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Journal

Annals of Emergency Medicine, 80(4)

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Publication Date

2022-10-01

DOI

10.1016/j.annemergmed.2022.05.024

Peer reviewed

Real-World Midazolam Use and Outcomes With Out-of-Hospital Treatment of Status Epilepticus in the United States

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Abstract

Study objective: Guidelines recommend 10-mg intramuscular midazolam as the first-line treatment option for status epilepticus. However, in real-world practice, it is frequently administered intranasally or intravenously and is dosed lower. Therefore, we used conventional

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and instrumental variable approaches to examine the effectiveness of midazolam in a national out-of-hospital cohort.

Methods: This retrospective cohort study of adults with status epilepticus used the ESO Data Collaborative research dataset (January 1, 2019, to December 31, 2019). The exposures were the route and dose of midazolam. We performed hierarchical logistic regression and 2-stage least squares regression using agency treatment patterns as an instrument to examine our outcomes, rescue therapy, and ventilatory support.

Results: There were 7,634 out-of-hospital encounters from 657 EMS agencies. Midazolam was administered intranasally in 20%, intravenously in 46%, and intramuscularly in 35% of the encounters. Compared with intramuscular administration, intranasal midazolam increased (risk difference [RD], 6.5%; 95% confidence interval [CI], 2.4% to 10.5%) and intravenous midazolam decreased (RD, −11.1%; 95% CI, −14.7% to −7.5%) the risk of rescue therapy. The differences in ventilatory support were not statistically significant (intranasal RD, −1.5%; 95% CI, −3.2% to 0.3%; intravenous RD, −0.3%; 95% CI, −1.9% to 1.2%). Higher doses were associated with a lower risk of rescue therapy (RD, −2.6%; 95% CI, −3.3% to −1.9%) and increased ventilatory support (RD, 0.4%; 95% CI, 0.1% to 0.7%). The instrumental variable analysis yielded similar results, except that dose was not associated with ventilatory support.

Conclusion: The route and dose of midazolam affect clinical outcomes. Compared with intramuscular administration, intranasal administration may be less effective and intravenous administration more effective in terminating status epilepticus, although the differences between these and previous results may reflect the nature of real-world data as opposed to randomized data.

INTRODUCTION

Generalized, convulsive status epilepticus is a neurologic emergency that relies on out-of-hospital EMS providers to administer first-line treatment when the status epileticus develops outside the hospital, making our out-of-hospital system critical for ensuring that patients are appropriately treated. Guidelines recommend midazolam as a single 10-mg intramuscular injection by out-of-hospital or hospital providers because its administration is simple and fast and there is high-quality (level A) evidence demonstrating its efficacy; however, intranasal midazolam is an alternative with level B evidence, and intravenous midazolam has not been mentioned.[1-4] However, outside of research settings, in the "real-world," midazolam is frequently administered intranasally or intravenously and delivered at doses lower than those recommended.[5-7]

Evidence from single-EMS-agency cohort studies has suggested that both lower midazolam dosing and intranasal administration lead to less effective seizure termination.[5,6] However, these studies are limited by the scope of their study population and because the providers may have altered the dose of midazolam administered based on the perceived severity of illness, leading to potential confounding, which previous cohort studies have been unable to address.[8]

In the absence of head-to-head randomized clinical trials, observational data that can account for confounding and reflect a broad population of patients with generalized, convulsive status epilepticus have the greatest potential to provide valid estimates of the

effectiveness of different combinations of midazolam dose and route. The objective of this cohort study was to leverage a large national research database of EMS electronic health records to examine the association among out-of-hospital midazolam administration, seizure termination, and respiratory failure before arrival at the hospital using conventional regression and instrumental variable approaches.[9-11]

MATERIALS AND METHODS

Study Design and Data Source

We conducted a retrospective cohort study of adults with status epilepticus encountered in the out-of-hospital setting and treated with midazolam to identify the real-world effect of differing midazolam doses and routes on the risk of recurrent seizures and respiratory failure. We used the ESO Data Collaborative public-use research dataset.[9] ESO is a provider of out-of-hospital electronic medical record software in the United States. The data elements in the electronic medical records include information related to dispatch, assessment, and treatment and are compliant with the National EMS Information System, version 3, standard.

