedation can lead to physical injury and metabolic disturbances.[4] The addition of parenteral medications to physical restraints results in a more rapid decline in agitation, facilitating a more efficient, safe removal of restraints.[5]

While expert guidelines recommend oral medications as a first-line treatment whenever possible,[6] many ED patients with agitation are either too violent or intoxicated for the safe administration of oral medications.[7] Parenteral sedation is required in nearly half of ED encounters for acute agitation.[8] Unless the patient has an existing intravenous (IV) line, intramuscular (IM) medications are preferred to IV medications because of obvious delays

related to obtaining IV access, IM administration is associated with fewer drug-related adverse events and a shorter duration of agitation compared to IV administration.[9,10]

First-line IM medications to treat agitation in the ED are typically antipsychotics or benzodiazepines,[6] though there is no consensus on a single preferred agent. Droperidol exhibits properties suggesting it may be the ideal agent for undifferentiated agitated patients, including rapid absorption via the IM route, typically within 5 minutes,[11] and a half-life of 2.3 hours[12], which may allow for timely reassessment of patients in the ED. Multiple randomized clinical trials suggest droperidol is a safe, rapid, effective treatment when compared to benzodiazepines and other antipsychotics,[13,14] though the majority of these studies examine the IV route only.[15–20] In 2013 the U.S. experienced a sustained shortage of droperidol,[21] necessitating the investigation of other agents.[22]

From 2004 - 2005 our institution performed a blinded, randomized, clinical trial (RCT) comparing IM droperidol, ziprasidone, and lorazepam for acute agitation in the ED; however these data were presented as an abstract only.[23] Because droperidol returned to the U.S. market in 2019,[24] we decided it was important to fully publish these data, which are presented in this manuscript. As only two previous RCTs studied IM droperidol in the ED,[25] these data have again become relevant as emergency physicians look to make evidence-based choices in this relatively understudied patient population. In addition, there are limited data supporting the use of ziprasidone for ED agitation, and to our knowledge, no RCT compares ziprasidone to lorazepam in ED patients.

The purpose of this study was to compare IM droperidol, ziprasidone, and lorazepam in patients with acute agitation in the ED, using the proportion of patients adequately sedated at 15 minutes as the primary outcome measure. Secondary outcomes included rates of rescue medication, respiratory depression, adverse medication effects, and ED length of stay (LOS).

METHODS:

Study Design and Setting:

We undertook a prospective, randomized, double-blind trial of adults with acute undifferentiated agitation requiring treatment in the ED of an urban, academic, safety net hospital with an annual ED census of approximately 100,000 patients. The study ED has a geographically separate, locked unit for agitated and intoxicated patients, described previously.[7]

If a family member or legal representative was available, we sought written informed consent before enrollment. Agitated adult patients, particularly when associated with alcohol or drug intoxication, are typically unable to provide informed consent.[26] Therefore, this trial also utilized Exception From Informed Consent (EFIC; 21 CFR 50.24). The local institutional review board (IRB) approved the study.

All elements of EFIC were completed, including submission of an investigational new drug application (IND) to the U.S. Food and Drug Administration (FDA) (**Figure 1**). This study protocol immediately followed a blinded, randomized trial under EFIC of intramuscular droperidol 5 mg vs. ziprasidone 20 mg vs. midazolam 5 mg.[13] The FDA and local IRB deemed the present study to be a modification of this existing protocol; therefore, an update was submitted rather than filing a completely new IND. Community consultation, performed before the first trial, consisted of protocol review with local detoxification facilities, acute psychiatric treatment facilities, and residents of residential housing facilities for homeless patients with ethanol use disorder (commonly referred to as "wet houses"). In addition, one investigator (MLM) and a member of the IRB attempted protocol presentation and discussion at a local Alcoholics Anonymous (AA) meeting; however, this presentation did not occur because of confidentiality concerns on the part of AA leaders. After consultation with the local IRB, community consultation from the first study was deemed adequate for the present study, which was then publicly disclosed with a press release as well as the placement of posters in the study ED (both in the main ED and the physically separate psychiatric ED), two local detoxification facilities, and two local homeless shelters. Details of the study were not posted to clinicaltrials.gov as data collection occurred before clinicaltrials.gov was publicly available and before the International Committee of Medical Journal Editors recommended that clinical trials be registered.

Selection of Participants

ED patients aged ≥18 years old were eligible for inclusion if the treating physician determined they needed parenteral sedation for acute agitation. Study enrollment occurred from July 2004 through March 2005. We excluded patients if they were a prisoner (or in police custody), previously enrolled in the trial, were known to be pregnant or breastfeeding, or

documented to have allergy to any of the study medications. Enrollment was dictated by patient and ED staff safety considerations; patients were not enrolled because of agitation scores alone.

Measurements and Key Outcome Measures:

A convenience sample of patients was randomized to receive droperidol 5 mg, ziprasidone 10 mg, ziprasidone 20 mg, or lorazepam 2 mg intramuscularly. We selected these doses based on information from the preceding RCT,[13] in which 20 mg of ziprasidone rendered patients more sedate for longer periods of time than either midazolam or droperidol. As there has been no dose-finding study on IM ziprasidone for ED patients with acute agitation, we added an additional lower-dose arm to determine if a smaller initial dose would be as effective, with fewer side effects and shorter duration of sedation. Similarly, lorazepam was substituted for midazolam because although midazolam was initially effective in the previous trial, the short duration of action resulted in more frequent rescue medication requirements than with either ziprasidone or droperidol. As such, the longer-acting lorazepam was substituted for midazolam.

