

The Hennepin Ketamine Study Investigators' Reply

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Abbreviations:

AMSS: Altered Mental Status Scale
ED: emergency department
EMS: Emergency Medical Services
EFIC: Exception from Informed Consent
FDA: Food and Drug Administration
IND: Investigational New Drug
IRB: Institutional Review Board
LAR: legally authorized representative
WIC: Waiver of Informed Consent

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We read with interest the recent editorial, “The Hennepin Ketamine Study,” by Dr. Samuel Stratton commenting on the research ethics, methodology, and the current public controversy surrounding this study.¹ As researchers and investigators of this study, we strongly agree that prospective clinical research in the prehospital environment is necessary to advance the science of Emergency Medical Services (EMS) and emergency medicine. We also agree that accomplishing this is challenging as the prehospital environment often encounters patient populations who cannot provide meaningful informed consent due to their emergent conditions. To ensure that fellow emergency medicine researchers understand the facts of our work so they may plan future studies, and to address some of the questions and concerns in Dr. Stratton's editorial, the lay press, and in social media,² we would like to call attention to some inaccuracies in Dr. Stratton's editorial, and to the lay media stories on which it appears to be based.

First, a brief overview of the study in question. This was a prospective, observational study of an EMS protocol change over a 12-month period regarding two medications commonly used for sedation within our EMS system: ketamine and midazolam. For the first six-month period, the EMS protocol recommended ketamine as a first line agent for sedation of agitated patients; for the second six-month period, midazolam was the recommended first line agent. There was no randomization. If a patient was deemed to need sedation based on the clinical judgment of the paramedic, the patient was given the medication per protocol. Importantly, no patients received medication for the sake of research; all sedatives were administered as part of usual clinical care. The only aspect of this work that was considered research was the careful observation of the effects of the sedative agents, and paramedic use of stopwatches to record the primary outcome (time to adequate sedation). We also recorded the frequency of adverse events.

Contrary to the *Forbes* report and Dr. Stratton's piece, our study was *not* approved under Exception from Informed Consent (EFIC; 21 CFR 50.24). Rather, the local Institutional Review Board (IRB) approved this study under Waiver of Informed Consent (WIC; 46 CFR 45.116). The two regulations are commonly confused. These regulations are similar in that they are both utilized in studies where informed consent is not possible, but are markedly different in their scope of practice and requirements. Our study was approved under WIC because it was deemed to be *minimal* risk by the IRB because it met all applicable criteria (shown in table).³ This study was deemed minimal risk because the only research interventions specifically related to the study were: (1) a stopwatch to measure time to adequate sedation; (2) the use of an agitation assessment scale (the Altered Mental Status Scale; AMSS);⁴ and (3) the use of a data collection form. Germane to the current study, research-related risks of these study types are typically limited to those of data collection and potential loss of confidentiality and do not usually include risks of the clinically-determined intervention. The US Food and Drug Administration (FDA; Silver Spring, Maryland USA) has provided guidance that “risks are not research-related when they are independent of the study and not associated with a trial intervention or protocol requirements.”⁵ To additionally protect their rights, safety, and welfare, patients were notified of their enrollment in the study and given a mechanism to have data removed from the database.

The EMS personnel, when encountering agitated patients, were explicitly instructed to use their clinical judgment to assess the need for sedation. The agitation scale (AMSS) was used so paramedics could describe the conditions during which normal sedation practices

took place in a standardized fashion; sedation was never mandatory for a given agitation score. While concern seems to exist that we may have lowered the threshold for sedation during the study periods, we explicitly instructed paramedics to use medication for sedation as they normally would. Internal EMS data support the notion that additional sedations did not take place during the study period. For example, in 2017, sedation for any behavioral disturbance occurred on 1.4% of EMS responses *outside* the study time period, and on 1.2% of EMS responses during the study time period.

Care for all patients in our EMS agency is dictated by our institutional EMS clinical treatment protocols, which by state statute are dictated by the EMS medical director.⁶ Both ketamine and midazolam have been standard treatments for agitation in our EMS system for many years (ketamine since 2008, midazolam since 2002), and analysis of our own peer-reviewed and published data suggests both drugs have similar risk profiles (including nearly identical intubation rates).⁷⁻⁹ As it was unclear if midazolam or ketamine was superior, changes in the first line recommendation, at the direction of the EMS medical director per state statute, were implemented so that each drug was the recommended first-line treatment for a six-month period, allowing for meaningful data collection to inform practice and improve care. During these periods, patients received the same medications whether data were collected for the study or not. This is not unlike any number of before/after EMS quality improvement projects,¹⁰ or recent groundbreaking work on intravenous fluid choices in the emergency department (ED).¹¹ At all times, both midazolam and ketamine were available for use on our ambulances, and per usual EMS standard operating procedures, if the paramedics' clinical judgment was such that midazolam or ketamine was superior for a patient, they were allowed to administer whichever drug they deemed optimal for the patient. Our data reflect this is what actually occurred: during the study in the "ketamine first-line" time period, paramedics opted for another drug in 49 patients; during the "midazolam first-line" time period, paramedics opted for another drug in 62 patients.

