Minneapolis
City of Lakes

MPD Involvement in Pre-Hospital Sedation

July 26, 2018

CONTENTS

OPCR RESEARCH AND STUDY PROGRAM ORIGINS

In 2017, a change to Minneapolis ordinance 172.90 gave the Office of Police Conduct Review (OPCR) the authority to conduct a wider range of research and study projects. Per the ordinance revisions,

> Office of police conduct review staff shall have full, free and unrestricted access, to the extent authorized by law, to the records of the Minneapolis Police Department in order to conduct investigations of police misconduct; facilitate research and study projects for the police conduct oversight commission; and conduct special reviews and programmatic reviews at the request of the mayor, city council, internal auditor, city departments, or boards and commissions. [1]

In the fall of 2017, City of Minneapolis Internal Audit requested assistance from the OPCR to complete the first audit of Minneapolis Police Department Body Worn Cameras (BWC). Internal Audit sought assistance from OPCR due to staff's depth of knowledge on MPD policies and procedure. OPCR staff was primarily tasked with reviewing videos involving use of force by MPD officers.

While reviewing video, OPCR analysts observed multiple instances of the injection of an unknown substance by Emergency Medical Services (EMS) professionals to police detainees. In some instances, the individuals appeared to fall unconscious.

Officers involved in these incidents often physically restrained detainees to assist EMS professionals while the EMS professionals injected the individuals with the substance. In addition to reviewing videos, OPCR analysts reviewed corresponding police reports to fully complete the audit. In some police reports, MPD officers noted that the substance administered by EMS professionals was ketamine. OPCR had not seen the practice in action prior to the audit, due to receiving no complaints regarding this issue.

In the fall of 2017, it was unclear to OPCR analysts how the MPD was involved in calls that resulted in sedation or whether this was a common EMS practice. In the winter of 2017, OPCR processed a complaint involving an individual who, upon review, was injected with a substance in a manner similar to what OPCR analysts saw during the Internal Audit review process. An OPCR staff member who assisted in processing the complaint recognized the incident from the BWC audit and had observed the individual being injected on multiple occasions.

As a regular part of its complaint process, OPCR routinely searches for related MPD policies. In connection with the above referenced complaint, OPCR analysts found there was no corresponding policy regarding the use of sedatives in the Minneapolis Police Department (MPD) policy and procedure

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[1] 172.90. - Requirement of cooperation by the Minneapolis Police Department and all other city employees and officials.

Office of police conduct review staff shall have full, free and unrestricted access, to the extent authorized by law, to the records of the Minneapolis Police Department in order to conduct investigations of police misconduct; facilitate research and study projects for the police conduct oversight commission; and conduct special reviews and programmatic reviews at the request of the mayor, city council, internal auditor, city departments, or boards and commissions. The failure by any official or employee of the Minneapolis Police Department or by any other City of Minneapolis employee or official to comply with lawful requests for information or access shall be deemed an act of misconduct. (90-Or-043, § 1, 1-26-90; 2003-Or-028, § 10, 3-21-03; 2012-Or-061, § 11, 9-21-12; Ord. No. 2017-076 , § 2, 12-8-17)

manual. OPCR staff sought additional information in order to have full context of what they were investigating. Because Hennepin County paramedics were involved in the above incident, the Hennepin County Medical Center (HCMC) policy was requested in a data practices request and includes the following guidelines for the use of ketamine:

> If the patient is profoundly agitated with active physical violence to himself/herself or others evident, and usual chemical or physical restraints (section C) may not be appropriate or safely used, consider Ketamine 5 mg/kg IM (If IV already established, may give 2 mg/kg IV/IO).[2]

Per this policy, situations involving the administration of ketamine involve "active physical violence" where "physical restraints. . . may not be appropriate or safely used." As such, these situations could involve some form of physical force on vulnerable individuals who are experiencing a medical crisis. Subsequently, these individuals may receive a sedative and the circumstances surrounding MPD participation in these situations carries inherent risk.[3] Adequate policies or guidelines for conduct may help control risk when followed, such as the policies covering the use of mace, tasers, or maximal restraints. Effective controls also create a standard for accountability. In this situation, MPD had neither a policy relating to participation in sedation or restraining emotionally disturbed persons.[4] As such, OPCR analysts perceived a risk lacking any control process. [5] To recommend meaningful control processes, OPCR analysts believed the conduct creating the risk merited further analysis, and informed the OPCR director.

In early 2018, the Director of the Office of Police Conduct Review reviewed the incidents. The Director of OPCR informed the Director of Civil Rights, who also reviewed the incidents viewed by OPCR analysts. The Civil Rights Director then requested that OPCR conduct further study to produce a program audit that explores the use of ketamine in calls for service involving the Minneapolis Police Department that could be presented to city leadership.

The program audit would follow a similar process used by the Police Conduct Oversight Commission found in Appendix 7. Initial discussions and planning would define the scope of the work, research questions to be answered, and the method used to obtain interactions for analysis. This process would be reviewed by the OPCR Director. Cases would be collected following this method and reviewed using the predetermined set of questions.

Once all cases collected were reviewed, OPCR analysts would create a working draft to be presented to the Director of Civil Rights. OPCR analysts would also seek additional information from those involved in the interactions under review to provide context and a response to any unanswered questions. The working draft would be revised to include this feedback, and before any final report would be issued, all

[2] Hennepin County Medical Center Policy, Protocol 3420, p.1, BEHAVIORAL EMERGENCIES – ADULT

[3] Risk is defined broadly by the Institute for Internal Auditors as "the possibility of an event occurring that will have an impact on the achievement of objectives." The broad objectives of the research and study process listed in Minneapolis ordinance 172 include lawful, effective, and nondiscriminatory policing.

[4] As research continued, OPCR learned that subjects were intubated and complications with the administration of ketamine occur. This contributed to the ongoing analysis of the risk involved.

[5] Control processes are defined broadly by the Institute for Internal Auditors as policies, procedures, and activities "designed and operated to ensure risks are contained" to an acceptable level.

contributors would have an opportunity to review their responses, make corrections, and provide any final comments. The report would then be considered final and ready to provide to policymakers.

OPCR analysts attempted to follow this procedure. They located reports and body camera recordings, and began reviewing them using the established criteria. In February of 2018, before creating the working draft, the OPCR director and analysts informed the MPD administration that ketamine was being used on police detainees. During this conversation, the OPCR Director and analysts felt it was important to notify MPD administration that MPD officers suggested the use of ketamine in at least one instance. The corresponding body camera video was also reviewed.

Without a full picture of the instances under review, the OPCR could not appropriately comment on the extent of the potential risk. Between February and May of 2018, OPCR analysts continued to follow the preestablished process which involved reviewing 158 instances and hundreds of body camera recordings, constituting hundreds of hours of video. On April 2, 2018, the OPCR hired a full-time video analyst accelerating the ability of the OPCR to conduct the program review. By May 2018, OPCR staff felt that they had assessed the data they had available to them to discuss an initial assessment of the risks raised with the Civil Rights Director. After discussing the significance of its draft findings with the Civil Rights Director, a meeting was set with the Mayor's policy staff on May 16, 2018. The OPCR analysts continued to work on the draft report requested by the Director of Civil Rights. In the meantime, a meeting was set for May 23, 2018, with the Mayor's office and the City Attorney to discuss the initial draft report.