Study medications were prepared in numbered, blinded syringes by the hospital pharmacy using block randomization. Each syringe contained 2ml of clear solution requiring refrigeration. We used the Altered Mental Status Scale (AMSS), a validated[14,27,28] ordinal agitation scale from -4 (coma) to 0 (normal) to +4 (most profoundly agitated) routinely used at our institution, to quantify the severity of agitation. (**Table 1**) Our institution is most familiar with AMSS, however to ensure our results would be generalizable the Behavioral Activity Rating Scale (BARS, **Supplementary Table 1**) was also recorded on each patient. The administration of additional medications, rescue sedation, was at the discretion of the treating physician if the patient's AMSS score was >0, 30 minutes after the administration of the study drug.

Trained research staff recorded AMSS and BARS scores, nasal end-tidal carbon dioxide (ETCO2), and pulse oximetry (SpO2) at the time of medication administration and 15, 30, 45, 60, 90, and 120 minutes after medication administration. Effective sedation was defined as an AMSS ≤0. A rhythm strip (Lead II) was obtained during the 120-minute period by research staff, if an electrocardiogram (ECG) was not performed for clinical indications, to calculate the corrected QT interval (QTc). Using the Bazett formula, a single investigator (MLM) calculated the QTc. When an ECG was available, the lead with the longest QT was used for this

calculation. The ECG and rhythm strip also served as an additional assessment for potential dysrhythmias.

Research staff also recorded the need for additional sedating medications, whether hypoxemia (SpO2 <90%, requiring oxygen supplementation), akathisia, dystonia, or an allergic reaction occurred, ED management including laboratory testing and radiologic imaging, length of stay in the ED, final discharge diagnosis, and disposition.

All patients received standard ED care, including standard nursing care and regular monitoring of sedation level, vital signs, and cardiac rhythms as indicated.

Outcome Measures:

The primary outcome was the proportion of patients adequately sedated at 15 minutes. Secondary outcomes included need for additional sedating medication, ED length of stay, and respiratory depression. We defined respiratory depression as hypoxemia (SpO2 <90%, requiring oxygen supplementation) or a decrease in ETCO2 >10 mmHg, an increase in ETCO2 >15 mm Hg, based on previous work on procedural sedation.[29]

Data Analysis:

With an assumed average baseline AMSS score of 3 (standard deviation of 1), we calculated that 25 patients per group (100 patients total) were required to detect a 1-point difference in the AMSS scores between groups with 90% probability, with an alpha value of 0.05. Research staff entered data into Microsoft Excel® (Microsoft Corp., Redmond, WA). Data were transferred to Stata® (Version 15, College Station, TX) and analyzed using descriptive statistics, chi-square, and the Kruskal-Wallis rank test (since the data were not normally distributed). We realize the outcome used for the sample size calculation is not the same as the primary outcome, but we present the trial as it was designed in 2004. To mitigate this important limitation, we present pairwise comparisons of absolute differences with associated 95% confidence intervals (CIs) for the proportion of patients adequately sedated (primary outcome) and the reduction in median AMSS from baseline to 15 minutes (outcome that the sample size is based). Lastly, to determine is AMSS and BARS recorded similar values for patients, we compared AMSS and BARS values with the Spearman rank-order correlation.

RESULTS:

We screened 149 patients for study eligibility. After excluding 34 ineligible patients (reasons for ineligibility are not available), 115 patients were enrolled, with a median age of 40 years (interquartile range {IQR} 29-46); 87 were male (76%). Supplementary Figure 1 outlines the CONSORT diagram of participant enrollment. Twenty-five patients received droperidol, 28 received ziprasidone 10 mg, 31 received ziprasidone 20 mg, and 31 received lorazepam. Baseline AMSS scores were similar among groups (**Table 2**).

With respect to the primary outcome of adequate sedation at 15 minutes, droperidol was most effective, with 64% of patients sedated at that time point, compared to 25%, 35%, and 29% for ziprasidone 10 mg, ziprasidone 20 mg, and lorazepam, respectively (**Table 3**). Pairwise comparisons between groups for the primary outcome are shown in **Table 4**. A parallel line plot showing AMSS scores at baseline and at 15 minutes for each patient is shown in **Figure 3**.

AMSS scores over time for each participant are shown in **Table 3** and **Figure 2**. Droperidol tended to have less deep sedation over time compared to the other medications. The need for additional sedating medication and ED length of stay are also shown in **Table 3**.

Regarding complications, respiratory depression was seen in 3 of 25 (12%) droperidol, 10 of 28 (36%) ziprasidone-10 mg, 12 of 31 (39%) ziprasidone-20 mg, and 15 of 31 (48%) lorazepam patients ($p = 0.04$). One patient who received ziprasidone 20 mg had persistent agitation and ultimately required intubation in the ED for management of an acute subdural hematoma (unrelated to study participation). One patient receiving droperidol experienced atrial flutter; no other dysrhythmias were observed. Two patients experienced dystonia, one who received droperidol and one who received ziprasidone 20 mg. QTc durations were similar in all groups ($p = 0.52$). No other significant complications were identified.

All AMSS and BARS scores from baseline through 120 minutes are displayed in a scatter-plot in **Figure 4**. The Spearman rank correlation coefficient for AMSS and BARS was 0.95 with a p-value < 0.001.

DISCUSSION:

We found IM droperidol to be superior to IM lorazepam or IM ziprasidone at two doses for the treatment of acute undifferentiated agitation in the ED. A greater proportion of patients were adequately sedated with droperidol compared to either lorazepam or ziprasidone at both 15

and 30 minutes after injection. In addition, droperidol appears to have a safety advantage as fewer patients receiving droperidol had evidence of respiratory depression. Droperidol also tended to have higher AMSS scores (less sedation) once adequate sedation was achieved, suggesting earlier re-evaluation may be more feasible with droperidol than lorazepam or ziprasidone (**Figure 3**). This has obvious benefits in patients requiring psychiatric evaluation and on total time patients spend in the ED who require medications for agitation management. We found no difference in effectiveness or safety between lorazepam and ziprasidone.