Annually, a public-use research dataset is constructed using all records from participating agencies and removing identifiable information related to the patients, EMS agency, and treating provider. The data elements are directly abstracted from the electronic medical records into the deidentified public-use research dataset, and no data abstraction was performed for this investigation. In 2019, there were 1,322 participating agencies out of the approximately 21,000 agencies nationally. These participating agencies contributed 8.3 million records, and there were EMS encounters from every state in the ESO Data Collaborative.[9] This study was approved by the institutional review board of the University of California, San Francisco.

Study Population

We identified adult patients (aged 18 years) with an out-of-hospital diagnostic impression of status epilepticus who received midazolam as the initial benzodiazepine during the out-of-hospital encounter from January 1, 2019, to December 31, 2019. We excluded pediatric patients because midazolam dosing is weight-based and would have complicated comparisons with standardized dosing for adults. In addition, we excluded patients who received diazepam or lorazepam as the initial medication administered by treating providers as well as patients with cardiac arrest, characterized by the presence of a diagnostic impression of cardiac arrest or undergoing cardiopulmonary resuscitation.

In the electronic medical records, the providers select a primary and secondary diagnostic impression from a predetermined list of options. A nationally defined list of options exists, although EMS agencies have clinical definitions that are specific to their agency protocol. Seizure with status epilepticus is included in the nationally defined list, and the clinical definition varies across agencies and can include persistent convulsive seizures, repeated seizures within a particular time frame, or alternative definitions.[7,10] We previously demonstrated that out-of-hospital diagnostic impressions of status epilepticus have moderate

sensitivity and high specificity for status epilepticus.[11] We restricted the analysis to individuals with a diagnostic impression of status epilepticus who also received midazolam to increase specificity for our target population—which included adults with generalized, convulsive status epilepticus—based on our prior work that demonstrated that this definition has a low sensitivity (25%) but a high positive predictive value (80%) and specificity (99%) for status epilepticus.[11]

Exposure

The primary exposure was the first out-of-hospital administration of midazolam. Out-of-hospital providers are expected to record any drug administered during the encounter in the electronic medical records, including medication name, dose, route, the time of administration, and the name of the administering EMS agency. Using the earliest recorded dose of midazolam as the initial administration, we conducted 1 set of analyses that isolated medication route as the exposure of interest (adjusting for dose as a potential confounder) and 1 set of analyses that isolated medication dose as the exposure of interest (adjusting for route as a potential confounder). The route of administration was coded as intramuscular, intranasal, intravenous, or other, which included intraosseous administration and encounters in which the route was not specified. The dose was coded in 1-mg increments. We also created a dichotomous indicator of whether the dose was 5 mg or greater and whether the dose was 10 mg or greater.

Covariates

We included patient age, sex, race, and suspected recreational drug use as covariates. The race was documented by the treating provider and was missing in 2% of the encounters. The race was categorized as White, Black, or other, which combined multiple categories to create an adequately sized stratum for the analysis (Table E1 [available at http://www.annemergmed.com]). Suspected recreational drug use is determined by the treating provider and is available as a separate data field in the medical record to report whether there is alcohol and/or drug paraphernalia at the scene, whether the patient reports using drugs, or whether the provider suspects use based on their physical examination. The variable has not been validated, and it is missing in 16% of the 2019 ESO dataset. We created a binary variable that coded patients as having suspected recreational drug use if the provider reported potential use for any of the reasons mentioned above. We defined patients without suspected recreational drug use as those who were specified as not reporting drug use or those for whom the variable was missing. These data do not provide direct information about seizure duration or etiology. We elected not to use response time as a predictor of seizure duration because this would not help eliminate confounding from seizure severity, and there was no observable association between our outcome and exposure (Table E2 [available at http://www.annemergmed.com]). We did not include data on comorbidities because the validity of these data based on the out-of-hospital electronic medical record data was unclear, and we did not include weight because this information was missing for approximately one third of the encounters in the dataset and because dosing is not weight-based in adults.