The MPD issued Administrative Announcement AA18-013 on May 18, 2018, directly addressing the issue of MPD participation in sedative use by EMS, namely that MPD should not suggest sedation to EMS personnel on the scene. Following the Administrative Announcement and the first working draft of the OPCR report, MPD added 7-350 Emergency Medical Response to the MPD Policy and Procedure Manual which clearly defines the role of MPD employees in medical emergency situations.[6]

After the Civil Rights Department met with the Mayor's office and City Attorney on May 23, 2018, OPCR staff continued to work on the draft report. City leadership then provided Hennepin county officials a copy of the first working draft. The Civil Rights Department was notified after dissemination that the Hennepin county officials had the report and wished to issue a response. Doctor Jeffrey Ho, Chief Medical Director of Hennepin EMS and Doctor Jon Cole, Medical Director of Minnesota Poison Control System, provided a response to the working draft of the report on June 13, 2018, noting that Hennepin County EMS was engaging in a study on the use of pre-hospital sedation involving ketamine during 2017-2018.[7] County representatives shared this information during the June 13, 2018, meeting that included several officials and attorneys from Hennepin County as well as the City Attorney, Chief of Police, and Deputy Chief of Professional Standards, and representatives from the Mayor's office. The county representatives also agreed to answer follow up questions from the OPCR while analysts revised the report.

Analysts began reviewing the materials provided by Hennepin county describing the use of ketamine and other sedatives as well as a summary of the research being conducted with the intention of

[6] See Appendix 1

[7] See Appendix 3 for information regarding the study *Ketamine Versus Midazolam for Prehospital Agitation*

incorporating it into the report. For context, the materials provided by the county are included in Appendix 2.

However, immediately following the receipt of these materials by OPCR analysts, the early working draft that prompted the response by Dr. Ho and Dr. Cole was released to media by unknown sources outside of the OPCR. OPCR anticipated further discussions, revisions to the report, and the ability to conduct independent analysis of the issues raised in the new materials. Per ordinance, OPCR is accustomed and directed to, "organize and administer programs of research and study to operate without interference or other influence that might adversely affect an independent and objective judgment of the analyst."[8]

Analysts did not have an opportunity to contact other emergency medical providers involved in pre-hospital sedation, and is unaware of whether they were provided a copy of the working draft. With the release of the report and subsequent statements, all parties have now taken clear positions in response to the early working draft and questioned the impartiality and independence of the work. Hence, it is no longer possible to finish an independent analysis of the issues involved.

The research that follows occurred prior to the release of the draft report and receipt of research materials from Hennepin County. Those materials are used in subsequent parts of this report to update definitions and information related to ketamine.

[8] See 172.80(g) Facilitation of research and study.

CAPRS AND CAMERA RECORDING ANALYSIS

To locate examples of MPD involvement in the administration of ketamine for this review, OPCR analysts queried police reports (CAPRS) for usages of the word "ketamine" between January 2010 and April 2018. Analysts read each report to determine whether ketamine was used on a police detainee. Analysts excluded cases that did not involve the Minneapolis Police Department. Incidents that did not involve the use of ketamine as a sedative were excluded, such as those where it was listed as a date rape drug.

Analysts retrieved all associated body camera recordings that corresponded with the police reports mentioned above, watched them in their entirety, and answered specific questions for each instance. This included watching BWC video from multiple officers that pertained to a single incident. Not all interactions were recorded prior to the body camera policy changes, and in some recorded instances, the camera did not capture the injection or decision to use ketamine.

The specific questions answered by watching recordings and retrieving reports were:

- Date and Time
- Location
- Computer Aided Dispatch (CAD) Problem
- Offense listed in report
- Whether body camera recordings captured the incident
- Whether the call was coded as emotionally disturbed person (EDP)
- Whether MPD discussed ketamine prior to the arrival of EMS
- Whether the decision to use ketamine was captured on video
- Whether MPD specifically called for ketamine
- Whether MPD assisted EMS when the ketamine injection occurred
- Whether the individual resisted either passively or actively
- Where the injection occurred (street, ambulance, hospital)
- Whether the individual was restrained and if so, how
- Whether the individual was a minor
- Whether the individual was reported to have used intoxicants prior to the injection[9]
- Demographic information

The sample was not collected to achieve an exhaustive review of each case in which ketamine, or any sedative, was used on a police detainee. It was collected to provide cases to analyze MPD's involvement in the administration of ketamine.

[9] In some instances, this was noted in police reports or body camera recordings

AGITATION AND KETAMINE

Authors of this program audit are not medical professionals and are not attempting to provide any opinion on medical courses of action in this report. This report does not evaluate whether ketamine (also known as ketalar) should be used on police detainees. It is, however, important to provide context about why ketamine is used, the effects of the drug, and specifically, any potential risks involved in its administration as provided in the cited texts.

Doctor Jeffrey Ho, Chief Medical Director of Hennepin EMS and Doctor Jon Cole, Medical Director of Minnesota Poison Control System, have published extensive work on the use of pre-hospital sedation, including the use of ketamine. In *A prospective study of ketamine as primary therapy for prehospital profound agitation*, they conclude that "ketamine provides rapid effective sedation when used as a primary therapy for prehospital profound agitation."[10] Dr. Ho and Dr. Cole state that the risk posed by profound agitation that would necessitate the use of ketamine is that an individual experiencing agitation will "continue their exertional behavior past usual fatigue and exhaustion" while restrained, leading to death from a condition known as "metabolic acidosis, a component of another life-threatening conduction, Excited Delirium Syndrome."[11]

Other sedatives may be used in treating an agitated patient.[12] Another study involving Dr. Cole and Dr. Ho compared ketamine and haloperidol in sedating agitated patients and notes that ketamine sedated patients 12 minutes faster than haloperidol.[13] They assert that "profound agitation requir[es] immediate sedation for the safety of the patient and their caregivers."[14]

In the work published by Dr. Cole and Dr. Ho, they also note complications with the use of ketamine. In the comparative study mentioned above, they note that 49% of patients receiving ketamine experienced complications versus 4% receiving haloperidol. In *A prospective study of ketamine as primary therapy for prehospital profound agitation*, they note that 57% of patients in the study received intubation after injection.[15]

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[10] This was an "IRB approved Waiver of Consent observational study of patients receiving ketamine for profound agitation (AMSS +4)." The AMSS scale can be found in Appendix 2 titled "Sedation Study AMS Scale." The study can be found at: https://www.ncbi.nlm.nih.gov/pubmed/29033344

[11] See Appendix 2, *Hennepin Health System Prehosptial Ketamine Information* and Appendix 4, *White Paper Report on Excited Delirium Syndrome*
But see *Ongoing issues with the diagnosis of excited delirium* for a discussion of the challenges related to excited delirium found at https://link.springer.com/article/10.1007/s12024-017-9904-3

[12] See Appendix 4, *White Paper Report on Excited Delirium Syndrome* Table 6.