Our data align with subsequent publications in the intervening years demonstrating IM droperidol to be a safe, effective first-line agent for acute agitation in the ED.[14,18,19,30] Similar to the other two published RCTs examining IM droperidol, we found droperidol effectively treated agitation in a timeframe similar to midazolam, the most rapid acting IM benzodiazepine.[13,14] Unlike with midazolam however, we found rescue sedation was uncommon for droperidol. Only 20% of patients who received droperidol required rescue medication, confirming findings from a retrospective chart review of 4,947 patients at our institution sedated with droperidol that demonstrated a 17% rescue sedation rate.[31] A prospective study from Australia of 1,403 patients receiving droperidol for acute agitation found a slightly higher rescue rate of 31%.[30] In the 6 years droperidol was absent from the U.S. market, data emerged that olanzapine 10 mg may be the most effective remaining IM antipsychotic, with rescue rates ranging from 16% - 23%[21,31,32] and a time to adequate sedation also similar to midazolam.[22] In retrospective analysis of 10,338 patients receiving either droperidol or olanzapine for acute agitation in the ED, olanzapine was, however, associated with a longer ED stay, consistent with its longer half-life and duration of action.[12] Droperidol and olanzapine have been compared head-to-head using the IV route and were found to have similar effectiveness and safety profiles.[18,19] To the best of our knowledge though, no prospective study has directly compared IM droperidol and olanzapine.

Lorazepam, a commonly used medication for agitation in the ED,[6,16,33,34] resulted in slower time to adequate sedation, increased need for rescue sedation, and an increase in adverse events compared to droperidol. While lorazepam has a longer duration of action than midazolam, its slower time to peak effect renders it less effective for the treatment of acute agitation. Nobay et al, in an RCT published just as the present study was launched, found midazolam to result in faster time to sedation than lorazepam as well as a faster time to arousal facilitating a more rapid reassessment with similar safety profiles (**Table 5**).[35] While our data support droperidol as a

first-line therapy, there are agitated ED patients where a benzodiazepine remains the preferred first-line drug class.[6,36] Our data align with Nobay, et al suggesting lorazepam is a slower, less effective initial treatment than midazolam.

Regarding ziprasidone, we found no difference in the proportion of patients sedated at 15 minutes between the 10 mg and 20 mg doses, nor did we find a difference in adverse effects, rescue sedation, or total time in the ED. Patients receiving 10mg of ziprasidone had a mean time of "ready for ED discharge" 40 minutes sooner than ziprasidone 20mg, 56 minutes sooner than droperidol and 94 minutes sooner than lorazepam. But, ziprasidone has a number of features that may limit its utility in the ED. Ziprasidone requires a timely reconstitution process before injection, is associated with QTc prolongation,[37] and is classified as "hazardous to handle" for female caregivers of child-bearing age, necessitating the use of cumbersome personal protective equipment.[38] Nevertheless, if the treating physician determines ziprasidone is the ideal drug, our data suggest a lower starting dose of 10 mg is equally effective as 20 mg.

Respiratory depression was less common with droperidol than ziprasidone or lorazepam, however this was driven entirely by changes in ETCO2, as hypoxia did not differ between groups. Placing our safety data in the context of other studies on treatments for agitation is difficult. First, our study cohort consisted mostly of patients with ethanol intoxication, who are at a higher inherent risk for respiratory depression.[39] Second, when hypoxia is used as a safety outcome measure, different SpO2 cutoffs are used between studies, though most typically range from 90%[14] to 92%.[40] While this range is not particularly wide, patients may be counted as experiencing hypoxia in one study and not in another, making inter-study comparisons difficult. Third, not all studies use hypoxia or $ETCO_2$ changes as an outcome, as both may occur during the course of usual care but may not be clinically significant. In our subsequent work since these data were collected, we noted in this patient population that although hypoxia may be common, clinical interventions for hypoxia are rare,[21,40] calling into question the use of hypoxia as a safety outcome.

The use of changes in $ETCO_2$ as a safety outcome may be additionally problematic. While $ETCO_2$ has proven to increase the safety of procedural sedation in the ED[41] by alerting physicians early to the presence of respiratory depression so hypoxia may be avoided[42], it is unclear if a change in $ETCO_2$ is, by itself, an adverse event, as large studies on the utility of ETCO2 in agitated patients are lacking. A more patient-centered outcome, such as intubation, is

at first appealing, however intubation in agitated patients is also a problematic outcome measure as it may occur due to concomitant traumatic injuries, medical illnesses, or intoxication.[43] Furthermore the threshold for individual emergency physicians to intubate a patient may vary substantially.[44,45] Ultimately, imprecision in the measurement of respiratory depression is a common problem in this patient population. While all classes of drugs carry some degree of risk of respiratory depression in agitated patients with ethanol intoxication,[7,39,45,46] our data align with other studies that suggest additional synergistic respiratory depression occurs with ethanol and benzodiazepines[14,17] or ziprasidone[47] compared to first generation antipsychotics such as droperidol.

