Adverse events following emergent prehospital sedation of patients with behavioral emergencies: A retrospective cohort study

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Summary

Background Patients presenting to emergency medical services (EMS) with behavioral emergencies may require emergent sedation to facilitate care, but concerns about sedation-related adverse events (AEs) exist. This study aimed to describe the frequency of AEs following emergent prehospital sedation with three types of sedative agents: ketamine, benzodiazepines and antipsychotics.

Methods This retrospective cohort study included patients ≥ 15 years who presented to 1031U.S. EMS agencies in calendar year 2019 with behavioral emergencies necessitating emergent prehospital sedation. Serious AEs (SAE) included cardiac arrest, invasive airway placement, and severe oxygen desaturation (<75%). Less-serious AEs included positive pressure ventilation, any oxygen desaturation (<90%), oropharyngeal or nasopharyngeal airway placement, and suctioning. The need for additional sedation was also assessed.

Findings Of 7973 patients, 1996 received ketamine; 4137 received a benzodiazepine; 1532 received an antipsychotic agent; and 308 received an indeterminant agent. Cardiac arrest occurred in 11 patients (0·1%) and any SAE occurred in 165 patients (2·1%). Invasive airway placement was more frequent with ketamine (40, 2·0%) compared with benzodiazepines (17, 0·4%) or antipsychotics (3, 0·2%). Oxygen desaturation below 75% also occurred more frequently with ketamine (51, 2·6%) than with benzodiazepines (52, 1·3%) or antipsychotics (14, 0·9%). Patients sedated with ketamine were less likely to require additional sedation. Propensity-matching to minimize potential confounding between patient condition, sedative choice and AEs did not meaningfully alter the results.

Interpretation Although SAEs were rare among patients receiving emergent prehospital sedation, prehospital clinicians should remain mindful of the potential risks and monitor patients closely.

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Introduction

Emergency Medical Services (EMS) personnel often encounter patients presenting with acute behavioral emergencies, including those who are uncooperative or even violent.[1–3] Such uncooperative or violent behavior

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Research in context

Evidence before this study

We searched MEDLINE using the OVID interface from January 2001 to August 20, 2021 to identify articles of any kind reporting prehospital sedation for patients experiencing behavior-related problems using combinations of search terms and text words including "prehospital", "out-of-hospital", "paramedics", "ambulances", "mental disorders", "behavioral", "delirium", "sedation", "antipsychotic agents", benzodiazepines", and "ketamine." We also reviewed the reference lists of the identified articles. Most identified articles were case series or observational descriptions of individual cohorts, although six studies reported comparative trials. Sedation was generally reported to be safe with few prehospital adverse events, but adverse event surveillance and reporting was inconsistent across studies. For the four comparative trials specifically including ketamine as a sedative agent, a total of only 315 patients had received ketamine. Whether emergent prehospital sedation—particularly sedation using ketamine—for patients with behavioral emergencies is safe remains controversial.

Added value of this study

This study specifically evaluated *emergent* prehospital sedation—that is, sedation as the first prehospital pharmacologic intervention. It takes advantage of a large multi-agency database, as well as propensity score matching to minimize potential confounding between patient characteristics and sedative choice, to explore the rate of cardiac arrest and other serious adverse events, as well as other less-serious adverse events, among patients presenting to emergency medical services (EMS) with behavioral-related problems who receive emergent sedation with ketamine, a benzodiazepine or an antipsychotic agent. We found that 10·5% of those patients experienced at least one adverse event of some kind, although cardiac arrest (0·1%) and other serious adverse events (2·1%) were rare. Adverse events occurred more frequently when ketamine was used for emergent sedation, but ketamine was also associated with a decreased need for additional sedation.

Implications of all the available evidence

While emergent prehospital sedation generally appears safe, adverse events do occur and may be more likely when ketamine is used. When emergent sedation is necessary, prehospital clinicians should remain mindful of the potential risks, monitor patients closely, and be prepared to intervene if required—regardless of the sedative agent used.

can pose potential risks to the patients themselves, responders or bystanders, and can impede urgent evaluation and treatment.[3–5] Physically restraining patients exhibiting uncooperative or violent behavior can exacerbate underlying problems, cause physical injury to patients or caregivers, and result in asphyxia.[4,6,7] When conventional de-escalation techniques fail or are otherwise impractical, prehospital sedation may be necessary.[6,7] Prehospital sedation should only be administered by appropriately trained and supervised EMS clinicians, and must be for the medical benefit of the patient—not solely for law enforcement restraint purposes.[7–9]

Some patients experiencing uncooperative or violent behavioral emergencies require *emergent* prehospital sedation—that is, administration of a sedative as the first intervention in order to facilitate patient care. In the United States (U.S.), recent high-profile media reports of post-sedation cardiac arrest and other adverse events (AEs) have raised concerns about emergent prehospital sedation, including questions about patient selection and the types of sedatives used. Most literature regarding prehospital sedation for patients presenting with behavioral emergencies emanates from descriptive series and single-center comparative studies[10–12] that do not explicitly focus on emergent sedation (see also **Table S1**, Appendix pp 3,4). The purpose of this study was to describe emergent prehospital sedation practices in a large sample of U.S. EMS systems, determine the frequency of cardiac arrest and other AEs following emergent sedation, and describe the incidence of AEs across three commonly-used types of sedative agents: ketamine, benzodiazepines and antipsychotics.