[13] This study was a "Waiver of Consent prospective observational study of patients with severe acute undifferentiated agitation" with "severe agitation" defined as an "Altered Mental Status Scale (AMSS) score of +2 or +3." The AMSS scale can be found in Appendix 2 titled "Sedation Study AMS Scale." The study can be found at https://www.ncbi.nlm.nih.gov/pubmed/27102743

[14] See *A prospective study of ketamine as primary therapy for prehospital profound agitation* found at: https://www.ncbi.nlm.nih.gov/pubmed/29033344

[15] See *A prospective study of ketamine as primary therapy for prehospital profound agitation* found at: https://www.ncbi.nlm.nih.gov/pubmed/29033344
And *Letter to FDA and OHRP Regarding Prospective Clinical Trials Testing Ketamine for Agitation* found in Appendix 9.

Historically, ketamine has been used on animals and humans during surgery for sedation.[16] John's Hopkins Medical Health Library describes effects of ketamine use as follows:

> Shortly after taking ketamine, people may enter a dream-like state or have hallucinations. Some users feel like they're floating or pleasantly detached from their bodies. However, ketamine also can cause a terrifying sense of almost complete detachment that may feel like a near-death experience. This is referred to as the 'K-hole' and is similar to having a bad trip on LSD.[17]

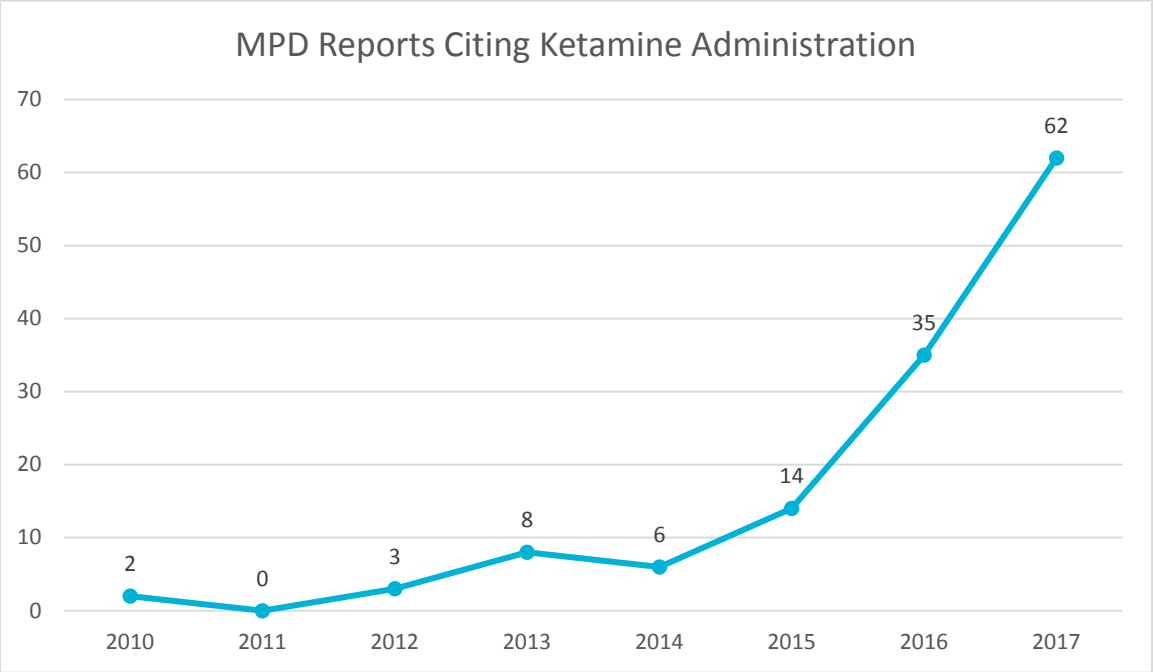
Prior to this report, MPD did not have a policy about sedatives or ketamine, but did classify ketamine among the "date rape drugs" in section 10-115.01 of the MPD policy and procedure manual.

The effects of ketamine typically last for about 30 to 60 minutes, but ketamine can continue to affect a user's coordination and judgment for up to 24 hours.[18] Ketamine may cause memory loss or amnesia.[19] An excess of ketamine or ketamine in combination with other drugs or alcohol may increase the chances of serious health problems.[20] Dr. Ho and Dr. Cole assert that ketamine does not "decrease respirations in the setting of alcohol intoxication."[21] Ketamine can also present risks to those on MAO inhibitors and for people with high blood pressure.[22] As noted in the work of Dr. Ho and Dr. Cole, ketamine use can necessitate mechanical intubation.[23]

[16] John's Hopkins Medical Health Library: https://www.hopkinsallchildrens.org/patients-families/health-library/healthdocnew/ketamine
[17] See footnote 16.
[18] See footnote 16.
[19] See footnote 16.
[20] See Appendix 2
[21] See footnote 16.
[22] University of Michigan Health Library: https://www.uofmhealth.org/health-library/d00272a1. MAO inhibitors include but are not limited to isocarboxazid, linezolid, methylene blue injection, phenelzine, rasagiline, selegiline, and tranylcypromine.
[23] *See A prospective study of ketamine as primary therapy for prehospital profound agitation* found at: https://www.ncbi.nlm.nih.gov/pubmed/29033344

RESULTS

The appearance of ketamine in reports increased from 2010 to 2018. [24] Prior to 2015, there were on average 4 mentions of ketamine use on detainees in police reports per year. In 2015, there were 14 clear instances of ketamine injections of police detainees cited in police reports. Usage of the term increased again in 2016, and in 2017, 62 instances were cited in reports.[25] From January 2018 through April 2018, there were 11 usages of ketamine mentioned in police reports, exceeding annual use between 2010-2014.



OPCR Analysts observed 8 cases between 2016 and 2018 where MPD officers participated in the decision to administer ketamine. Participation ranged from instances where officers asked EMS professionals for ketamine ("When EMS gets here, just tell them to bring the ketamine in") to instances where EMS professionals asked officers for their opinion about sedation (prior to ketamine administration, "You guys want us to give him something?"). These 8 instances occurred when either calling for EMS services or upon arrival of the ambulance. These instances were located through notations in CAPRS reports or through direct review of body camera recordings. Demographic information for cases from 2016-2017 can be found in Appendix 5.

[24] Analysts retrieved all associated body camera recordings, watched them in their entirety, and answered specific questions for each instance. All CAPRS reports between 2010 and 2018 were reviewed.
Analysts removed all cases in which it was unclear whether MPD was specifically involved in the instance as well as all cases in which it was unclear whether a detainee was injected with ketamine. OPCR analysts counted instances where multiple officers cited ketamine in a report as one instance.

[25] In 2016-2017, Dr. Ho and Dr. Cole note that there were 358 instances where ketamine was administered to patients. See Appendix 2, *Hennepin Health System Prehosptial Ketamine Information*

Of incidents that could be analyzed using body camera recordings or in police reports[26], MPD officers assisted EMS while they injected individuals with ketamine in 85% of cases (n=90). At no point did OPCR analysts observe MPD officers injecting or possessing ketamine. Typically, MPD assisted by holding the individual down or assisting in restraining the individual while EMS administered the injection. Individuals who were injected with ketamine were in handcuffs in 88% (n=95) of recordings reviewed, secured with hobbles in 15% (n=97) of the time, and restrained by EMS devices (typically stretchers with straps) in 43% of cases (n=97). Additionally, individuals had spit hoods placed on them in 33% (n=93) of cases. There are lingering questions regarding how much risk MPD, thus the City, is assuming by assisting in the injection of sedatives, regardless of whether MPD participates in decision-making.