The difficulty in obtaining informed consent in agitated ED patients has likely contributed to the relative paucity of literature on this topic. As ED patients with acute agitation are frequently intoxicated and unable to provide informed consent, we utilized EFIC to conduct this RCT. Given the vulnerable nature of patients enrolled in EFIC trials, the requirements to use EFIC are substantial. The final rules, published in October 1996, state patients must have a life-threatening condition with unproven treatments in addition to not being able to provide consent in a timely manner.[48] EFIC trials must also be approved by the FDA, via submission of an IND.[49] In the years since the present study, however, the FDA's position on whether ED patients with acute agitation qualify for EFIC appears to have changed. Since the completion of the present study, FDA has twice denied IND submissions for follow-up studies[22,50] citing insufficient evidence these patients could not provide informed consent. In response, our institution studied several alternative mechanisms by which patients could be consented for agitation trials in the ED. As the majority of agitated patients in our ED are intoxicated, we attempted to administer a standardized consent tool to a random sample of 415 intoxicated ED patients and found that only 16 (3.9%) could provide consent; moreover only 8 of these 16 (1.9%) recalled the consent process at all once clinically sober, suggesting informed consent from the patient is not feasible. Theoretically a legally authorized representative (LAR) could provide surrogate consent, however in our previous RCT only 3 of 144 patients were successfully enrolled using an LAR, making it unlikely this could be used as the sole method of consent to complete a trial. Furthermore, in a prehospital agitation study of 146 patients, we found only 6% had a LAR available to even approach for consent.[50]

We also studied if it would be possible to obtain consent from patients at high-risk for future episodes of acute agitation during a visit where the patient was clinically sober and not agitated. We sought to enroll them ahead of time in an RCT that would compare two treatment regimens, should they have a future visit for acute agitation; this approach was suggested by the FDA. When this methodology was used, we screened 1,461 patients and were unable to enroll a single patient via "preconsent."[51] Even if enough resources were available to utilize LARs, pre-consent, and consent tools each to maximum capacity, the resulting study would likely contain highly biased data. As such, it is likely a waiver or exception from informed consent will be needed to obtain high quality data to inform practice and improve care for these patients. In July 2017, FDA issued IRB guidance for immediate implementation stating they did not intend to object to a local IRB approving a study that waives or alters informed consent provided the study met criteria for minimal risk, as outlined in 45 CFR 46.116(f)(3).[52] To our knowledge, since the issuance of the 1996 EFIC final rule, there have been three RCTs on ED (or prehospital) agitated patients, two conducted under waiver of informed consent (45 CFR 46.116) before[35,53] the 2017 FDA IRB guidance and one after.[54] The future of comparative effectiveness research for ED agitation in the U.S. is uncertain. Agitated ED patients, when interviewed about their experiences, strongly value a trusting relationship with their caregivers (and presumably their clinical investigators).[55] Use of EFIC for future studies would ensure that high quality data are obtained in a way that allows for patients to engage in the process, and to build trust between investigators and subjects via community consultation.

LIMITATIONS:

This study has several limitations, the first of which is the age of our data. At the completion of this study in 2005, all three original investigators were faced with professional obligations that interfered with prioritizing publication of these data. Eventually, these data were lost to time. As the use of droperidol had become a relevant topic again after its return to the US, and FDA's interpretation of EFIC regulations appears to have changed since this study was conducted, the investigators met and agreed publication of these data was both clinically useful given the resurgence in use of droperidol and meaningful regarding the future direction for research on acute agitation in the ED. Similarly, we were reminded of the importance of

disseminating the results of the trial; patients were subjected to the risks of the protocol with the understanding that the results would improve future care.

An important limitation of these data, because of their age, is that they were collected before the emergence of novel psychoactive substances, such as "K2," "Spice," and "Bath Salts."[56,57] Furthermore, the incidence of methamphetamine intoxication has increased since the time of the trial.[58] As such, our results may not apply to agitated patients intoxicated on these substances and may alter the medications needed to best treat the resulting agitation. While our data are old, they were obtained in the context of a blinded RCT. As RCTs for this condition are rare (**Table 5**), they are extremely valuable in the context of existing published data on this topic. Furthermore, for several reasons, including various drug shortages and a relative dearth of high-quality trials to advance understanding, the care of such patients has not changed substantially since these data were obtained.

Second, while we did observe a difference in respiratory complications, the relatively small size of this study did not allow for a meaningful assessment of cardiovascular complications, specifically QTc changes or episodes of dysrhythmias. Despite the relatively stern FDA black box warning,the incidence of torsades des pointes is uncommon with droperidol. We recently estimated it to occur in approximately 0.006% of ED patients receiving droperidol.[24] While ziprasidone is described to cause QTc prolongation, the incidence of associated torsades des pointes is less clear. Larger studies are needed on the use of ziprasidone in ED patients to better estimate cardiovascular and arrhythmogenic risk in this population.

Third, a single-site employing a dedicated unit[7] for the care of agitated, intoxicated or decompensated mental health patients is uncommon in emergency medicine. Although staffing and care models are similar in this area, it may impact the generalizability of our findings.

Last, the majority of our patients were agitated secondary to ethanol intoxication. As such, our data may not apply to patients with agitation secondary to acute decompensation of mental illness, drug intoxication, or underlying medical illness. Nevertheless, our data highlight an important feature of agitation in the emergency department - that it is frequently due, at least in part, to acute drug and ethanol intoxication.[1] This highlights the importance of conducting RCTs in the ED setting. Presumably rates of intoxication on psychiatric wards are lower than in the ED and as such, extrapolation of existing data from such units may not be applicable to ED patients.

CONCLUSIONS:

In this randomized, double-blind trial of patients with acute undifferentiated agitation in the emergency department, droperidol was more effective for sedation and was associated with fewer episodes of respiratory depression than lorazepam or either dose of ziprasidone. Larger studies are needed to confirm these findings, particularly safety outcomes.

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Table 1: The Altered Mental Status Scale

Score	Responsiveness	Speech	Facial Expression	Eyes
+4	Combative, very violent, or out of control	Loud outbursts	Agitated	Normal
+3	Very anxious, agitated, mild physical element of violence	Loud outbursts	Agitated	Normal
+2	Anxious, agitated	Loud outbursts	Normal	Normal
+1	Anxious, restless	Normal	Normal	Normal
0	Responds readily to name in normal tone	Normal	Normal	Clear, no ptosis
-1	Lethargic response to name	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (< half eye)
-2	Responds only if name is called loudly	Slurring or prominent slowing	Marked relaxation (slacked jaw)	Glazed and marked ptosis (> half eye)
-3	Responds only after mild prodding	Few recognizable words	Marked relaxation (slacked jaw)	Glazed and marked ptosis (> half eye)
-4	Does not respond to mild prodding or shaking	Few recognizable words	Marked relaxation (slacked jaw)	Glazed and marked ptosis (> half eye)

Table 2: Baseline Demographic Information and Clinical Assessments of Enrolled Patients.