Outcome

The primary outcome was the administration of rescue therapy, defined as the administration of any additional benzodiazepine following the first midazolam administration during the out-of-hospital encounter. This outcome measure has been used as an indicator for ongoing seizure activity in randomized controlled trials.[3,4] The secondary outcome was the provision of ventilatory support, defined as the use of endotracheal intubation, supraglottic airway, a continuous positive airway pressure device, or a bag valve mask (Table E3 [available at http://www.annemergmed.com]). Ventilatory support is recorded in structured data fields. Out-of-hospital providers are instructed to record the device type, the timing of placement, and whether the placement was successful. The individuals who required ventilatory support included those for whom advanced airway placement was attempted, regardless of whether the attempt was successful.

Statistical Analysis

We used descriptive statistics to examine the demographic data and clinical characteristics of the patients in the study cohort. For the main analyses, we used a conventional as-treated analysis and a complementary instrumental variable approach. For the as-treated analysis, we estimated the crude risk difference (RD) using an unadjusted logistic regression model, and we estimated a marginal RD using a hierarchical multivariable logistic regression model that incorporated an agency-level random intercept to quantify between-agency treatment variability and was adjusted for age, sex, race, and suspected drug use. In addition, we adjusted for dose while examining route as the exposure and adjusted for route while examining dose as the exposure.

There is potential confounding in this as-treated approach to the quantification of medication effectiveness because patients who receive midazolam at particular doses (eg, low versus high) and through particular routes (eg, intramuscular versus intravenous) may have underlying differences associated with their likelihood of needing rescue therapy. Without the ability to account for this confounding, the estimates of the effect of dose and route could be biased. This risk may be amplified using out-of-hospital data, which are more limited in this setting than they are in other clinical settings.

To address the risk of residual confounding, we performed an instrumental variable analysis. In this approach, we used the finding that EMS agencies have substantial between-agency variability in their midazolam use (Table E4 [available at http://www.annemergmed.com]).[12] This variability is likely driven by agency-specific treatment protocols and practice patterns rather than underlying differences in patients evaluated by a given agency. Thus, these local treatment patterns are associated with exposure and receiving midazolam at a particular dose or through a particular route and likely independent of patient characteristics that determine the risk of rescue treatment, leading to their potential use as an instrumental variable (Table E5 [available at http://www.annemergmed.com]).

Prescribing patterns have been used as instrumental variables in prior studies of medication effectiveness because of the strong association between provider medication preference and patients of that provider receiving that medication. However, their validity relies on

2 additional assumptions: first, there are no variables influencing both the instrumental variable and the outcome that are not included in the model, and second, any effect of the instrumental variable on the outcome is explained by primary exposure.[13-15] In other words, we assumed that factors (such as agency-specific treatment protocols) affecting the proportion of encounters from a specific agency where midazolam was administered intranasally as opposed to an agency where it was administered intramuscularly did not affect the risk of rescue therapy for a breakthrough seizure except by altering the route or dose of treatment received, conditional based on the other factors included in the model.

It is possible that providers may forget to record or may incorrectly document medications administered during the encounter, but we assumed that this would occur at random and, specifically, would not be related to the overseeing EMS agency. We also assumed that there was between-agency variability in the route and dose of benzodiazepine but less variability in the administration of rescue therapy if a patient continued to have seizures.