Methods

Design and data sources

Data for this retrospective cohort study were obtained from the ESO Data Collaborative research dataset for January 1 through December 31, 2019. ESO provides electronic health record (EHR) software for U.S. EMS agencies, and a subset of users voluntarily contributes all EHR records to the de-identified dataset. The annual public-use dataset includes information regarding EMS dispatch, patient demographics, clinical presentation, assessment findings, and treatments provided as recorded by the attending EMS clinicians. EHR elements are defined and data are collected in compliance with the National EMS Information System (NEMSIS) data standard.[13] For 2019, the dataset contained 8·3 million EMS encounters attended by 1322 agencies in 50U.S. states.[14]

Study population

Our target population included patients 15 years of age or older who presented with a behavioral problem and who received emergent sedation.

We first identified patients presenting with a behavioral emergency. There is no single, universal EHR field that identifies patients with behavioral emergencies;

instead, there are multiple EHR fields where EMS clinicians select from drop-down menus or check-boxes to document behavioral presentations or characterize combativeness. We defined a behavioral emergency as any EMS encounter with EHR documentation of: (a) a chief complaint, primary impression, secondary impression, or dispatcher-reported complaint indicating a behavioral problem (e.g., "behavioral / psychiatric disorder," "mental disorder"); (b) documentation of a self-inflicted injury; (c) utilization of a behavioral emergency protocol or transport to a behavioral health hospital; (d) signs or symptoms indicating a behavioral problem (e.g., "homicidal ideation," "hallucinations"); or (e) a primary or secondary impression, signs and symptoms or a reported barrier to care indicating combativeness or violence (e.g., "uncooperative patient," "violent behavior"). The complete list of EHR fields and entries used to identify patients with behavioral problems and characterize combativeness are detailed in **Tables S2** and **S3** (Appendix pp 5,6).

Excluded from the analyses were: (1) interfacility transfers; (2) responses by non-paramedic (e.g., basic life support) EMS agencies; (3) responses by air-medical services; and (4) patients in cardiac arrest when EMS arrived. We excluded children less than 15 years of age, as well as patients without a documented age, because agency protocols and paramedic thresholds for emergent sedation likely differ for young children. Also excluded were patients presenting with paramedic-documented clinical conditions that might mimic behavioral emergencies: seizures, hypoglycaemia, stroke, transient ischaemic attack, head injury, and multi-system trauma. Alcohol or drug intoxication alone, in the absence of other indications of a behavioral problem, was not considered a behavioral emergency.

We next identified the subset of patients presenting with behavioral emergencies who received emergent sedation. Emergent sedation was defined as the intramuscular (IM) administration of ketamine, a benzodiazepine or an antipsychotic as the first pharmacologic intervention, before establishment of intravenous (IV) access. These patients formed the sample for our study.

Exposure

The primary exposure of interest was the type of initial emergent sedative agent administered: ketamine, a benzodiazepine, or an antipsychotic medication. Patients who received more than one type of sedative were excluded from the primary analysis if conflicting or missing timestamps made it impossible to identify the first emergent sedative administered.

Choice of outcome measures and variable definitions

As there are no established definitions or criteria for AEs associated with prehospital sedation, we adapted definitions from the World Society of Intravenous Anaesthesia's procedural sedation AE reporting tool.[15] The primary outcome was cardiac arrest occurring after the initial sedative administration, or the composite of any serious AE (SAE), including cardiac arrest, post-sedation invasive airway placement (endotracheal tube or supraglottic airway) or new-onset severe oxygen desaturation (pulse oximeter reading < 75%). Secondary outcomes included the frequency of other AEs, including use of positive pressure ventilation (PPV), any oxygen desaturation (pulse oximeter reading < 90%), oropharyngeal or nasopharyngeal airway placement, and suctioning (potentially indicating emesis or hypersalivation). We also determined the frequency of additional prehospital sedative administrations, including both redosing of the initial sedative agent and additional dosing with other agents.

AEs were captured from the EHR as documented by the attending paramedics. Cardiac arrest, advanced airway placement, positive pressure ventilation and basic airway interventions are affirmatively documented using drop-down menus or check-boxes; serial oxygen saturation levels are electronically captured through an interface with the vital signs monitor or manually entered by the paramedics. To be included as an AE in this analysis, the event had to be timestamped as newly occurring after the administration of the first sedative. Assessment of AEs was limited to events occurring during the prehospital phase of care.

For each type of initial sedative agent, we report the frequency of cardiac arrest, individual SAEs, the composite of any SAE, as well as other AEs.

Propensity score matching and covariates

The choice of prehospital sedative is complex and potentially driven by clinical circumstances, an EMS agency's formulary, treatment protocols, and an individual paramedic's comfort with or preference for certain sedatives. Because the choice of sedative agent is not random, we also conducted a propensity score matched analysis in an attempt to minimize potential confounding between patient condition, sedative choice and AEs.

We created three pairwise matched cohorts based on the initial emergent sedative agent: (1) ketamine vs. benzodiazepines; (2) ketamine vs. antipsychotics; and (3) antipsychotics vs. benzodiazepines. Each pairwise cohort was created using Stata's -psmatch2- commands[16] with 1:1 nearest neighbor matching, a maximum calliper width of 0·05, and without replacement. Matching variables included several demographic, clinical and situational characteristics potentially associated with the choice of sedative: patient age, sex, race, and weight; the characterization of combativeness ("not documented" vs. "uncooperative" vs. "combative" vs. "violent"); documentation of a specific behavioral condition (vs. combativeness alone); law enforcement involvement and conducted energy device (e.g., TASER)

involvement; use of physical restraints; alcohol or drug use or indications of withdrawal; location urbanicity as designated by the Centers for Medicare and Medicaid Services (CMS), and vital signs. Vital signs were categorized as "not obtained", "normal," "slow/low" or "fast/high" based on the following reference ranges: respiratory rate, 12–20 / min; heart rate, 60–100 / min; systolic blood pressure, 90–160 mmHg; GCS ≥ 13; oxygen saturation, > 90%.