Parameter	Droperidol (n = 25)	Ziprasidone-10mg (n = 28)	Ziprasidone-20mg (n = 31)	Lorazepam (n = 31)
Age, median (IQR) - y	39 (31-44)	40 (28-46)	41 (29-52)	39 (26-46)
Male gender - no. (%)	21 (84)	19 (68)	24 (77)	23 (74)
Baseline AMSS, median (IQR)	3 (3-4)	3 (2.5-4)	3 (3-4)	3 (3-4)
Baseline BARS, median (IQR)	7 (5-7)	6 (6-7)	7 (6-7)	7 (6-7)
Initial Clinical Assessment[a]				
Alcohol intoxication	19 (76)	19 (68)	25 (81)	25 (81)
Drug intoxication	1 (4)	2 (7)	4 (13)	3 (10)
Head injury	3 (12)	3 (11)	5 (16)	8 (27)
Primary psychiatric etiology	3 (12)	5 (18)	4 (13)	5 (17)
Final Diagnoses[a]				
Alcohol intoxication	20 (80)	22 (79)	25 (81)	29 (94)
Drug intoxication	0	4 (14)	3 (10)	1 (3)
Head injury	1 (4)	8 (29)	7 (23)	5 (16)
Psychiatric disease	3 (12)	4 (14)	5 (16)	5 (16)
Other	2 (8)	2 (7)	3 (10)	1 (3)
Disposition				
Discharged home	14 (56)	20 (71)	16 (52)	15 (48)
Alcohol detoxification center	2 (8)	3 (11)	5 (16)	4 (13)
Psychiatric ED	6 (24)	5 (18)	7 (23)	4 (13)

Hospital admission	0	0	0	4 (13)
Jail	1 (4)	0	2 (7)	2 (6)
Unknown	2 (8)	0	1 (3)	2 (6)

a. Patients could have more than 1 value for initial clinical assessment and final diagnosis, hence the total exceeds the number of patients in each group. IQR = Interquartile range.

Table 3: Outcome data.

Data	Droperidol (n = 25)	Ziprasidone-10mg (n = 28)	Ziprasidone-20mg (n = 31)	Lorazepam (n = 31)
AMSS score, median (IQR) - min				
Baseline	3 (3-4)	3 (2.5-4)	3 (3-4)	3 (3-4)
15	0 (-2 to 1)	1 (0.5 to 2)	2 (0-3)	2 (-1 to 3)
30	-2 (-3 to -1)	0 (-3 to 2)	-1 (-2 to 1)	0 (-1.5 to 2)
45	-2 (-3 to 0)	-1.5 (-4 to 0)	-1 (-3 to 0)	0 (-2 to 1)
60	-1 (-3 to 0)	-1.5 (-3.5 to 0)	-2 (-3 to 0)	-1 (-3 to 0)
90	-1 (-2 to 0)	-3 (-3 to -1)	-3 (-4 to 0)	-3 (-4 to -1)
120	-1 (-3 to 0)	-3 (-3 to 0)	-2 (-3 to -1)	-3 (-4 to -2)
Proportion adequately sedated, No. (%)				
15	16 (64)	7 (25)	11 (35)	9 (29)
30	22 (88)	16 (57)	22 (71)	15 (48)
45	21 (84)	22 (79)	24 (77)	18 (56)
60	22 (88)	24 (86)	25 (81)	23 (74)
90	20 (80)	24 (86)	25 (81)	25 (81)
120	20 (80)	20 (71)	23 (74)	26 (84)
Additional sedative medications, No. (%)				
Entire encounter	5 (20)	7 (25)	5 (16)	12 (39)
Before adequate sedation achieved	2 (8)	4 (14)	4 (13)	7 (23)
Time until additional sedative, median (IQR) - min	90 (32-149)	46 (30-60)	38 (34-40)	60 (49-78)

Time in the ED, median (IQR) - min				
Time from drug until ready for discharge	341 (235-400)	285 (236-383)	325 (257-412)	379 (199-524)
Total time in the ED	563 (477-615)	540 (438 - 720)	551 (455-640)	611 (439-782)
Respiratory outcomes - No. (%)				
Hypoxemia (SpO_2 < 90%)	2 (8)	2 (7)	6 (19)	7 (23)
Change in $ETCO_2$[a]	2 (8)	9 (32)	10 (32)	14 (45)
Respiratory depression[b]	3 (12)	10 (36)	12 (39)	15 (48)
Corrected QT, median (IQR, range) - ms[c]				
	413 (389-452, 327-510)	410 (385-432, 280-510)	428 (391-459, 286-485)	414 (380-429, 225-478)

This table shows study outcomes and complications. Comparisons between groups for AMSS scores and the proportion adequately sedated are shown in Table 3. Between group comparisons, analyzed using chi-square or Kruskal-Wallis, for additional sedative medications, time in the ED, respiratory outcomes, and corrected QTc revealed no statistically significant differences except for change in $ETCO_2$ ($p = 0.03$), and respiratory depression ($p = 0.04$). IQR = Interquartile range.

a. Change in $EtCO_2$ is defined as $ETCO_2$ >10 mm Hg from baseline or an increase in $EtCO_2$ > 15 mm Hg from baseline.
b. Respiratory depression is a composite variable for patients who had either change in $ETCO_2$ or hypoxemia.
c. 16 patients had missing QTc values: 2 in droperidol, 4 in ziprasidone 10 mg, 3 in ziprasidone 20 mg, and 7 in lorazepam.

Table 4: Pairwise comparison of treatment groups at 15 minutes.