[26] In some instances, the actions of MPD or EMS professionals could not be seen or were not discussed in reports. Those instances were excluded.

CASE STUDIES

To provide appropriate context for the data presented, OPCR analysts cultivated case studies to illustrate how ketamine is practically being used as well as exceptions to the common practice.

COMMON PRACTICE CASE

MPD responded to an emotionally disturbed person (EDP) call at a hotel in downtown Minneapolis. The individual was described in the police report as, "running in and out of traffic and had been throwing chairs around." When officers arrived on scene, the individual was being detained by hotel security, and was repeatedly shouting, "one, two, three! One, two, three!" The individual was quickly detained by several officers who pinned the individual to the ground until EMS arrived. The individual was given ketamine by EMS professionals and became unconscious several minutes later. The individual was then loaded onto a stretcher and into an ambulance for transport to Hennepin County Medical center.

EXCEPTIONS

The Office of Police Conduct Review also observed cases that differed from the common observed practice.

CASE 1

One MPD squad car with two officers respond to an emotionally disturbed person (EDP) call involving an individual threatening suicide. Upon officers entering the residence, the individual can be seen sleeping face down on a couch and is easily double-handcuffed with relatively little struggle. Upon arrival of EMS personnel, one of the officers makes an "injection" motion toward the individual, and laughs. The officer then radios that the call is nearly "code 4"[27] but to, "tell them [EMS] they're going to have to bring a shot in."

As the incident progresses, the individual begins telling officers to "taze me" and implying that officers will kill them, but is under physical control. Shortly before being taken to the ambulance, the individual says, "let me go!" to which the officer replies, "in about two seconds when they shove a needle in your ass. They'll give you a little ketamine." The individual is escorted by MPD from the home to a waiting stretcher, and strapped down. The individual is transported by ambulance to North Memorial Medical Center, and the ride lasts about 5 and a half minutes. Throughout, the individual is verbally combative with EMS and MPD, asking to be tazed and accusing officers of having killed a family member.

Once at the hospital, the individual is taken to a room. An officer then states, "[The individual] needs a locker [sic] room unless you're going to give [the individual] a shot, because [the individual] needs a shot right now." [redacted] The MPD officer asks, [redacted]? [redacted]' then when the individual again says, "taze me!" the officer says, "We don't have to[redacted]" The MPD officer continues to banter with the individual and medical personnel, saying, [redacted]? [redacted]?" and [redacted]? [redacted]?' [redacted]. Eventually,

[27] Code 4 indicates that the scene is stable.

[redacted] the officer states, [redacted]. That's what they said when we took that class. [redacted]."[28]

CASE 2

MPD responds to a seemingly intoxicated individual in downtown Minneapolis who had recently been maced by MPD, and is having an apparent asthma attack. Upon arrival, the individual states, "I need an asthma pump. I don't have my asthma pump and you sprayed me." MPD requests EMS to come to the scene, and handcuffs the individual without active resistance. [29] Throughout the video, it is possible to hear the individual's labored breathing. EMS then arrives and instructs the individual to breathe more slowly. The individual is then strapped onto a stretcher, re-handcuffed, and put into an ambulance without physically resisting or being combative with officers. Throughout the interaction, the individual continues to breathe heavily and occasionally yell for their sister. Shortly before body camera is deactivated, an EMS professional can be heard saying, "what does ketamine do to asthmatics?"

Body camera resumes in the Stabilization (STAB) Room[30] of HCMC for force review following the use of mace. One of the officers involved appears to be asked by an MPD supervisor why the individual was sedated, and a subsequent video records a conversation between the officer and paramedics. Per the police report, "They [EMS] administered 200 milligram [sic] of ketamine which was less than the normal amount they administered [sic] to patients and S1 immediately stopped breathing." This appears to be substantiated by the recording in which one EMS professional also states, "If [the individual] was having an asthma attack, giving ketamine actually helps patients and we're doing a study for agitation anyway so I had to give [the individual] ketamine."[31]

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[28] BWC video contains references to training conducted by unknown sources for MPD officers that apparently included content regarding ketamine. More information on these trainings is needed to fully understand MPD officers' approach to incidents involving ketamine such as the content and goals of training, the trainers' credentials, funding sources, and who attended, among other information.

[29] Minneapolis Police and Procedure Manual, 5-302 Use of Force defines these two types of resistance by a detainee as justifications for use of force:

Active Aggression: Behavior initiated by a subject that may or may not be in response to police efforts to bring the person into custody or control. A subject engages in active aggression when presenting behaviors that constitute an assault or the circumstances reasonably indicate that an assault or injury to any person is likely to occur at any moment. (10/01/10) (04/16/12)

Active Resistance: A response to police efforts to bring a person into custody or control for detainment or arrest. A subject engages in active resistance when engaging in physical actions (or verbal behavior reflecting an intention) to make it more difficult for officers to achieve actual physical control

[30] See https://stabroom.com/what-is-the-stab-room/

[31] The video containing this statement was first reviewed in Mid-May of 2018. Thus far in the program review, the question to be answered concerned whether Minneapolis police officers were conducting themselves appropriately when detained persons were injected with a sedative, and if not, what should be done about it. When this statement was heard, it raised an additional question of whether a medical study involving the injection of a sedative was being conducted in Minneapolis on Minneapolis residents with the assistance of City of Minneapolis employees and whether policymakers knew of the study.

CASE 3

In one calendar year, ketamine was used on one individual in at least four separate incidents that stemmed from alleged obstruction of justice to jaywalking. In this instance, the individual can be seen engaged in a conversation with Metro Transit Police when MPD officers walking their beat enter the scene. The presence of MPD officers appears to irritate the individual, who becomes increasingly antagonistic towards officers by calling them names and questioning the efficacy of their policing. As the incident progresses, multiple officers surround the individual and a sergeant intervenes, asserting that the individual is bothering citizens and using foul language. The individual does use foul language over the course of the incident. Numerous random individuals can be seen cheering the individual on as they pass by the scene, shouting, "Black Lives Matter!" and even hugging the individual.

After a final warning to cease using profanity, the individual uses profanity one additional time and is restrained by multiple MPD officers. The individual actively resists arrest and scratches one of the officers before being handcuffed, hobbled, fitted with a spit hood, strapped down to a stretcher and loaded into an ambulance. The individual was punched in the face by an officer but exhibited no clear signs of injury. Inside the ambulance, the individual is extremely loud, objecting both to his arrest and the force being exerted by MPD officers. An EMS professional says, "are you gonna draw it [ketamine] up" and the individual objects. An MPD officer assisting EMS professionals inside the ambulance by restraining the individual refers to ketamine as, "the good stuff."

When the individual does not fall unconscious, giving the individual more ketamine is discussed. The individual again objects saying, "don't give me anything." An MPD officer states to the individual, "what's going on, buddy? This is happening too much with you." A subsequent conversation between MPD and EMS takes place as follows:

"[MPD] Last time it took I think two doses"
"[EMS] Oh, you've had [the individual] before?"
"[MPD]Yeah, [the individual] ran a couple nights—week and a half ago, I think?"
"[EMS] [Unintelligible] and some of this other stuff that's floating around? It's taking a ton of this stuff to drop [the individual]."