Weight data were missing for nearly one-quarter of the included patients, and disproportionately for patients initially sedated with a benzodiazepine or antipsychotic agent (which generally do not depend on weight-based dosing). We used the "missing indicator" approach to address missing weight data: a binary "weight missing" indicator was created and missing patient weights were assigned a place-holder value of "0." For the remaining variables, missing values were categorized as follows: Sex missing (n = 26) was included as a distinct category. When race and ethnicity were not documented (n = 176) the patient was categorized as being of unknown race. Events with missing urbanicity data (n = 3) were categorized as non-urban. The remaining matching variables—police involvement, conducted energy device use, restraint use, and alcohol/drug involvement—were expected to be documented only when they occurred; the absence of such documentation was interpreted as meaning they did not occur rather than as missing information.

Matching success was assessed using the standardized percentage bias, with values exceeding ± 10% indicating residual imbalance. Within each pairwise matched cohort we again report the frequency of cardiac arrest, individual SAEs and the composite of any SAE, and other individual AEs. We also calculated the differences in the risk of SAEs and AEs between patients treated with each type of sedative, along with their exact 95% confidence intervals, using Stata's -cs- commands.[17]

Sedative dosing analysis

To explore possible dose-response relationships between SAEs and sedation, the dose of the initial IM sedative was compared for patients who did and did not experience SAEs using Wilcoxon Rank Sum test.

Additional analyses

To assess for any differential risk of SAEs across patient and event characteristics, we conducted post-hoc analyses comparing SAE and AE rates in the pairwise matched cohorts stratified by sex, age, race and ethnicity, the characterization of combativeness, alcohol or drug use, and use of physical restraints. To assess how well our inclusion and exclusion criteria identified patients with actual behavioral emergencies, we obtained emergency department and hospital discharge diagnoses for patients with linked hospital data available, and determined the proportion of patients with a mental health related diagnosis (ICD 10 = F01-F99).[18]

All analyses were conducted using Stata (Version 16.1, College Station, TX). An alpha value of 0.05 was used to establish statistical significance.

Ethical approval

The Office of Research Support and Compliance at the University of Texas affirmed *a priori* that this analysis did not constitute human subjects research.

Role of the funding source

There was no external funding source for this study. The authors are solely responsible for the design, interpretation and reporting of this study.

Results

Study sample

Of 8·3 million encounters included in the 2019 ESO dataset, 433,139 (5·2%) involved eligible patients with behavioral emergencies attended by 1031 paramedic-level EMS agencies (**Figure 1**). Paramedics administered emergent sedation to 7973 (1·9%) of these patients. A benzodiazepine was the most frequently administered initial sedative agent (4137; 51·9%), followed by ketamine (1996; 25·0%) and antipsychotic agents (1532; 19·2%). There were 308 (3·9%) events for which missing or conflicting timestamps precluded identification of the first sedative agent.

The demographic, clinical and situational characteristics of the 7973 events differed considerably across the initial sedative agents (**Table 1**). Generally, most patients were male and in their late 20's to early 50's. More than half of the patients (4394; 55·1%) were explicitly documented as "violent" and police involvement was noted in 2468 (31·0%) of the events. Approximately half of the included patients received sedation before vital signs could be obtained.

The frequency of individual SAEs and other AEs among the included patients, overall and by initial sedative agent, are shown in **Table 2**. In the total sample, cardiac arrest was rare (n = 11) regardless of initial sedative agent. SAEs occurred in 165 patients (2·1%), and 816 patients (10·2%) experienced at least one post-sedation AE of some kind. SAEs and AEs were more frequent among patients initially sedated with ketamine. However, patients initially sedated with ketamine were also less likely to receive additional sedation than those initially receiving a benzodiazepine or an antipsychotic.

Propensity-matched cohorts

Table S4 (Appendix p 7) shows the characteristics of the events retained after propensity matching. Within each paired cohort, the matching successfully minimized the