To study the route of administration, we performed 2 pairwise analyses: intranasal versus intramuscular midazolam and intravenous versus intramuscular midazolam. We first performed unadjusted and adjusted conventional analyses as well as an adjusted instrumental variable analysis in which we included patient age, sex, race, and suspected drug use to account for any potential differences in patient populations among the agencies. For the instrumental variable analysis, we used the proportion of patients per agency who received intramuscular administration as the instrument and performed 2-stage least squares regression for both the outcomes after excluding agencies with less than 5 encounters. This instrument was strongly associated with exposure (intranasal versus intramuscular F-statistic 4,755, intravenous versus intramuscular F-statistic 1,778; Table E5 [available at http://www.annemergmed.com]).

To study midazolam dose, we repeated the conventional analysis with 3 different exposures: dose as a continuous variable, a dichotomous indicator of a dose of 5 mg or higher, and a dichotomous indicator of a dose of 10 mg or higher. Midazolam was administered most frequently at doses of 2, 3, and 5 mg and rarely at other doses. Thus, a model incorporating dose as a linear predictor could be misleading. For the instrumental variable analysis, we used the average midazolam dose across the encounters at a given agency as the instrument for the continuous variable (F-statistic, 6,067), and we used the proportion of encounters per agency in which the initial midazolam dose was 5 mg or higher and 10 mg or higher as instruments for the 2 dichotomous variables (dose 5-mg: F-statistic, 5,701; dose 10-mg: F-statistic, 4,370; (Table E5 [available at http://www.annemergmed.com]). We performed 2-stage least squares regression for both the outcomes after adjusting for patient age, sex, race, and suspected drug use after excluding agencies with less than 5 encounters.

For individuals who received intranasal midazolam, it was possible that a single intranasal dose was delivered as 2 smaller doses into each nostril, which would have led to the misclassification of both the exposure and outcome because 1 of the doses would have been inaccurately identified as rescue therapy. To address this possibility, we identified individuals who received 2 doses of midazolam delivered intranasally in whom the time elapsed between the 2 doses was 60 seconds or less. For these individuals, we calculated

the sum of their first and second doses, defined rescue therapy as receiving a third benzodiazepine dose, and performed a sensitivity analysis by repeating the adjusted, as-treated analysis.

There may be agency-level factors associated with the second dose of a benzodiazepine that could represent a source of residual confounding. We performed a series of falsification tests to address this possibility. We examined patient-level and agency-level characteristics across our instrumental variables for midazolam route (Table E6 [available at http://www.annemergmed.com]). The proportion of patients who received intranasal and intravenous midazolam was imbalanced with respect to the time elapsed before treatment, and the proportion of patients who received an intravenous midazolam instrument was also imbalanced with respect to transport time and the rurality of the agency. To address the possibility that these variables were a source of bias, we repeated our instrumental variable analysis examining the administration route after adjusting for the number of minutes elapsed before treatment, the number of minutes to transport the patient to the destination hospital, and whether the agency was located in a rural region. The statistical analyses were performed using Stata, version 15.1 (StataCorp LLC).

RESULTS

Study Population

There were 7,634 out-of-hospital encounters for status epilepticus treated with midazolam across 657 EMS agencies. The EMS agencies were located in all 9 Census Bureau-designated divisions, and 110 (16.7%) were located in rural settings. The mean age of the patients was 46 years (SD 18), and 3,752 (49.5%) were women (Table 1). Treatment with midazolam matched the expert guideline recommendations (10-mg intramuscular injection) in 4.1% (310) of the encounters. Rescue therapy was administered in 29.6% (2,248) and ventilatory support provided in 6.1% (467) of the encounters (Table 2).

Midazolam administration varied by its route and dose. The initial route of midazolam administration was intranasal in 19.7% (1,500) of the encounters, intravenous in 45.6% (3,462) of the encounters, and intramuscular in 34.7% (2,635) of the encounters. There was an approximately 6-minute treatment delay with intravenous administration compared with other routes (intravenous, 14.8 minutes; intramuscular, 8.6 minutes; intranasal, 8.6 minutes; Table 1). The dose was 2 mg in 1,355 (18%) encounters, 3 mg in 1,625 (21%) encounters, and 5 mg in 3,809 (50%) encounters, representing the most common doses administered (Table 2). The selected dose varied by the route of administration, with lower doses used when midazolam was administered as an intravenous injection: the median intranasal dose was 5 mg (interquartile range [IQR], 3 to 5 mg), the median intravenous dose was 3 mg (IQR, 2 to 5 mg), and the median intramuscular dose was 5 mg (IQR, 5 to 5 mg) (Table E7 [available at http://www.annemergmed.com]).