Pair	Difference in proportion adequately sedated at 15 minutes (95% CI)	Difference in reduction in median AMSS from baseline to 15 minutes (95% CI)
Droperidol vs lorazepam	33 (8 to 58)	2 (0 to 3)
Droperidol vs ziprasidone 10 mg	39 (14 to 64)	1 (0 to 2)
Droperidol vs ziprasidone 20 mg	29 (3 to 54)	1 (0 to 2)
Ziprasidone 10 mg vs lorazepam	-6 (-29 to 17)	1 (-1 to 1)
Ziprasidone 10 mg vs ziprasidone 20 mg	-10 (-34 to 13)	0 (-1 to 1)
Ziprasidone 20 mg vs lorazepam	4 (-19 to 28)	0 (-1 to 0)

A positive value for difference in proportion adequately sedated indicates that the first listed drug resulted in a higher proportion of patients with adequate sedation at 15 minutes. A positive value for the difference in reduction in median AMSS indicates greater sedation at 15 minutes for the first listed drug.

Table 5: Existing Randomized Clinical Trials of Parenteral Medications for Acute Agitation in the Emergency Department or Prehospital Setting.

Authors	Year Published	No. of subjects	Country	Interventions*	Drug Route	Key features
Rosen, et al.[20]	1997	46	USA	droperidol (5mg) vs. placebo	IV	Droperidol was superior to placebo in controlling agitation in a prehospital population. Study conducted prior to publication of EFIC guidelines in 1996.
Battaglia, et al.[34]	1997	98**	USA	haloperidol (5mg) vs. lorazepam (2mg) vs. haloperidol + lorazepam (5+2mg)	IM	Combination results in faster sedation than either drug alone; no difference between haloperidol & lorazepam monotherapy. Study conducted prior to publication of EFIC guidelines in 1996.
Richards, et al.[15]	1997	146	USA	lorazepam (4mg) vs. droperidol (5mg)	IV	Sub-analysis of methamphetamine patients only from Richards, et al 1998, with similar findings.
Richards, et al.[16]	1998	202	USA	lorazepam (4mg) vs. droperidol (5mg)	IV	Similar times to sedation, rescue sedation needed more commonly with lorazepam. Study launched prior to publishing of EFIC guidelines in 1996.
TREC collaborative[59]	2003	301	Brazil	midazolam (15mg) vs haloperidol (10mg) + promethazine (50mg)	IM	Midazolam more effective at 20 minutes; similar effectiveness at 60 minutes. No difference in adverse events. Conducted in a psychiatric ED.
Nobay, et al.[35]	2004	111	USA	haloperidol (5mg) vs. midazolam (5mg) vs. lorazepam (2mg)	IM	Midazolam resulted in faster time to sedation and faster time to awakening compared to haloperidol or lorazepam. No difference was observed between haloperidol and lorazepam. WIC used for consent.
Martel, et al.[13]	2005	144	USA	droperidol (5mg) vs.	IM	Droperidol and midazolam had similar times

				ziprasidone (20mg) vs. midazolam (5mg)		to adequate sedation; both were faster than ziprasidone. Rescue sedation was needed more often with midazolam. Conducted under EFIC.
Knott, et al.[17]	2006	153	Australia	droperidol (5mg) vs. midazolam (5mg)	IV	No difference in time to sedation between groups. All patients needing active airway management received midazolam.
Isbister, et al.[14]	2010	91	Australia	droperidol (10mg) vs. midazolam (10mg) vs. droperidol + midazolam (5 + 5mg)	IM	Similar times to adequate sedation between droperidol and midazolam; more adverse events with midazolam.
Chan, et al.[18]	2013	336**	Australia	placebo vs. olanzapine (5mg) vs. droperidol (5mg) all as adjuncts to midazolam (2.5 - 5mg)	IV	Droperidol and olanzapine, as adjuncts to titrated midazolam, similarly decrease time to adequate sedation versus midazolam alone. Droperidol and olanzapine required less rescue sedation than midazolam alone; adverse events were similar between all three groups.
Asadollahi, et al.[60]	2015	80	Iran	haloperidol (5mg IM) vs. valproic acid (20 mg/kg IV)	Both	Haloperidol was faster, but both drugs effective at 30 minutes. Fewer side effects with valproic acid.
Jacobs & Isenberg[53]	2015	10	USA	haloperidol (5mg) vs. midazolam (5mg)	IM	Prehospital setting only. No blinding. Conducted under WIC. Midazolam resulted in more rapid sedation than haloperidol.
Taylor, et al.[19]	2017	349**	Australia	droperidol (10mg) vs. olanzapine (10mg) vs. droperidol + midazolam (5 + 5mg)	IV	Midazolam - droperidol combination resulted in faster time to adequate sedation than either olanzapine or droperidol monotherapy. Adverse events were similar between all three groups.
Yap, et al[61]	2017	92**	Australia	droperidol (10mg) vs. olanzapine (10mg) vs. droperidol +	IV	Sub-analysis of methamphetamine patients only from Taylor, et al, 2017, with similar findings.

				midazolam (5 + 5mg)		
Heydari, et al.[28]	2018	90	Iran	ketamine (4mg/kg) vs. haloperidol (5mg)	IM	Ketamine with faster time to sedation, no difference in intubations.
Lin, et al.[54]	2020	93	USA	ketamine (4mg/kg IM or 1mg/kg IV) vs. haloperidol (10mg) + lorazepam (2mg)	Both	Majority received IM meds. Ketamine with faster time to sedation; no difference in intubation. One cardiac death with haloperidol + lorazepam. Conducted under WIC. No blinding.