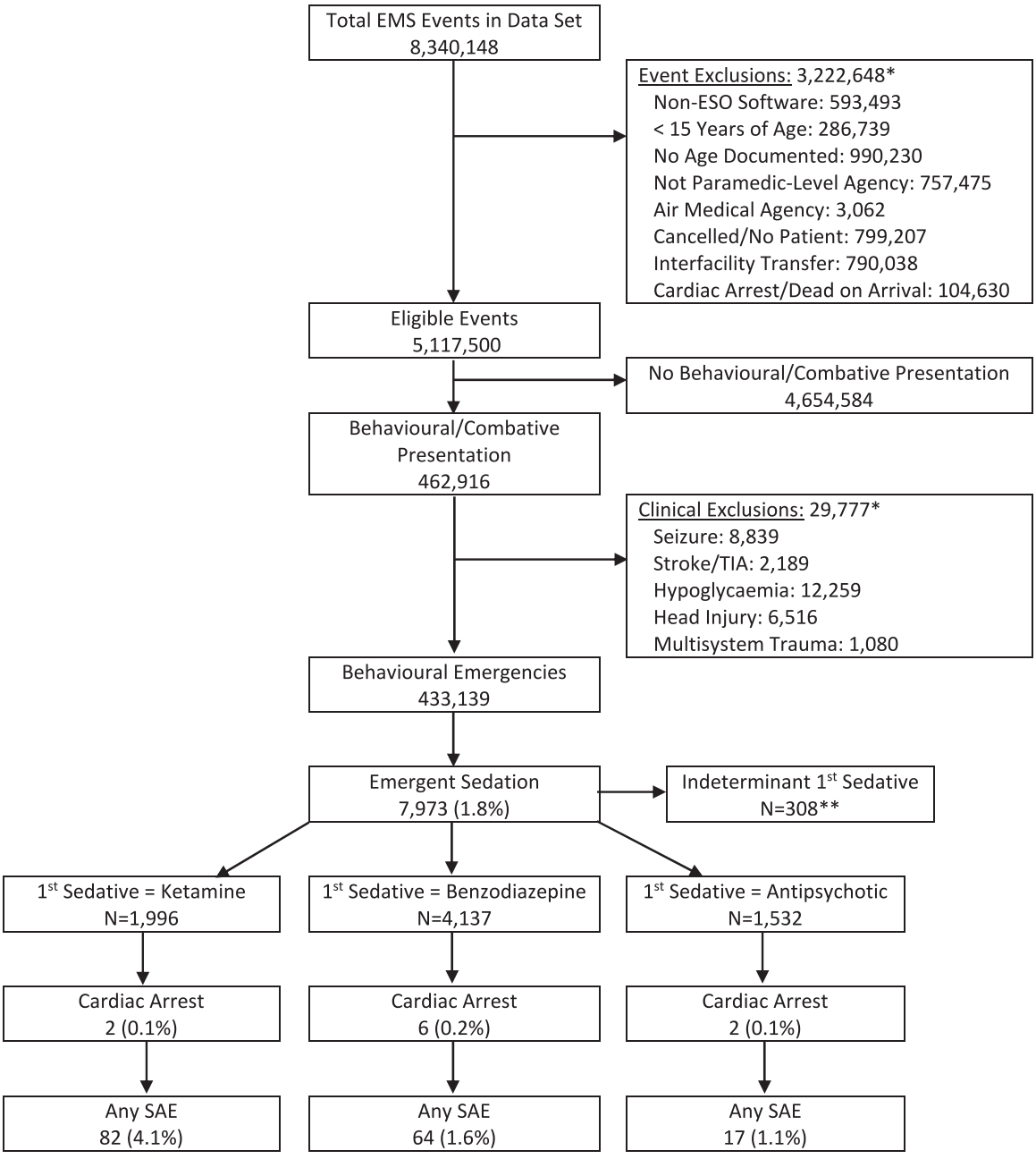

Figure 1. Accrual and Primary Outcomes of the Full Unmatched Study Cohort.
*Patients could meet multiple exclusion criteria. **308 patients, including 1 with cardiac arrest and 2 with any SAE, excluded due to indeterminant first sedative agent. TIA = transient ischaemic attack; SAE = serious adverse event.

differences between patients receiving each type of sedative, with standardized differences less than 10% for all covariates.

Figure 2 shows the incidence of cardiac arrest and other SAEs in the propensity matched cohorts, and a tabular summary of these data is shown in **Table S5** (Appendix p 8). After propensity matching, the risk of post-sedation cardiac arrest remained small (0·1% to 0·2%) and similar across the three types of sedatives. SAEs overall remained infrequent as well but were more frequent among patients emergently sedated with ketamine, whether compared with benzodiazepines (difference, +2·4%, 95% CI: +1·3% to +3·4%) or antipsychotics (difference, +2·1%, 95% CI: +0·8% to +3·3%).

Figure 3 shows the incidence of other AEs and additional sedation in the propensity matched cohorts,