We recognize the vulnerable nature of our patient population, and we have taken great care to ensure we have protected the rights, safety, and welfare of our patients. Over the years, we have sought to determine the optimal way to address consent in the patient population at-risk for agitation. Previously, we attempted to use a validated capacity to consent tool¹² to determine if consent was even possible; however, when we studied this consent tool in 415 ED patients, only eight (1.9%) had meaningful capacity to consent in the setting of alcohol intoxication.¹³ We have also studied if a legally authorized representative (LAR) is commonly present to provide consent at the time prehospital sedatives are administered and found of 146 prehospital sedation encounters, in only nine cases (6.2%) was a LAR present at the scene.⁸ Lastly, we screened nearly 1,500 patients at-risk for agitation in the ED to "pre-consent" for another agitation study, and were unable to enroll a single patient using this mechanism in a trial of two treatments for agitation.¹⁴

Based on available literature and expert opinion, it seems clear that meaningful informed consent in patients who are agitated or altered is not possible.^{13,15,16} Furthermore, in the context of severe agitation, obtaining consent before sedative administration would be unethical and dangerous, as research would have been placed ahead of clinical care. Some argue against research at all in this context in order to protect this vulnerable population. However, if all prospective research examining this patient population was halted, our collective approach as a specialty would rely on anecdote

and retrospective chart reviews - both common sources of data that often produce inferior information.^{17,18} This would potentially result in poorer care delivered to these vulnerable patients. In fact, Dr. Stratton notes recent data suggest ketamine is gaining favor among EMS providers - this despite scant data to support its use.^{19,20}

The EFIC studies are utilized to examine research questions related to "life-threatening conditions" where treatments are "experimental or unproven" when study subjects are unable to give informed consent, provided that five conditions are met, including community consultation for opinion and concern and filing the intervention as an Investigational New Drug (IND) with the FDA.³ We have previously used EFIC to study acute agitation in the ED;²¹ however, the FDA has recently determined patients with acute agitation in the ED (or prehospital) may not meet criteria for EFIC and subsequently declined requests for an IND for a study of patient-level randomization for several common agents in the ED and for a prehospital study.^{8,22} In both of these instances, we conducted extensive community consultations with patients at high-risk for agitation (one of which was concurrent to the ketamine/midazolam study in question), which revealed substantial support for our work within our local community and the at-risk population. With local community and IRB support, we sought input from national experts on WIC and EFIC research and re-designed our studies as open-label observations of protocol changes.

The FDA has recognized that a gap exists in regulations regarding informed consent for patient populations that cannot provide consent, but are not experiencing a life-threatening condition. Although agitation can cause death when untreated,²³ the FDA has recently declared that there is not sufficient evidence that agitation is a life-threatening condition.²² In 2016, the 21st Century Cures Act was passed, giving the ability to the FDA to grant an EFIC for randomized trials where the trials pose no more than minimal risk, though the exact mechanism for this has not been delineated.¹⁵ In July 2017, the FDA issued IRB guidance stating that until these regulations are finalized, FDA does not plan on objecting to local IRBs approving WIC studies provided they document the interventions are both standard of care and the study poses minimal risk.²⁴ While this authority has only recently been explicitly granted, local IRBs have, occasionally, approved interventional randomized studies via WIC. In fact, *Prehospital and Disaster Medicine* published a randomized trial comparing haloperidol and midazolam for prehospital agitation in 2015 approved under WIC.^{25,26}

Due to the undeserved negative media coverage, we elected to cease study data collection. The study was not suspended by the institution in a disciplinary manner; rather, the investigators voluntarily paused data collection in a good-faith effort to maintain the public trust for the benefit of our institution, community, and patients. The same medications continue to be available to EMS personnel for treatment of prehospital agitation; however, the cessation of data collection precludes a detailed accounting of the efficacy and complications of each drug. Unfortunately, these facts were not correctly represented by the media, and this appears to have influenced Dr. Stratton's editorial in the same way it influenced public opinion. Such incorrect representations serve to inflame public opinion but do little to protect vulnerable subjects or advance clinical care.

Maintaining the public trust is of paramount importance when it comes to WIC and EFIC research. We have learned much from

our experience interacting with our community, the media, and colleagues in recent months. We are currently working to engage our community in all research more deeply than we have in the past. In the meantime, we hope that providing an accurate account of the

study's methodology and consent provides clarity for our colleagues and our community in order to allow informed debate on the best approach to performing research in this important and largely under-studied aspect of emergency patient care.

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