CASE 4

Four MPD officers and two Hennepin County EMS professionals respond to an EDP call in which [redacted] contacted 911 due to concern that the individual was experiencing a mental crisis. Upon arrival, the individual appears to be extremely confused, continually asking why they had to go, and saying that they did not want to go when told it was time to go to the hospital. Per MPD policy, this constitutes passive resistance as he is verbally refusing to comply with commands.[32]

[32] Minneapolis Police and Procedure Manual, 5-302 Use of Force definitions: Passive Resistance: A response to police efforts to bring a person into custody or control for detainment or arrest. This is behavior initiated by a subject, when the subject does not comply with verbal or physical control efforts, yet the subject does not attempt to defeat an officer's control efforts. (10/01/10) (04/16/12)

After a considerable amount of time negotiating and trying to help the individual put on shoes and pants, MPD officers handcuff the individual. It should be noted that the individual is of small stature. MPD and EMS make the decision that the individual will be taken to the hospital, and an MPD officer can be heard saying, "do you want to just sedate him?"

An EMS professional tells the individual that they will be given medication to, "calm [the individual] down," at which point they see the needle and object, "whoa, whoa, that's not cool! I don't need that! I don't need no shot!" Despite the individual's objections, the individual is given a ketamine injection. At this point, a stair chair is retrieved to assist officers and EMS professionals in transporting the individual to the ambulance.[33] The individual is placed into and strapped down on the stair chair. The individual is not sitting still in the chair. EMS professionals then call for "more meds [ketamine]" and the individual is given a second injection. Shortly after the injection, the individual becomes largely nonverbal, making only unintelligible sounds, to the extent that an MPD officer notes, "he just hit the K-hole."

After leaving the residence and reaching the main stairs of the apartment building, transport efforts temporarily cease. The individual is restrained and appears to be calm. At this point, the decision is made to give the individual a third dose of ketamine:

"[EMS 1] Hey, [EMS 2] how much more ketamine you got on ya?"
"[EMS 2][laughs] I can go draw more."
"[EMS 1] You're my favorite."
"[EMS 2] We can do Versed[34]. We've maxed out the ketamine dosage, for [the individual's] size."
"[EMS 1] We'll do more ketamine."
"[EMS 2] How much?"
"[EMS 1] Do another 100[mg]"
"[EMS 2] OK."
"[MPD] We'd better get the air stuff ready because—"
"[EMS 1] That is what's going to happen."
"[MPD] We'll have to end up putting a [breathing] tube in."
"[EMS 1] It's my fault for saying we don't need the bed [?]. I'm the senior medic. You can put that when you make your complaint."

[33] A stair chair is a device used to transport patients in a sitting position in spaces such as a staircase either up or down or in any other spaces that may be difficult for some patients to navigate.
[34] Versed is a brand name for midazolam and is used to produce sleepiness or drowsiness and to relieve anxiety before surgery or certain procedures. See https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0011217/?report=details

CONCLUSIONS AND RECOMMENDATIONS

1. The lack of policy covering interactions between EMS professionals and MPD officers in instances of sedation creates a risk that officers will participate in decision-making. As such, MPD shall create a policy covering appropriate actions with EMS professionals and requirements for writing reports and reporting to a supervisor when assisting EMS professionals.

COMPLETED: See MPD Policy 7-350 EMERGENCY MEDICAL RESPONSE

2. After a new policy is created, officers should be provided guidance for its implementation. MPD officers should receive training regarding appropriate interactions with EMS professionals.

3. No definition of "emotionally disturbed person" is found in the Policy and Procedure manual nor are there policies for what to do when encountering an emotionally disturbed individual. MPD should explore additions to the Policy and Procedure Manual regarding interactions with emotionally disturbed persons.

4. As medical research involving police detainees may prove controversial, MPD should establish a protocol with Hennepin County surrounding any potential future involvement in medical research.

5. Further, City leadership should explore options for notification of medical research involving constituents and visitors.

6. The OPCR reviewed how officers interacted with EMS professionals in cases leading to sedation. City leadership should request answers to any remaining questions about the use of ketamine outside the scope of this report.

7. The dissemination of the draft report to parties outside of the City hampered the ability of the OPCR to conduct its work. OPCR will establish control processes to prevent unauthorized dissemination of reports.

COMPLETED: See Appendix 6 OPCR Research and Study Controls

APPENDIX 1: 7-350 EMERGENCY MEDICAL RESPONSE

MINNEAPOLIS POLICE DEPARTMENT

SPECIAL ORDER

BY ORDER OF THE CHIEF OF POLICE

DATE ISSUED:	DATE EFFECTIVE:	NUMBER:	PAGE:
June 15, 2018	June 18, 2018	SO18-013	1 of 2
TO: Distribution "A"			RETENTION DATE: Until Rescinded
SUBJECT: **Manual Revision – 7-350 Emergency Medical Response**			APPROVED BY: *Chief Arradondo*

MP-8806

Introduction: This policy is being added to clearly define the role of MPD employees in medical emergency situations. It also replaces language previously included in 5-106 and 7-311.01 regarding medical emergencies.

Effective with the issuance of this Special Order, Section 7-350 of the MPD Policy and Procedure Manual shall be amended as follows:

7-350 EMERGENCY MEDICAL RESPONSE (06/15/18)

I. PURPOSE

The purpose of this policy is to lay out the roles and responsibilities of MPD employees in MPD incidents involving a medical emergency.

II. POLICY

A. MPD employees shall request emergency medical services (EMS) as soon as practical if any employee has come into contact with an individual having an acute medical crisis and any delay in treatment could potentially aggravate the severity of the medical crisis, or as otherwise required by policy.

1. While awaiting EMS, MPD employees assisting an individual having an acute medical crisis shall provide any necessary first aid consistent with MPD training, as soon as practical.

2. Naloxone (NARCAN) shall be administered only in accordance P&P 7-348.

B. MPD employees assisting individuals who are not in an acute medical crisis but may need medical attention shall offer EMS response, and shall document the offer and answer in a report, or if no report will be made via added remarks in CAD.

C. MPD employees shall not make any suggestions or requests regarding medical courses of action to be taken by any medical personnel. Determinations made by medical personnel regarding medical courses of action must be clearly made by medical personnel.

1. MPD employees shall provide medical personnel with any necessary information related to the subject's observed or known conditions and behaviors, so the medical personnel can conduct a quick and accurate assessment and determine the best medical course of action.

2. MPD employees shall provide medical personnel the names of any MPD employees who provided first aid or assisted with a person's care, so that notifications can be made to involved officers of possible exposure to any pathogens discovered through further medical examination.

D. MPD employees responding to incidents where EMS has already been requested shall not cancel EMS unless the employees determine that the call was unfounded or the subject is no longer at the scene. *[Moved from 7-311.01]*

E. MPD employees shall document in a report any assistance provided to medical personnel regarding the medical crisis, including actions taken by the employees, the effects of those actions on the subject, and the outcome of the situation. Any physical control applied by MPD personnel should be reported in accordance with the P&P 5-306 Use of Force- Reporting and Post-Incident Requirements.