Comparison of Differing Routes of Midazolam Administration

Compared with intramuscular midazolam, intranasal midazolam was associated with a 6.5% (95% CI, 2.4% to 10.5%) absolute increased risk of rescue therapy and intravenous

midazolam was associated with an 11.1% (95% CI, −14.7% to −7.5%) absolute decreased risk of rescue therapy in the as-treated analysis after adjusting for patient characteristics and midazolam dose. The instrumental variable analysis also demonstrated that intranasal midazolam had a higher risk of rescue therapy and intravenous midazolam had a lower risk of rescue therapy, with effect sizes that were larger than those in the as-treated analysis (Table 3).

Compared with intramuscular midazolam, intranasal midazolam was associated with a decreased provision of ventilatory support in the unadjusted analysis (RD, −1.9%; 95% CI, −3.4% to −0.4%); however, these differences in ventilatory support were not statistically significant with the as-treated approach after adjustment (RD, −1.5%; 95% CI, −3.3% to 0.3%) or with the instrumental variable approach (RD, −1.8%; 95% CI, −4.3% to 0.6%). The differences in ventilatory support did not reach statistical significance when intravenous midazolam and intramuscular midazolam were compared in all the analyses (adjusted as-treated RD, −0.3%; 95% CI, −1.9% to 1.2%) (Table 3).

Comparison of Differing Midazolam Dose

Higher initial doses of midazolam had a lower associated risk of rescue therapy (Table 4). Each additional milligram of midazolam was associated with a 2.6% absolute decreased risk of rescue therapy (95% CI, −3.3% to −1.9%). Receiving midazolam at a dose of 5 mg or higher was associated with an 11.1% (95% CI, −14.9% to −7.3%) absolute decreased risk of rescue therapy; the point estimate for receiving midazolam at a dose of 10 mg or higher was similar, with a 10.7% absolute decreased risk of rescue therapy (95% CI, −15.3% to −6.0%). The instrumental variable analyses yielded similar findings, with effect sizes that were slightly attenuated (Table 3).

With respect to ventilatory support, each additional milligram of midazolam was associated with a 0.4% absolute increase (95% CI, 0.1% to 0.7%) in the likelihood of ventilatory support, but these differences did not persist with the instrumental variable approach when midazolam was treated as a continuous or dichotomous variable (RD, 0.1%; 95% CI, −0.3% to 0.6%; Table 4).

Sensitivity Analysis

In the sensitivity analysis, we evaluated the initial midazolam dose and the receipt of rescue therapy for all individuals who received 2 doses of intranasal midazolam within 60 seconds of one another and repeated the adjusted, as-treated analysis, which yielded results similar to the main analysis. Additionally, we repeated the adjusted comparison of intravenous and intramuscular midazolam with the time between arrival at the scene and delivering treatment as a covariate. This attenuated the benefit of intravenous midazolam, but the intravenous route continued to be associated with an absolute decreased risk of rescue therapy (as-treated adjusted RD, −6.9%; 95% CI, −3.6% to −0.1%).

LIMITATIONS

There are important limitations to mention. First, the cohort was derived from all EMS agencies that use ESO for their out-of-hospital electronic medical records, but the cohort

was not sampled or weighted to be nationally representative. Although we cannot consider this a population-based cohort, the agencies provided data from every out-of-hospital encounter, they were geographically distributed across all Census Bureau divisions, and they included care in both urban and rural settings, all of which strengthen the generalizability of our findings.