	FullSample	By Emergent Sedative Agent*		
		Ketamine	Benzodiazepine	Antipsychotic
N	7973	1996	4137	1532
Age, median (IQR) yrs	36 (27–51)	34 (26–46)	36 (27–50)	40 (29–56)
Male, *N* (%)	4684 (58·8)	1328 (66·5)	2371 (57·3)	817 (53·3)
Race/Ethnicity, *N* (%)				
White, non-Hispanic	4486 (56·3)	1185 (59·4)	2362 (57·9)1	834 (54·4)
Black, non-Hispanic	2336 (29·3)	493 (24·7)	1145 (27·7)	517 (33·8)
Hispanic	784 (9·8)	208 (10·4)	437 (10·6)	125 (8·2)
Weight, median (IQR) kg	77 (68–91)	82 (68–100)	77 (66–91)	77 (64–91)
Weight Missing, *N* (%)	1814 (24.0)	349 (17.5)	924 (22.3)	471 (30.7)
Indication				
Behavioral Issue Only	1945 (24·4)	300 (15·0)	1044 (24·2)	541 (35·3)
Behavioral Issue & Combative	4505 (56·5)	1210 (60·6)	2269 (54·9)	800 (52·2)
Combative Only	1523 (19·1)	486 (24·4)	824 (19·9)	191 (12·5)
Combativeness Level, *N* (%)				
Not Documented	1945 (24·4)	300 (15·0)	1044 (25·2)	541 (35·3)
Uncooperative	1308 (16·4)	305 (15·3)	727 (17·6)	235 (15·3)
Combative	326 (4·1)	81 (4·1)	184 (4·5)	53 (3·5)
Violent	4394 (55·1)	1310 (65·6)	2182 (52·7)	703 (45·9)
Police Involved, *N* (%)	2468 (31·0)	670 (33·6)	1280 (30·9)	415 (27·1)
CED Involved, *N* (%)	228 (2·9)	111 (5·6)	92 (2·2)	18 (1·2)
Physically Restrained, N (%)	2728 (34·2)	602 (30·2)	1484 (35·9)	494 (32·3)
Substance Use, N (%)				
Alcohol Involved	1554 (19·5)	344 (17·2)	862 (20·8)	301 (19·7)
Drugs Involved	2662 (33·4)	825 (41·3)	1373 (33·2)	378 (24·7)
Bystander Naloxone	29 (0·4)	12 (0·6)	13 (0·3)	3 (0·2)
Indications of Withdrawal	28 (0.4)	6 (0·3)	16 (0·4)	6 (0·4)
Urban Location, N (%)	**7128 (89·4)**	**1759 (88·1)**	**3721 (89·9)**	**1373 (89·6)**
Vital Signs, *N* (%)				
Bradypnea (RR < 12)	40 (0·5)	19 (1·0)	15 (0·4)	6 (0·4)
Tachypnoeic (RR > 20)	1636 (20·5)	390 (19·5)	942 (22·8)	247 (16·1)
Bradycardic (HR < 60)	30 (0·4)	10 (0·5)	16 (0·4)	4 (0.3)
Tachycardic (HR > 100)	2273 (28·5)	532 (26·7)	1264 (30·6)	419 (27·4)
Hypotensive (SBP < 90)	41 (0·5)	14 (0·7)	20 (0·5)	4 (0·3)
Hypertensive (SBP > 160)	523 (6·6)	125 (6·3)	277 (6·7)	110 (7·2)
Altered Mental Status	638 (8·0)	213 (10·7)	326 (7·9)	82 (5·4)
Hypoxic (saturation < 90%)	114 (1·4)	30 (1·5)	68 (1·6)	15 (1·0)
None Documented	4016 (50·4)	1095 (54·9)	2034 (49·2)	715 (46·7)
All Documented	1844 (23·1)	353 (17·7)	1001 (24·2)	425 (27·7)

***Table 1*: Patient and event characteristics in the full study cohort.**
* 308 subjects excluded due to indeterminant first sedative agent. CED = conducted energy device (e.g., TASER).

which are also summarized in **Table S5** (Appendix p 8). After propensity matching, patients initially sedated with ketamine remained statistically more likely than those sedated with a benzodiazepine or antipsychotic to experience other less serious AEs. Patients sedated with a benzodiazepine were also more likely than those sedated with an antipsychotic to experience any AE (difference, 2·2%, 95% CI: 0·5% to 4·7%), and specifically oxygen desaturation below 90% (difference, 2·1%, 95% CI: 0·4% to 3·7%).

Sedative dosing

Table S6 (Appendix p 9) shows the dosing for each initial sedative agent for patients who did and did not experience a SAE. When ketamine was the initial sedative agent, patients who experienced an SAE received statistically higher doses than those who did not experience an SAE, although the practical relevance of this difference is questionable [median (IQR): 300 (250–400) mg vs. 300 (200–400) mg, p = 0.0065]. Indeed, weight-based ketamine dosing did not differ for those who did

	Full Sample	By Emergent Sedative Agent*		
		Ketamine	Benzodiazepine	Antipsychotic
N	7973	1996	4137	1532
Cardiac Arrest	11 (0·1)	2 (0·1)	6 (0·2)	2 (0·1)
Invasive Airway Placement	61 (0·8)	40 (2·0)	17 (0·4)	3 (0·2)
Severe Oxygen Desaturation (<75%)	118 (1·5)	51 (2·6)	52 (1·3)	14 (0·9)
Any SAE	165 (2·1)	82 (4·1)	64 (1·6)	17 (1·1)
Positive Pressure Ventilation	120 (1·5)	84 (4·2)	30 (0·7)	3 (0·2)
Any Oxygen Desaturation (<90%)	634 (8·0)	253 (12·7)	302 (7·3)	68 (4·4)
Oral/Nasal Airway	208 (2·6)	123 (6·2)	70 (1·7)	13 (0·9)
Suctioning	46 (0·6)	35 (1·8)	10 (0·2)	1 (0·1)
Any AE	816 (10·2)	360 (18·0)	360 (8·7)	82 (5·4)
Additional Sedation	2800 (35·1)	560 (28·1)	1549 (37·4)	691 (45·1)

***Table 2*: Frequency of individual adverse events in the full study cohort.**
* 308 subjects, including 1 with cardiac arrest and 2 with any SAE, excluded due to indeterminant first sedative agent. SAE = serious adverse event. AE = adverse event.

and did not experience an SAE [3.8 (3.1–4.6) mg/kg vs. 3.8 (2.5–4.3) mg/kg, p = 0.27]. Similarly, when lorazepam was the initial sedative agent, patients who experienced an SAE received statistically higher doses than those who did not experience an SAE, although again with questionable clinical meaning [2 (2,2) mg vs. 2 (1,2) mg, p = 0.025]. Repeating the dosing analysis using only the paired matched cohorts produced essentially identical results.

Additional analyses

Figs. S1–S3 (Appendix pp 14–16) display the risk of SAEs stratified across various patient and event characteristics. Although the risk difference varied across demographic, clinical or situational strata, these results generally mirrored those of the main analysis. There was no stratum for which initial sedation with ketamine was associated with significantly fewer SAEs.