F. Arrest or detention of individuals receiving treatment under this policy shall also be in accordance P&P 9-108 (Arrest or Detention of Injured Adults).

APPENDIX 2: HCMC Materials

Hennepin Health System Prehospital Ketamine Information May 30, 2018

Jeffrey Ho, MD, Chief Medical Director, Hennepin EMS

Jon Cole, MD, Medical Director, Minnesota Poison Control System

*Ketamine (generic name) or Ketalar (brand name) is a medication used primarily in the prehospital environment for dissociative sedation and control of pain. Hennepin EMS (HEMS) has been using ketamine since 2008 and has led the nation in studying ketamine in this environment as well as developing safe standards for use. We (Drs. Cole, Ho and other Hennepin Health System (HHS) physicians) have been leaders in publishing scientific work about safe patient sedation (including ketamine) for more than 2 decades.[1,2,3,4,5,6,7,8,9] Use in the prehospital environment has been driven by the experience of us and other HHS emergency physicians who have been using ketamine as a sedative in the emergency department since the mid-1990s.

*Ketamine is used by other EMS services in the US. A survey of 14,739 paramedics showed 33% have access to it.[10]

*Ketamine is used in many other areas of medicine such as for adjunctive pain control and procedural sedation.

*The need for prehospital sedation is based upon the early work by HHS physicians that demonstrated when agitated people in public who are being restrained are left to continue their exertional behavior past usual fatigue and exhaustion, they are at high risk for sudden death due to a life-threatening condition known as metabolic acidosis, a component of another life-threatening condition, Excited Delirium Syndrome.[11] This condition has been verified by prospective study.[12] It has also been recognized as a life-threatening syndrome by the American Academy of Emergency Medicine and the American College of Emergency Physicians.[13]

*Treatment of acidosis is a time sensitive emergency. Average onset of action for ketamine is 4 minutes versus Versed/midazolam (10 minutes) or Haldol/haloperidol (17 minutes) which are also available to HEMS.

*Ketamine effect lasts 30-90 minutes (midazolam 60-120 min, haloperidol 300-600 min) allowing earlier hospital evaluation by emergency physicians.

*Ketamine has a side effect profile that can make it better for prehospital sedation. Midazolam is known to decrease respirations in the setting of alcohol intoxication – preliminary data suggest ketamine does not. Ketamine time of onset is faster than midazolam and haloperidol, and it can be administered without an IV minimizing danger of occupational injury to the responders.

*Our ketamine work has been recognized as leading edge and has received national and international awards.[14,15] We stand by our research on this topic and its conclusions.

*HEMS uses ketamine as a treatment for agitation in situations where an agitated patient is at risk of or has already injured themselves or others when it reasonably is concluded by a qualified HEMS paramedic that other options are not going to be optimal. Reaching this conclusion takes into account the paramedic's perspective, experience, training, urgency of the situation, and special situational factors such as underlying medical conditions, size and abilities of the patient, size and abilities of the paramedic, etc.

*HEMS has completed studies on prehospital use of ketamine, and is now engaged in a follow-up study that began in 2017. All studies involving HEMS or HHS adhere to strict, institutional review board requirements including patient safety review, conflict of interest review, and waiver of informed consent (45 CFR 46.116). Dr. Cole is the principal investigator of the current study and the study has received full approval by the HHS institutional review board that is governed by the Minneapolis Medical Research Foundation.

*Though well-intentioned, the "Ketamine" draft report from the City of Minneapolis is a reckless use of anecdotes, partial snapshots of interactions with police, and incomplete information and statistics to draw uninformed and incorrect conclusions. This draft report prevents progress we are making to understand and improve the use of sedation to manage patient agitation and in some cases, this draft report will prevent the saving of lives by promoting the concept of allowing people to exhaust themselves to death.

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[7] Olives TD, Nystrom PC, Cole JB, Dodd KW and JD Ho. Intubation of Profoundly Agitated Patients Treated with Prehospital Ketamine. Prehosp Disaster Med, 2016;6:593-602.

[8] Cole JB, Klein LR, Nystrom PC, Moore JC, Driver BE, Fryza BJ, Harrington J, Ho JD. A prospective study of ketamine as primary therapy for prehospital profound agitation. Am J Emerg Med. 2018 May;36(5):789-796.

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[11] Hick JL, Smith SW and MT Lynch. Metabolic Acidosis in Restraint-Associated Cardiac Arrest: A Case Series. Acad Emerg Med, 1999;6:239-243.

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[14] Reference 6 was awarded the Best Platform Research Presentation at the 2015 North American Congress of Clinical Toxicology in San Francisco, CA

[15] Reference 8 was named a top research paper of 2017 at the 2018 Congress of the European Association of Poison Centres and Clinical Toxicology in Bucharest, Romania

Hennepin EMS
Statistics on Behavioral Emergencies

- Data based on calls for symptoms consistent with a behavioral emergency
- 2014-2016 data based on legacy charting software and field mapping may not exactly match charting software from 2017 to current.
- Sedation Study
  - Ketamine only arm: 8/1/17 – 1/31/28
  - Versed only arm: 2/1/18 – current
- Ketamine shortage nationwide beginning early Spring 2018