IM = intramuscular

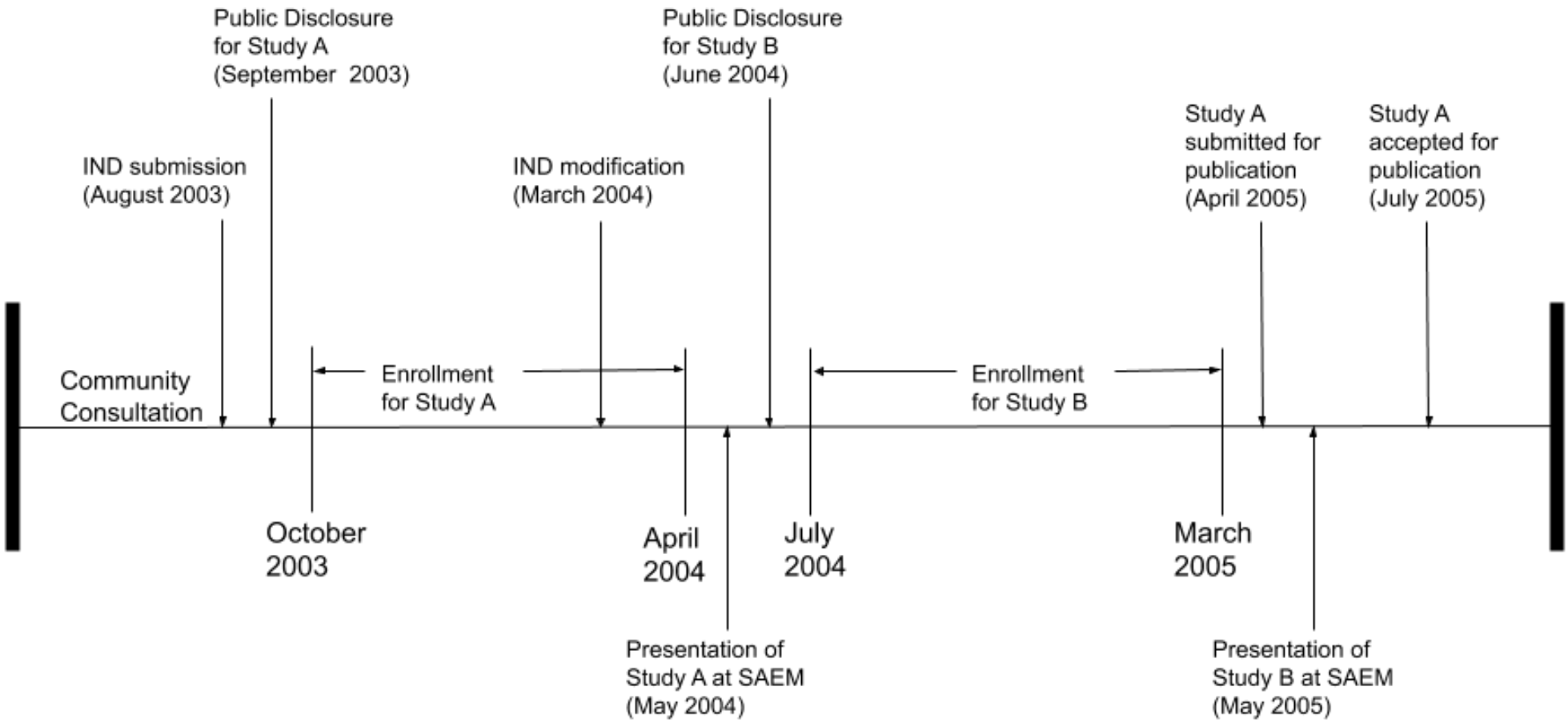
IV = intravenous

WIC = Waiver of Informed Consent (45 CFR 46.116(f)(3))

EFIC = Exception From Informed Consent (21 CFR 50.24)