Linked hospital diagnosis data were available for 2141 patients, and 1554 (72·8%) were assigned mental health related ICD-10 codes. This was consistent across the three initial sedative agents, both in the full sample and in the three pairwise matched cohorts (**Table S7**, Appendix p 10).

Discussion

In this pragmatic analysis including data for more than 400,000 patients presenting to a large cross-section of U.S. EMS agencies with a behavioral problem in 2019, less than two percent of patients received emergent prehospital sedation as the first pharmacologic intervention. Cardiac arrest following emergent sedation was exceedingly rare—occurring in only 11 (0·1%) patients—regardless of the type of sedative used. Overall, 165 patients (2·0%) experienced a SAE. Although SAEs were more frequent when ketamine was the initial sedative agent, this finding might be partly explained by event and patient characteristics that influence the choice of sedative agent. However, SAEs remained more frequent with ketamine even after propensity matching intended to minimize such confounding, although the absolute differences in SAE rates with ketamine vs. other sedative agents was small. While this study did not specifically assess rapidity of onset or efficacy of the sedative types, initial sedation with ketamine was associated with a decreased need for additional sedation.

Invasive airway placement was the most frequent SAE in this study. Some previous case series have reported few intubations following prehospital sedation using ketamine, while others have reported intubation rates ranging between 7% and 63% (see **Supplementary Table S1**). Those analyses, however, were not limited to emergent sedation and included intubations subsequently performed in the emergency department, which might have been independent of prehospital interventions or indications. Small clinical trials reporting intubation following prehospital sedation, again including non-emergent sedation and intubations performed in the emergency department, have provided mixed results. Cole et al.[19] reported more intubations among patients sedated with ketamine (25/64; 39%) compared with haloperidol (3/82; 4%), and O'Connor et al.[20] found more intubations with ketamine (11/95; 12%) than with haloperidol and benzodiazepines combined (1/68; 2%). In contrast, Holland et al.[21] reported no difference in intubation rates when comparing ketamine (6/97; 6%) with midazolam (5/66; 8%), and Lebin et al.[22] reported fewer intubations with ketamine (1/59; 2%) compared with benzodiazepines (17/82; 21%). Few instances of oxygen desaturation were reported in these prior analyses, although it is often unclear whether desaturation did not occur or was simply not evaluated. One prior study did report PPV, with rates that were

