Midazolam with Haloperidol versus Lorazepam with Haloperidol for Agitation: Effect on Emergency Department Lengths of Stay

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To the Editor:

Emergency department (ED) encounters for acute agitation are common. Although nonpharmacologic interventions such as verbal de-escalation and patient engagement are first-line interventions for acute agitation, parenteral medications are often required to ensure safety and facilitate patient care. There is no consensus recommendation on pharmacologic agents for acute agitation, however emergency clinicians have historically utilized an anti-psychotic, benzodiazepine, and/or antihistamine – as monotherapy or in some combination.[1,2]

Pharmacological agents for agitation have been shown to increase ED length of stay (LOS).[3] While lorazepam has traditionally been combined with haloperidol for acute agitation,[4] midazolam has been shown to have faster onset and shorter time to awakening than lorazepam.[5] Although several high quality studies have compared the clinical efficacy of various pharmacologic agents for acute agitation,[6-10] to our knowledge no study has directly compared the combination of midazolam with haloperidol versus lorazepam with haloperidol on ED LOS.

In January 2019, our urban academic ED (>91,000 annual visits) instituted a departmental guideline change recommending co-administration of midazolam/haloperidol for severe agitation unresponsive to nonpharmacological interventions, replacing the previous recommendation of lorazepam/haloperidol due to midazolam's faster onset and shorter time to awakening. The guideline was created by a workgroup of ED physicians and pharmacists intended to improve the management of acutely agitated patients; the guideline was formally announced via email and posted throughout the ED physical space but was not enforced or incentivized in any specific manner. Nevertheless, the guideline change resulted in a dramatic shift in medication use (Figure) and created a unique natural experiment to retrospectively evaluate the differential impact of midazolam versus lorazepam, when given in combination with haloperidol, on ED

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LOS. Given midazolam's shorter duration of action compared to lorazepam, we hypothesized that ED LOS would be shorter among visits receiving midazolam/haloperidol.

We obtained Institutional Review Board approval to conduct a retrospective study of ED visits occurring from 3/1/18 to 10/31/19. Although there were no major changes to ED operations during the study period, there were minor changes to physical space and staffing (Supplemental eTable 1) typical of any ED operating over two years. We used structured query language to extract ED visit information from our institution's electronic data warehouse among all adult ED visits parenterally administered haloperidol, olanzapine, lorazepam, or midazolam (n=6,165); these medications were selected for initial query because they may be given for acute agitation. However, due to potential competing clinical indications for these medications when given as monotherapy (e.g., anxiolysis, alcohol withdrawal, intractable migraine), we then selected only those ED visits in which the combination of 5mg midazolam/5mg haloperidol or 2mg lorazepam /5mg haloperidol was co-administered (n=1,173; 618 receiving midazolam/haloperidol, 555 receiving lorazepam/haloperidol),

ED visit information included demographic (age, sex) and clinical characteristics (repeat medication dosing, blood ethanol level , computed tomography imaging, psychiatric consultation, and ED disposition. Psychiatric consultation at our institution occurs directly in the ED after medical clearance. We also obtained the median ED LOS for the entire department for the day on which each ED visit occurred; this allowed us to account for possible secular trends in ED throughput not attributable to the guideline change. Our primary outcome of interest was ED LOS, defined as minutes elapsed between the ED arrival and departure timestamps in the electronic medical record. We also evaluated the following serious adverse events: intensive care unit (ICU) admission, intubation, cardiopulmonary resuscitation, cardioversion, or death.

Our primary analytic approach was a multivariable zero-truncated negative binomial regression with ED LOS as the dependent variable and medication group as the primary independent variable. We selected this regression model because ED LOS are count data, rightward skewed, and by definition cannot be zero. The regression model included all available covariates, except for ethanol level because it was highly zero inflated (value of zero in 47.0% of sample; not obtained in 15.0% of sample); we also included month in the study period as a fixed effect. We then computed the difference in ED LOS between visits receiving midazolam/haloperidol and lorazepam/haloperidol if all covariates were held at their mean

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values (i.e., the marginal effect of midazolam versus lorazepam) using the *margins* and *atmeans* commands in STATA v16.1 (StataCorp, College Station, TX) and 95% confidence intervals (95% CI).

We additionally calculated differences in median ED LOS between ED visits receiving midazolam/haloperidol and lorazepam/haloperidol for the key subgroups of ED disposition, psychiatry consult, and repeat medication dosing using Stata's *cendif* function. We selected these subgroups a priori based on a clinical expectation of highly skewed longer ED LOS in ED visits awaiting an inpatient bed, undergoing psychiatric consultation, and receiving repeat doses of medication.