Second, we lacked data on a patient's stay in the emergency department and hospital and could not confirm whether they had a breakthrough seizure or received ventilatory support after the out-of-hospital team had transferred care. Intramuscular midazolam is faster to administer than intravenous midazolam, which could have led to a shorter out-of-hospital encounter and made it more likely that a breakthrough seizure had occurred after the out-of-hospital encounter.[4] To address this possibility, we included time to treatment as a covariate in our sensitivity analysis and demonstrated similar findings. This does not address the possibility that agencies that were more likely to use an intravenous route of administration may have systematically had a higher threshold for delivering the second dose of the benzodiazepine.

Third, a minority of patients received intravenous midazolam above a dose of 5 mg, which highlights the need for more data to determine the safety of intravenous therapy when delivered at the guideline-recommended dose of 10 mg.

Fourth, we lacked data on clinical indications for receiving the second benzodiazepine dose. EMS agency protocols instruct providers to administer the second dose for breakthrough seizures, and this analysis assumed that subsequent benzodiazepine administration reflected a recurrent seizure. However, there are other clinical indications for benzodiazepine use, including sedation and anxiolysis, that may have been the indication for the second dose, and there may have been patients who experienced breakthrough seizures and failed to receive treatment with the second benzodiazepine dose and were, thus, missed in this analysis. This misclassification of the outcome is, however, nondifferential with respect to exposure. Thus, if anything, it would bias our results toward the null, implying the true effect sizes are larger than those demonstrated.

Fifth, out-of-hospital electronic medical records do not offer complete clinical details. The records lack information about the timing and true degree of respiratory depression; thus, we relied on the coding of attempted airway interventions as a proxy for respiratory status. The variable specifying suspected recreational drug use was also missing in 16% of the larger dataset. These are potential sources of misclassification that weaken the ability to establish a causal association between our treatment and the outcomes.

Finally, the dataset did not allow us to confirm the diagnosis of status epilepticus or determine whether there were systematic differences in the severity of status epilepticus across the agencies. Although this seems unlikely, it could lead to residual confounding and explain some of the between-agency variability in medication dose and route.

DISCUSSION

In this large cohort study of adults with status epilepticus who were administered midazolam in the out-of-hospital setting, we found that the route of administration and dose both affected the clinical outcomes and that the patients rarely received treatment that matched the midazolam dose and route recommended by the guidelines. Our findings suggest that the intranasal administration of midazolam is less effective and the intravenous administration of midazolam more effective in terminating status epilepticus than the intramuscular administration of midazolam. The findings also reinforce prior evidence that a higher dose leads to more effective seizure termination. Reassuringly, the differences in the need for ventilatory support were small and did not reach statistical significance in most comparisons and the instrumental variable approach was taken.

To our knowledge, prior studies evaluating benzodiazepine efficacy have not successfully isolated the effect of medication route on seizure control.[6,16-18] One single-center cohort examined intranasal administration compared with the combined effect of intramuscular and intravenous administration, but the analysis did not compare intramuscular and intravenous administration and was confounded by medication dose.[6] A previous randomized trial, RAMPART, reached a broad population, but by comparing intramuscular midazolam with intravenous lorazepam, the trial combined the route of administration and medication type into a single exposure and was unable to disentangle the isolated effect of medication dose and medication route.[4] Many attribute the superiority of midazolam in RAMPART, in which it was compared with intravenous lorazepam, to the shorter time required to administer an intramuscular medication compared with that required to administer an intravenous medication. Yet, we found that despite intramuscular administration occurring 6 minutes faster than intravenous administration, intravenous midazolam led to lower rates of rescue therapy. The superiority of intravenous midazolam over intramuscular midazolam despite the delay in treatment suggests that the better rates of seizure control in the intramuscular midazolam arm of RAMPART are related to 10-mg midazolam having a superior antiseizure effect in addition to a shorter time used for treatment. However, these results are taken from real-world observational data, which have an increased likelihood of a bias compared with results from randomized trial data.