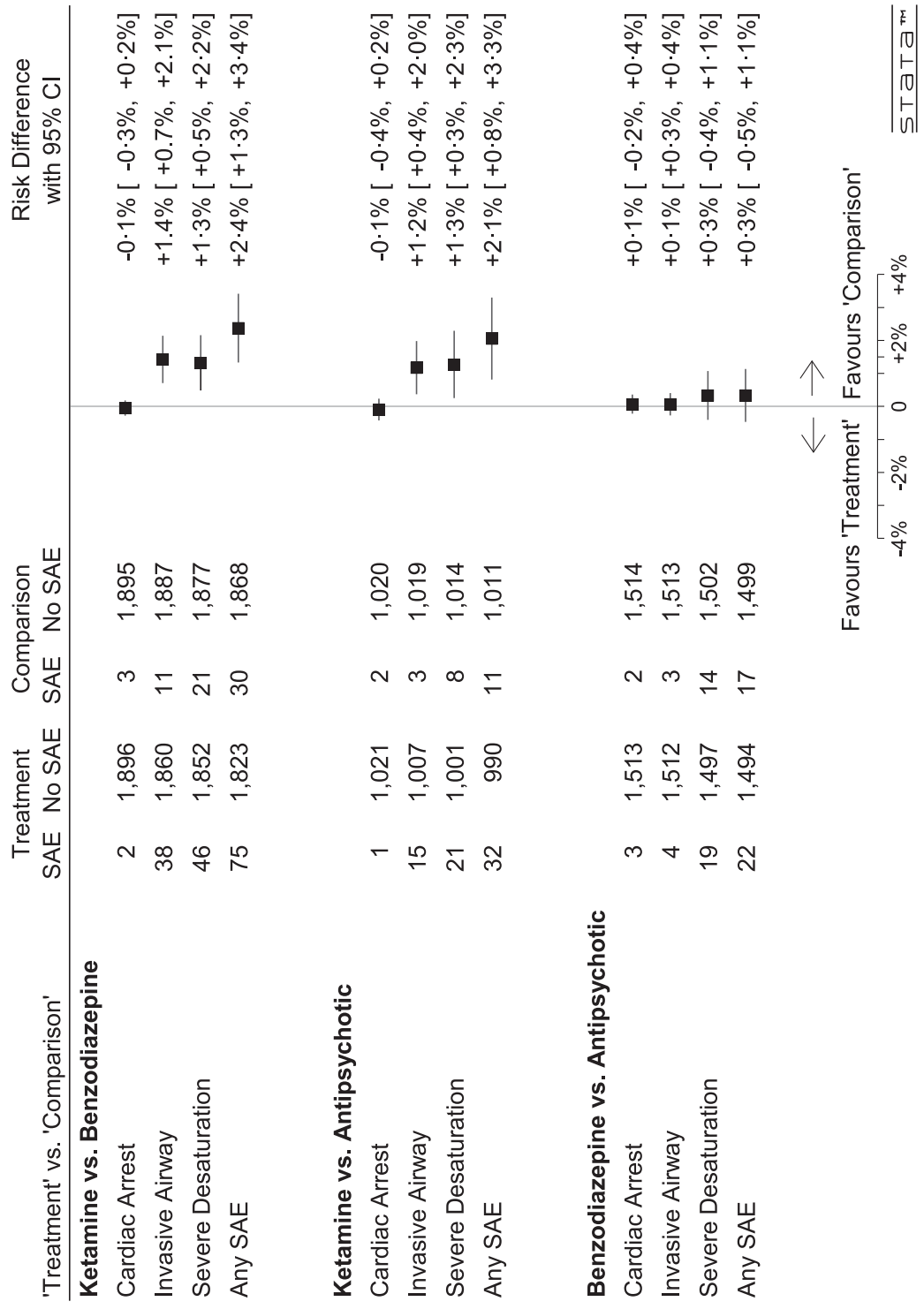

Figure 2. Incidence and Comparative Risk of Serious Adverse Events in the Three Propensity-Matched Cohorts.
SAE = serious adverse event; CI = 95% confidence interval.

slightly higher than those observed in our study: ketamine (7/97; 7%); midazolam (3/66; 5%).[21] In our study, invasive airway placement occurred approximately 1% to 1·5% more often when ketamine was used for emergent sedation, and severe oxygen desaturation occurred approximately 1% more often. Importantly, the observed

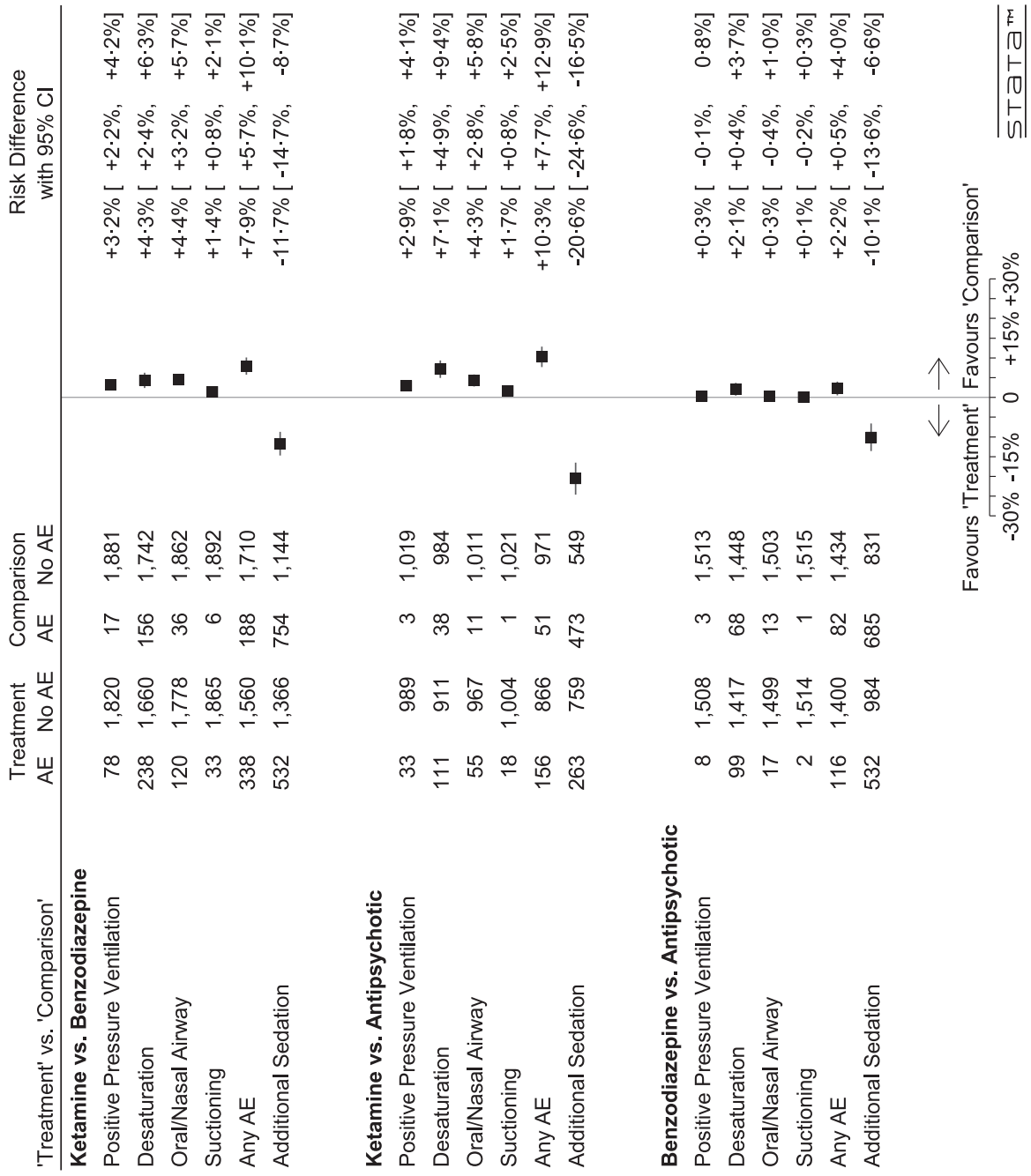

Figure 3. Incidence and Comparative Risk of Other Adverse Events and Additional Sedative Administration in the Three Propensity-Matched Cohorts.