Medication utilization trends during the study period are displayed in the Figure. There was a clear shift towards midazolam/haloperidol and away from lorazepam/haloperidol following the guideline change in January 2019 (Day 300 block). The total number of daily ED visits increased over the study period, as did the mean department-wide daily median ED LOS (450 vs 486 minutes for lorazepam/haloperidol and midazolam/haloperidol, respectively; p<0.001), reflecting a secular trend biased towards the null hypothesis (i.e., favoring a longer ED LOS in the midazolam/haloperidol group).

Most ED visits were among patients aged 18-39 years (55.2% and 54.6% for midazolam/haloperidol and lorazepam/haloperidol, respectively, p=0.09). Fewer patients in the midazolam/haloperidol group were female (26.2% vs. 35.5%, p=0.001), had ethanol levels obtained (82.4% vs 87.9%, p=0.008), had a psychiatry consult obtained (49.4% vs 56.8%, p=0.01), and required a repeat medication dose (22.0% vs 27.4%, p=0.03). No other demographic or clinical characteristics differed between the groups (Supplemental eTable 2).

The unadjusted median ED LOS in the midazolam/haloperidol group was 764 minutes (interquartile range [IQR] 557-1240) compared to 908 minutes (IQR 655-1486) in the lorazepam/haloperidol group (difference -128 minutes, 95% CI: -76 to -180). In the adjusted zero-truncated negative binomial regression model, the ED LOS for midazolam/haloperidol was 1027 minutes (95% CI 977-1077) compared to 1169 minutes (95% CI: 1108-1230) for lorazepam/haloperidol (marginal effect of midazolam/haloperidol: -142 minutes, 95% CI -51 to -232); full model output available in Supplemental eTable 3).

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Subgroup analyses re-demonstrated shorter ED LOS for midazolam/haloperidol in all comparisons, however only the subgroup classifications for discharged visits, no psychiatry consult obtained, and no repeat medication given were statistically significant (Supplemental eFigure and eTable 4). Point estimates for admitted visits, psychiatry consult obtained, and repeat medication given favored a shorter ED LOS for midazolam/haloperidol but were not statistically significant.

Four patients (0.65%) in the midazolam/haloperidol group were intubated (primary diagnoses of basilar skull fracture, rectal laceration, aspiration pneumonitis, and heroin overdose) compared with two patients (0.36%) in the lorazepam/haloperidol group (primary diagnoses of sepsis and epilepsy). Four patients (0.65%) in the midazolam/haloperidol group were admitted to the ICU compared with eight patients (1.44%) in the lorazepam/haloperidol group. No ED visits required cardioversion or cardiopulmonary resuscitation in either group; there were also no deaths.

In summary, we conducted a quasi-experimental study comparing ED LOS among visits receiving midazolam/haloperidol versus lorazepam/haloperidol for agitation. ED LOS were shorter for midazolam/haloperidol in both unadjusted and adjusted analyses, and among a priori defined subgroups, despite a secular trend of longer departmental-wide ED LOS among ED visits receiving midazolam/haloperidol.

We found that the marginal effect of midazolam versus lorazepam, when given in combination with haloperidol, was a 142-minute shorter ED LOS. This suggests that the shorter duration of action for midazolam monotherapy, as compared to lorazepam,[5] also extends to their use in combination with haloperidol – although the marginal time benefit cannot be directly extrapolated from the pharmacokinetics of single agents. Notably, we did not collect data on clinical assessments of sedation. These study findings should therefore not be used to infer the clinical effectiveness of midazolam/haloperidol or lorazepam/haloperidol in achieving sedation.

Serious adverse events were similarly rare in ED visits receiving either midazolam/haloperidol and lorazepam/haloperidol. Six ED visits required endotracheal intubation, although the primary diagnoses for these visits suggest additional clinical complexity that may have contributed to the need for intubation. Nevertheless, these data are an apt reminder that both benzodiazepines and butyrophenones have the potential for oversedation and should be used only when verbal de-escalation fails and should be accompanied by close clinical observation.[11]

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This study is limited by its retrospective design and reliance on electronic medical record data. However, our use of structured query language to extract the variables of interest, including exact timestamps for medication administration and ED arrival and departure, limits bias in outcome ascertainment. Additionally, some ED visit characteristics associated with longer evaluation time were more frequent in the midazolam/haloperidol group, such as psychiatric consultation. Although our adjusted regression model included these covariates, and we also present subgroup analyses demonstrating consistent effects, it is possible that unmeasured confounders exist. Finally, while this study's focus on a single academic ED limits the generalizability, the single-center design allowed us to leverage the quasi-experimental condition created by a formal guideline change from lorazepam to midazolam. Although additional studies in more diverse settings are required to confirm these findings, these data indicate that the use of midazolam/haloperidol for acute agitation is associated with shorter ED LOS compared to lorazepam/haloperidol.