Search Criteria

2014-2016

- Agitated
- Hallucination
- Hostile
- Irritable
- Suicidal
- Violent

2017-Current

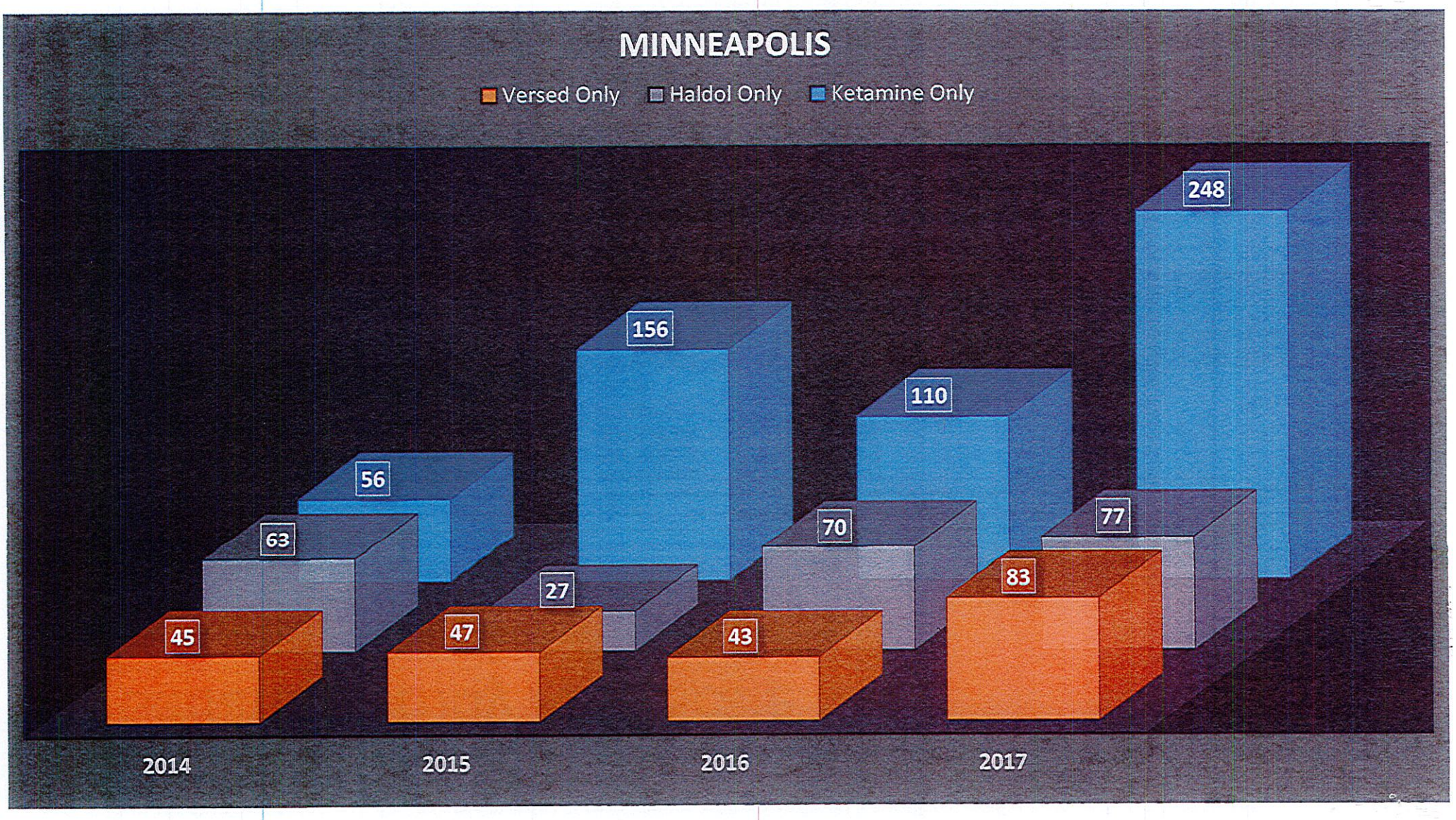
- Combative or Violent Behavior
- Hallucinations Auditory
- Hallucinations Visual
- Homicidal Ideations
- Irritability and Anger
- Restlessness and Agitation
- Suicidal Ideations
- Visual Disturbances