AE = adverse event; CI = 95% confidence interval.

rates of SAEs in our study are lower, and the differences in rates for the various sedative agents are smaller, than those reported in randomized trials comparing ketamine with benzodiazepines and antipsychotics for sedation of agitated patients in the emergency department.[23,24]

Sedative dosing in our study was similar to that in previous observational studies, and we found no clinically meaningful association between initial sedative dose and SAEs. This is consistent with a recent study by Cunningham et al.[25] that found no reduction in

intubation rates or "adverse reactions" after their EMS system reduced initial ketamine dosing for agitated patients from 4 mg/kg to 3 mg/kg.

Ketamine has pharmacological advantages, particularly its rapid onset, that make it desirable in critical and difficult cases. In our study, patients emergently sedated with ketamine were less likely to require additional sedation (28% for ketamine; 37% for benzodiazepines; 45% for antipsychotics). Previous studies have reported additional sedative administrations ranging from 0% to 62% for patients sedated with ketamine and from 0% to 40% for patients sedated with benzodiazepines and antipsychotics (**Table S1**, Appendix pp 3,4). However, the indications for sedation, specific agents, routes of administration and duration of follow-up varied greatly across those studies. In a national survey, paramedics generally viewed ketamine as safe and effective but less than 25% of the respondents' agencies authorized ketamine for emergent sedation in behavioral emergencies.[26]

While we selected and compared cohorts of similar patients through propensity matching, it remains possible that ketamine administration is a surrogate marker for sicker, higher risk patients, and that residual confounding by unmeasured situational or clinical characteristics explains the increased frequency of SAEs and other AEs when ketamine was the initial sedative agent. For example, ketamine (as well as benzodiazepines) can be used with the intention of facilitating airway management—that is, invasive airway placement might be a planned rather than an untoward post-sedation intervention. However, our focus on patients with behavioral emergencies whom paramedics chose to emergently sedate with an IM injection makes it unlikely that the initial sedative administration was part of a planned airway intervention. Indeed, the median time from first sedative administration to advanced airway placement was 20 min (IQR: 13–31), and only three patients received an advanced airway within five minutes of the first sedative dose (data not shown).

Limitations

The principal limitation of this study is that sedative choice may have been influenced by factors that are difficult, if not impossible, to fully identify in a retrospective analysis. While propensity matching should minimize the risk of confounding, it cannot control for unmeasured variables that might differ between patient groups. Other limitations include that the represented agencies are not a random sample of all U.S. EMS agencies. Nonetheless, this dataset provided a large sample of patients treated by a broad array of U.S. EMS agencies. This study was dependent upon information documented in the EHR. No single EHR field uniquely identifies patients with mental health conditions. Similarly, the EHR does not include any validated measure of agitation such as the Richmond Agitation Scale[27] or Sedation Assessment Tool.[28] We therefore used a combination of EHR variables to identify patients presenting with behavioral emergencies and to characterize combativeness. We did not include alcohol or drug intoxication, in the absence of other indications, in our definition of a behavioral emergency because EMS providers frequently encounter patients who have been drinking or using recreational drugs with non-mental health emergencies (e.g., an intoxicated person who has fallen or who is having a myocardial infarction). We also excluded patients with documented conditions like hypoglycaemia or stroke that might mimic behavioral emergencies. That nearly three-quarters of included patients with linked hospital diagnosis data were assigned a mental health related ICD 10 code gives us some confidence in our selection criteria. There are also no established, standardized definitions for AEs associated with emergent prehospital sedation, so we adapted our definitions from those used for in-hospital procedural sedation.[15] Side effects like hypotension and dystonia were not specifically captured as AEs, although we did record suctioning as a potential indirect indication of emesis or hypersalivation. Our inclusion of alcohol or drug use as potential covariates is based on the attending paramedics' impression, not laboratory testing, and also cannot differentiate between specific toxins (e.g., cocaine vs. methamphetamine vs. psychoactive substances). Our dose-response analysis was limited to only the first sedative administration, and additional sedation was classified simply as "yes" or "no." In reality, additional sedation could be with the same or other medications administered either IM or IV.

In summary, post-sedation cardiac arrest and other SAEs were rare among patients presenting to EMS with behavioral emergencies who received emergent prehospital sedation, regardless of the initial sedative agent. While SAEs and other AEs were statistically more frequent when ketamine was the first agent used for emergent sedation, the absolute differences were small and might represent residual confounding between patient acuity, sedative choice, and AEs. Patients initially sedated with ketamine were less likely to require additional sedation. No matter what sedative agent is used, prehospital clinicians should remain mindful of the potential risks associated with emergent sedation, monitor patients closely, and be prepared to intervene if necessary.

LHB, RPC, SSB and JBM conceived the study and all authors contributed to the refinement of the study question and the development of the methodology. LHB and RPC acquired and analyzed the data, which all other authors helped to interpret. LHB, RPC, MLM and BLW drafted the initial manuscript; all authors critically revised the manuscript for important intellectual content. RPC, ARF, SSB and JBM also provided administrative and technical support for the study. LHB and RPC had full access to all of the data in the study and take

responsibility for the integrity of the data and the accuracy of the analysis.

Data sharing

The 2019 ESO Research Dataset and supporting materials (e.g., data dictionary) are available from ESO Inc. through their established data request processes (email: research@eso.com). Requests for additional information can be directed to Dr. Crowe (email: remle.crowe@eso.com).

Declaration of interests

The authors declare no competing or conflicting financial interests. RPC, ARF, SSB and JBM are employed by ESO Inc., which provided the underlying data for this analysis. JBM receives ESO stock options as a component of his employment compensation package. JBM has also engaged in advocacy related to prehospital sedation on behalf of the National Association of EMS Physicians and the American College of Emergency Physicians.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2021.100183.

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