Regardless, administering midazolam intravenously and intramuscularly were both associated with better clinical outcomes compared with administering midazolam intranasally. Prior studies have demonstrated that providers believe that intranasal administration is safer, faster, and less painful, which likely explains why intranasal administration occurs in 20% of encounters. However, these findings suggest that this leads to worse seizure control and represents a specific area where out-of-hospital care can be improved. Currently, the National Association of State EMS Officials guidelines have listed intranasal administration as a recommended route for delivering midazolam, and this standard is reflected in multiple EMS agency protocols nationally.[7,19,20] This has previously been justified by evidence from cohort studies demonstrating that intranasal therapy is safe and effective.[16-18] These studies, however, did not compare the routes of administration within a single class of medication. By addressing that limitation in this analysis, our findings call that standard of care into question.

These results also confirm our work demonstrating that midazolam is routinely administered at doses lower than 10 mg and that lower doses are associated with worse clinical outcomes.[5] The use of the larger, more diverse cohort maximized generalizability, and the use of the instrumental variable approach minimized confounding. Our findings support the use of intramuscular midazolam as a single 10-mg dose and suggest that intravenous midazolam has similar or improved efficacy.

In conclusion, the majority of the patients with status epilepticus received suboptimal out-of-hospital care. Although there continue to be important clinical questions regarding the best approach to treatment, our results suggest that a targeted intervention that reduces the frequency of intranasal administration and midazolam underdosing has the potential to improve clinical outcomes in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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Editor's Capsule Summary

What is already known on this topic

Although guidelines recommend intramuscular midazolam (10 mg) for out-of-hospital status epilepticus treatment, clinicians inconsistently adhere to the guideline.

What question this study addressed

In a retrospective cohort, the authors examined the real-world use of midazolam for status epilepticus treatment using a large corporate dataset.

What this study adds to our knowledge

Guideline adherence occurred in 4.1% of encounters. When compared with intramuscular administration, the risk of rescue therapy was elevated with the intranasal route and decreased with the intravenous route.

How this is relevant to clinical practice

Status epilepticus is a life-threatening event that requires effective and efficiently administered therapy. In this study, a vast majority of out-of-hospital patients with status epilepticus did not receive guideline-compliant treatment. These findings suggest that further training of out-of-hospital care personnel is needed.

Table 1.

Baseline characteristics based on the route of initial midazolam administration.

Patient Characteristics	Intranasal	Intravenous	Intramuscular
Number of encounters	1,500	3,462	2,635
Age (y), mean	46 (17)	46 (18)	45 (18)
Female sex, n (%)	781 (52.2%)	1,660 (48.1%)	1,311 (49.9%)
Race			
White	849 (56.6%)	2,155 (62.2%)	1,398 (53.1%)
Black	556 (37.1%)	1,036 (29.9%)	996 (37.8%)
Other	95 (6.3%)	271 (7.8%)	241 (9.1%)
Hispanic ethnicity	115 (7.7%)	233 (6.7%)	170 (6.5%)
Suspected alcohol/drug use	109 (7.3%)	232 (6.7%)	219 (8.3%)
Systolic BP (mmHg), mean (SD)	145 (30)	144 (31)	142 (29)
Oxygen saturation (%), mean (SD)	95 (6)	95 (6)	95 (7)
Pulse (beats/min), mean	110 (27)	107 (25)	109 (27)
GCS category			
3-8	686 (47.3%)	1,463 (43.8%)	1,229 (48.3%)
9-12	333 (23.0%)	712 (21.3%)	545 (21.4%)
12-15	430 (29.7%)	1,162 (34.8%)	772 (30.3%)
Initial midazolam dose (mg), median (IQR)	5.0 (3.0-5.0)	3.0 (2.0-5.0)	5.0 (5.0-5.0)
Time from on-scene arrival to treatment (minutes), median (IQR)	8.6 (4.9-14.6)	14.8 (9.3-21.7)	8.6 (5.0-15.6)

GCS, Glasgow Coma Scale; *BP*, blood pressure; *IQR*, interquartile range.