**if tiered dosing was utilized, the largest dose is displayed*

***denotes multi-centered trials*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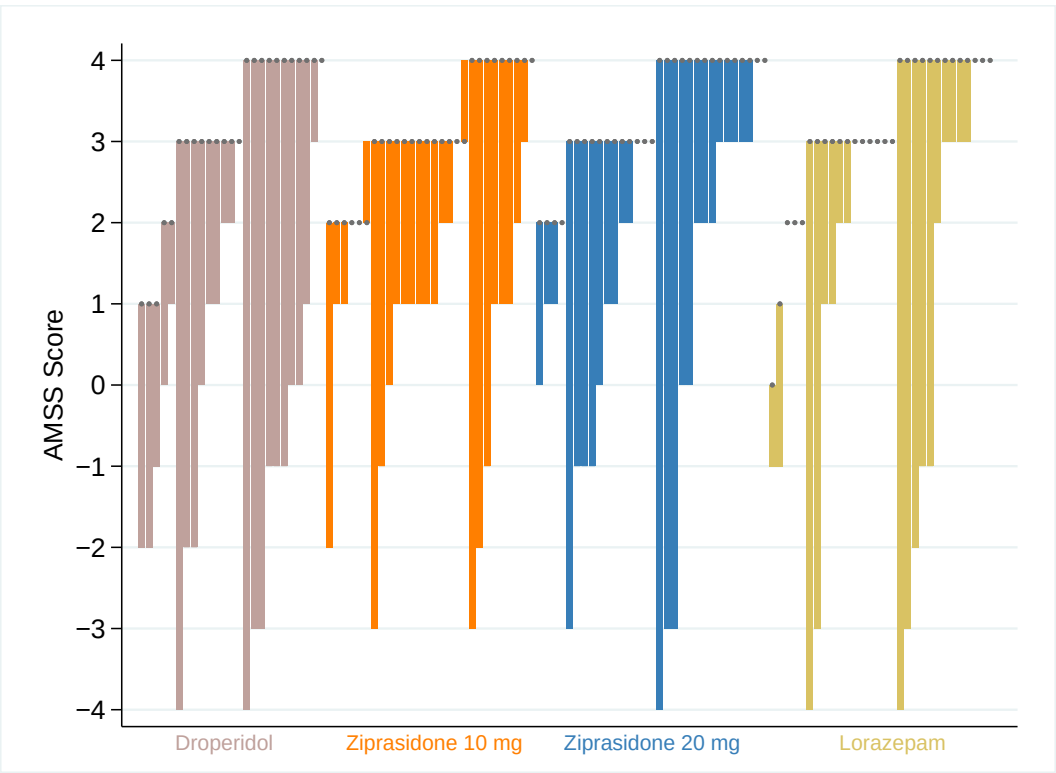
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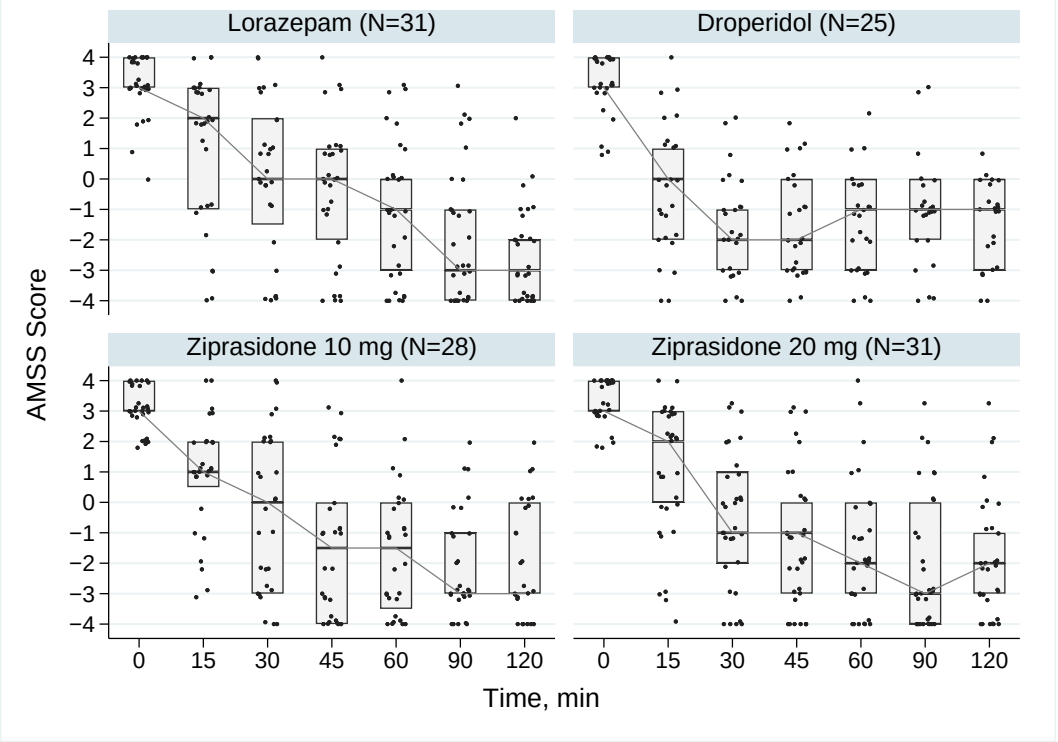
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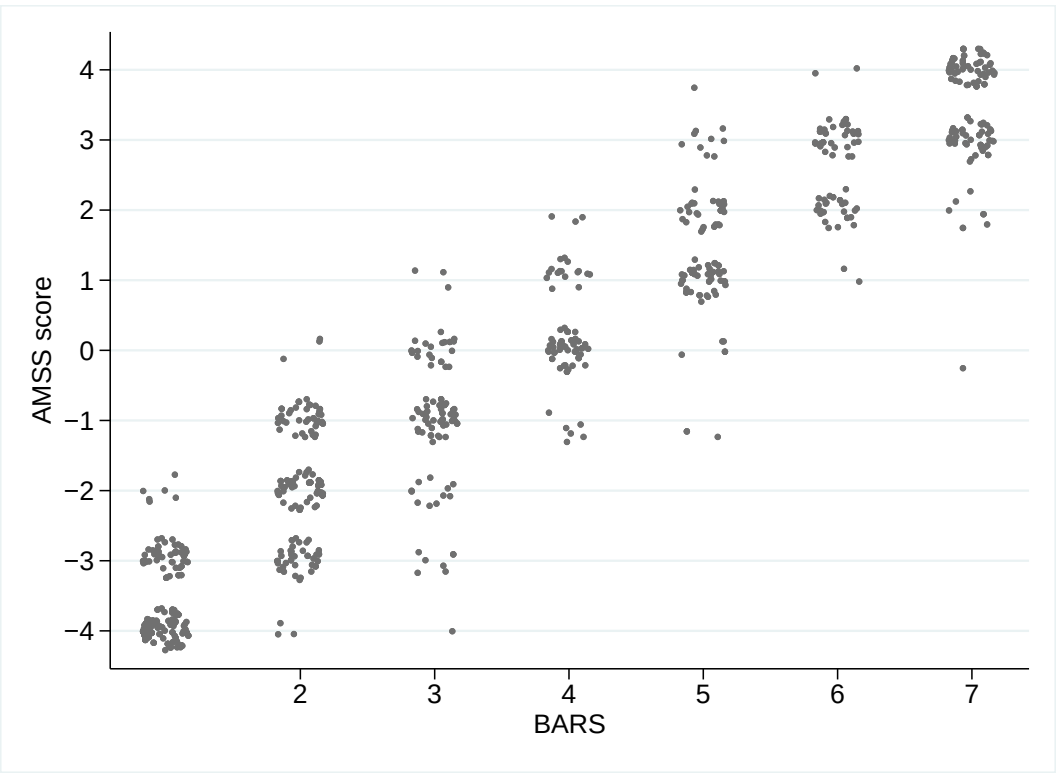
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