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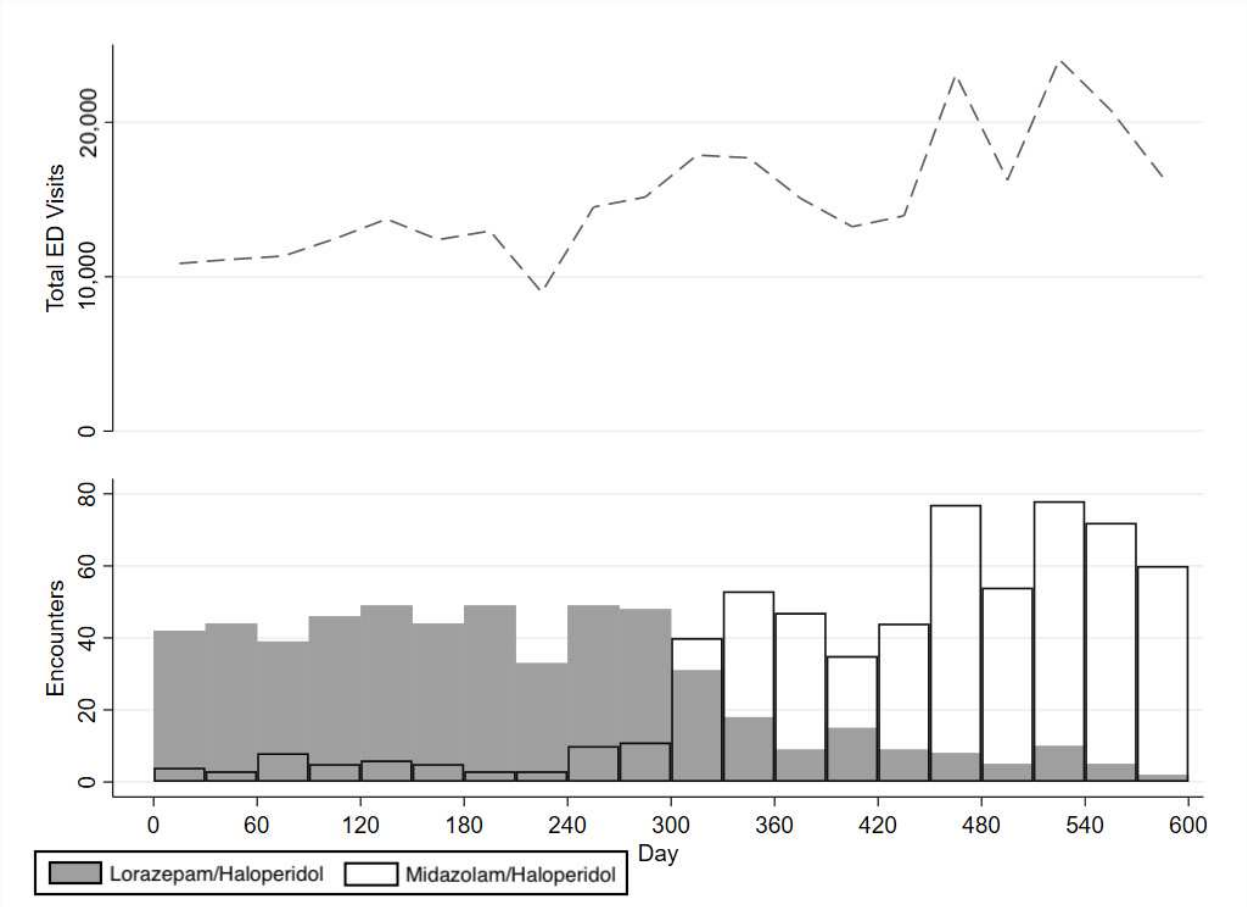
Figure 1: Change in Benzodiazepine Use Over Time By 30 Day Period



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