Table 2.

Crude clinical outcomes based on midazolam route and dose.

Route and Dose	N	Rescue Therapy, n (%)	Ventilatory Support, n (%)
5 mg of midazolam			
Intramuscular	635	516 (30.8)	119 (7.1)
Intranasal	308	281 (35.7)	27 (3.4)
Intravenous	306	223 (16.9)	83 (6.3)
Total	1,249	1,020 (27.0)	229 (6.1)
10 mg of midazolam			
Intramuscular	116	70 (22.6)	46 (8.6)
Intranasal	70	43 (27.9)	27 (8.7)
Intravenous	22	8 (11.1)	14 (9.1)
Total	126	121 (22.6)	5 (6.9)

Table 3.

Crude and adjusted marginal risk differences as a function of midazolam route estimated from as-treated and instrumental variable analyses.

Comparison	Rescue			Ventilatory Support		
	Crude (%)	Adjusted (%)	95% CI	Crude (%)	Adjusted (%)	95% CI
Intranasal versus intramuscular						
As-treated	7.38	6.47	2.40%-1.05%	-1.91	-1.47	-3.27% to 0.33%
Instrumental variable [*]	5.27	4.42	-0.29% to 9.13%	-2.38	-1.84	-4.29% to 0.60%
Sensitivity analysis [†]		4.35	-0.31% to 9.01%		-1.86	-4.36% to 0.63%
Intravenous versus intramuscular						
As-treated	-7.22	-11.1	-14.7% to -7.52%	-0.84	-0.33	-1.88% to 1.22%
Instrumental variable [‡]	-9.01	-15.9	-21.8% to -10.0%	1.65	2.76	-0.49% to 6.0%
Sensitivity analysis [†]		-14.1	-20.1% to -8.12%		2.63	-0.74% to 6.0%

CI, Confidence interval.

[*] Two-stage least squares regression using the proportion of patients who received intranasal midazolam as the instrument.

[†] Sensitivity analysis repeating 2-stage least squares regression after adjusting for time to treatment, transport time, and rurality.

[‡] Two-stage least squares regression using the proportion of patients who received intravenous midazolam as the instrument.

Table 4.

Crude and adjusted marginal risk differences for rescue therapy and ventilatory support as a function of midazolam dose estimated from as-treated and instrumental variable analyses.

Comparison	Rescue			Ventilatory Support		
	Crude (%)	Adjusted (%)	95% CI	Crude (%)	Adjusted (%)	95% CI
Dose (mg)						
As-treated	−1.84	−2.63	−3.33% to 1.9%	0.36	0.4	0.14%–0.67%
Instrumental variable [*]	−1.41	−1.77	−2.63% to 0.91%	0.12	0.13	−0.33% to 0.58%
Dose 5 mg [†]						
As-treated	−7.71	−11.1	−14.9% to 7.26%	0.72	0.75	−0.45% to 1.95%
Instrumental variable [‡]	−7.78	−8.45	−12.0 to 4.87%	−0.54	−0.57	−2.46% to 1.33%
Dose 10 mg [§]						
As-treated	−7.61	−10.7	−15.3% to 6.03%	2.53	2.70	0.06%–5.35%
Instrumental variable [∥]	−3.42	−8.19	−15.4% to 0.99%	1.86	1.86	−1.94% to 5.66%

CI, Confidence interval.

[*]
Two-stage least squares regression using the average midazolam dose per agency as the instrument.

[†]
Reference is receiving a dose less than 5 mg.

[‡]
Two-stage least squares regression using the proportion of patients who received a midazolam dose of 5 mg or higher per agency as the instrument.

[§]
Reference is receiving a dose less than 10 mg.

[∥]
Two-stage least squares regression using the proportion of patients who received a midazolam dose of 10 mg or higher per agency as the instrument.