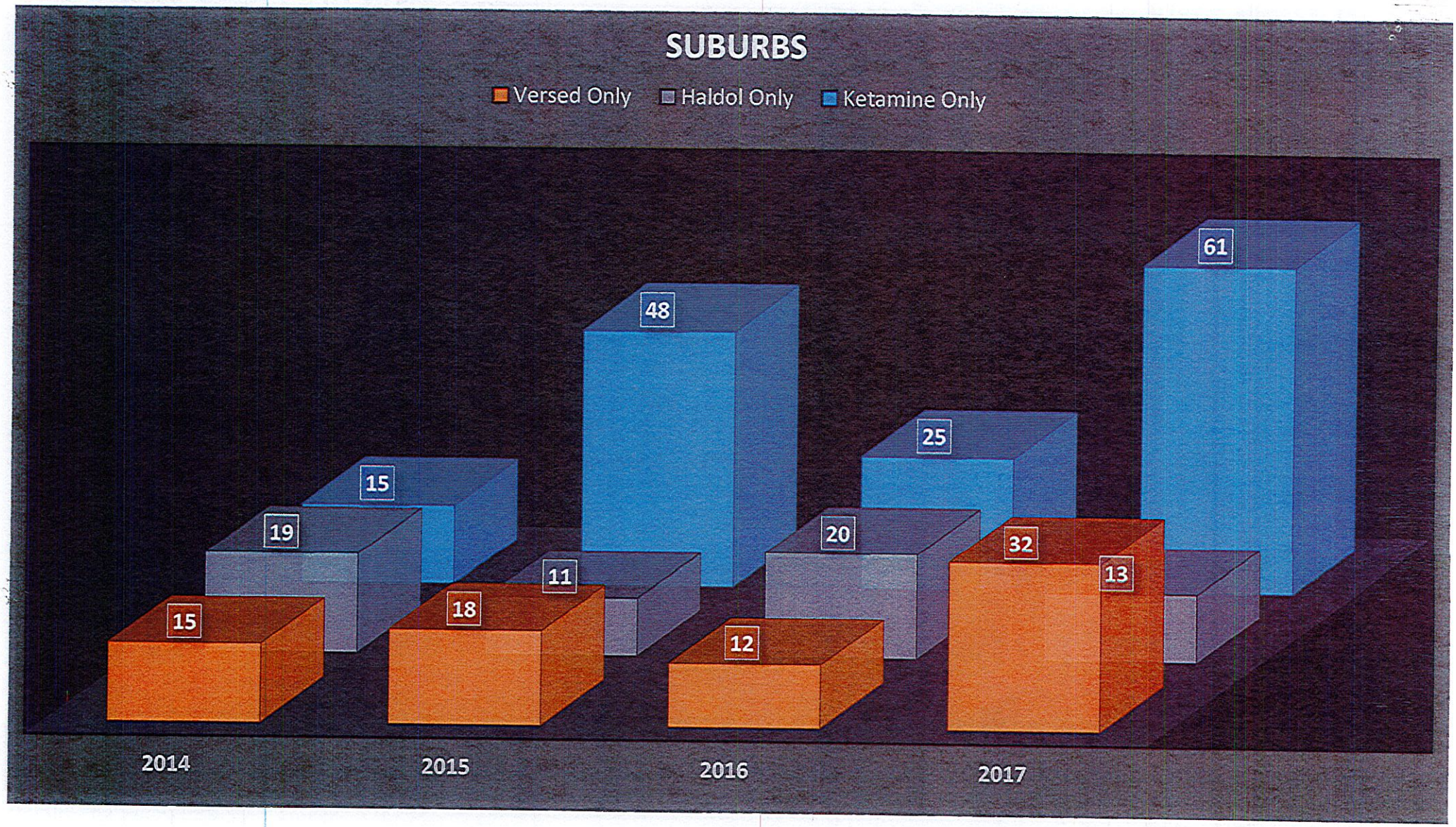
Sedation Study AMS Scale

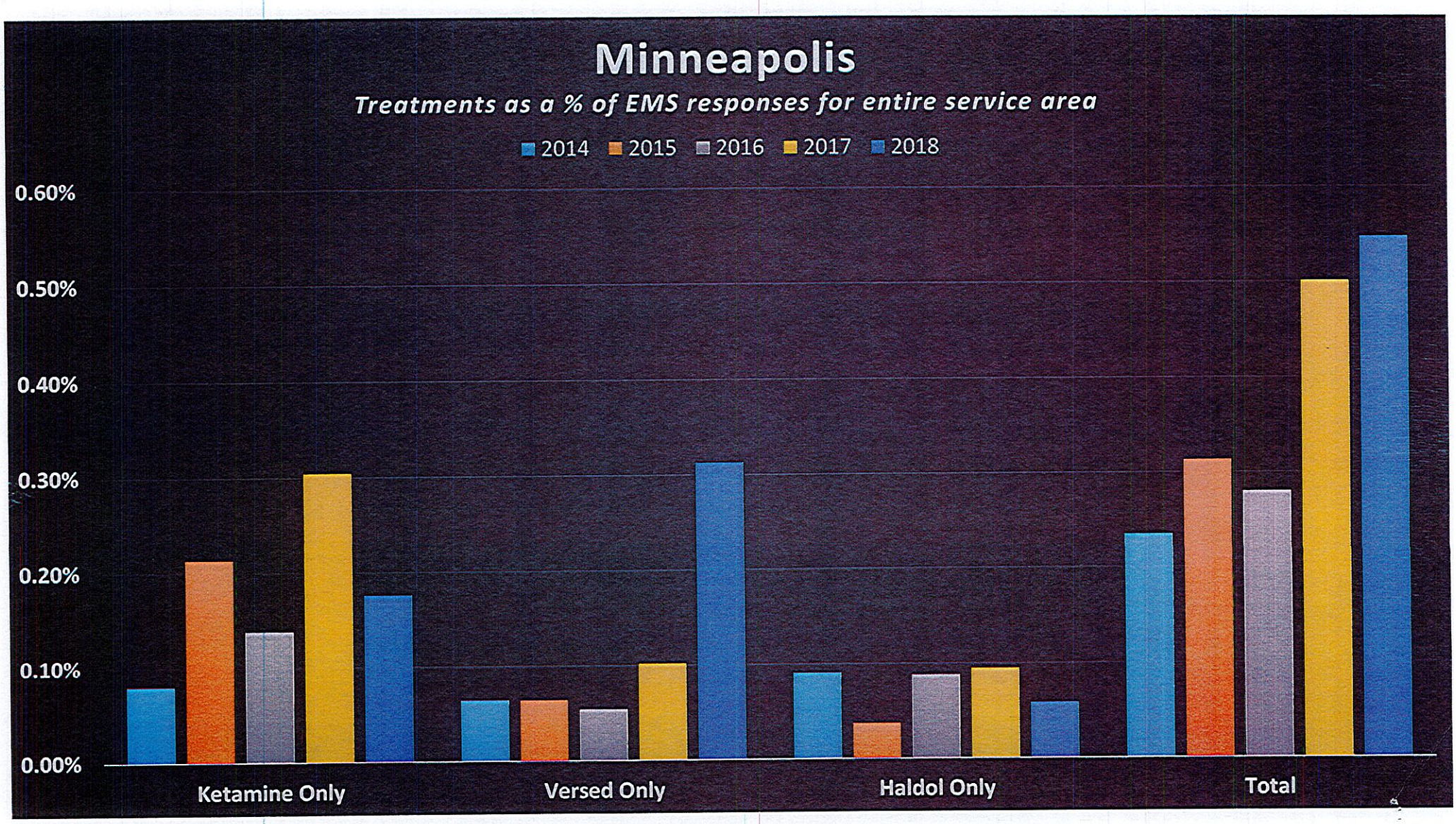
The Altered Mental Status Scale.

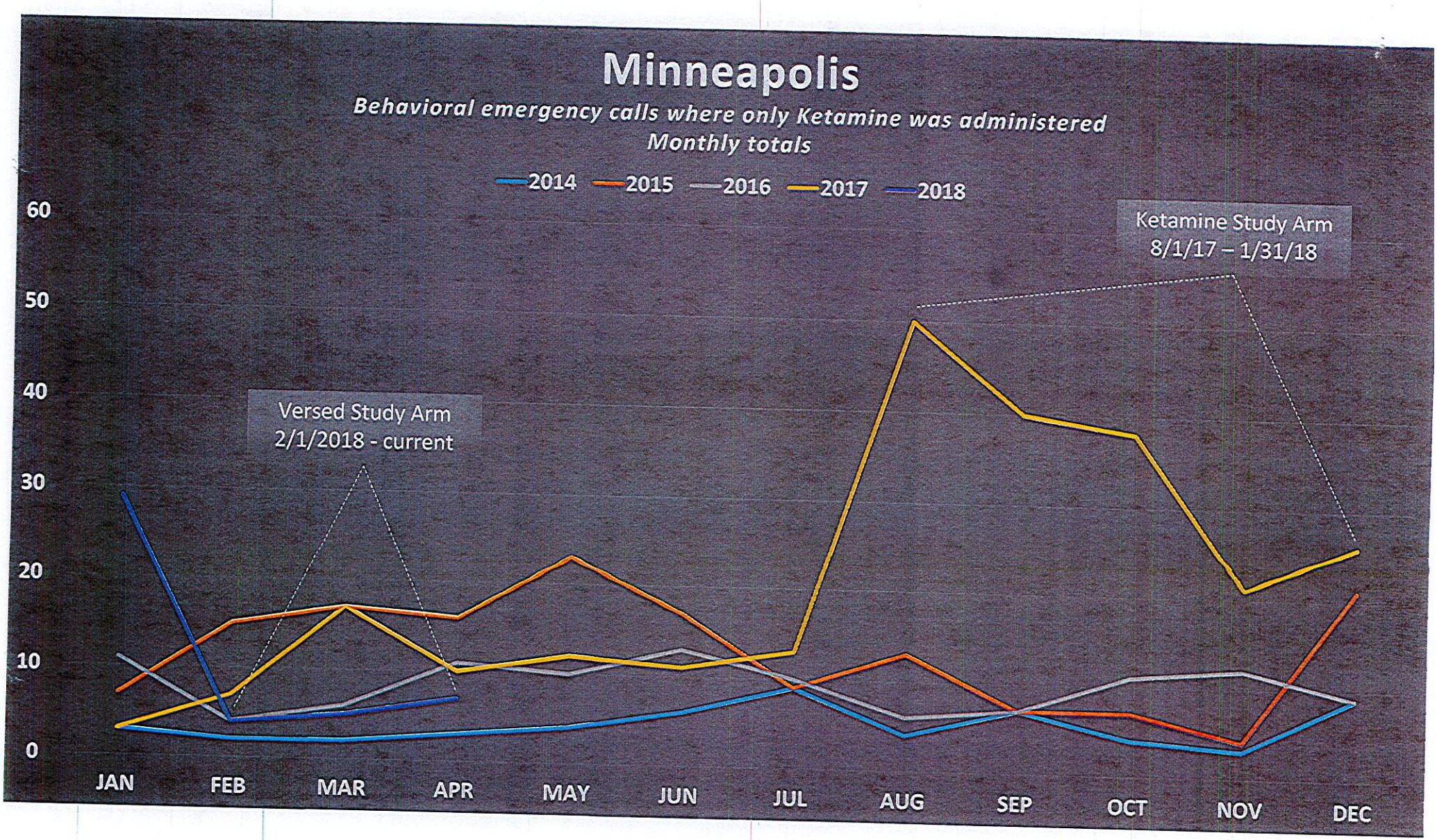
Score	Responsiveness	Speech	Facial expression	Eyes
+4	Combative, very violent, or out of control	Loud outbursts	Agitated	Normal
+3	Very anxious, agitated, mild physical element of violence	Loud outbursts	Agitated	Normal
+2	Anxious, agitated	Loud outbursts	Normal	Normal
+1	Anxious, restless	Normal	Normal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

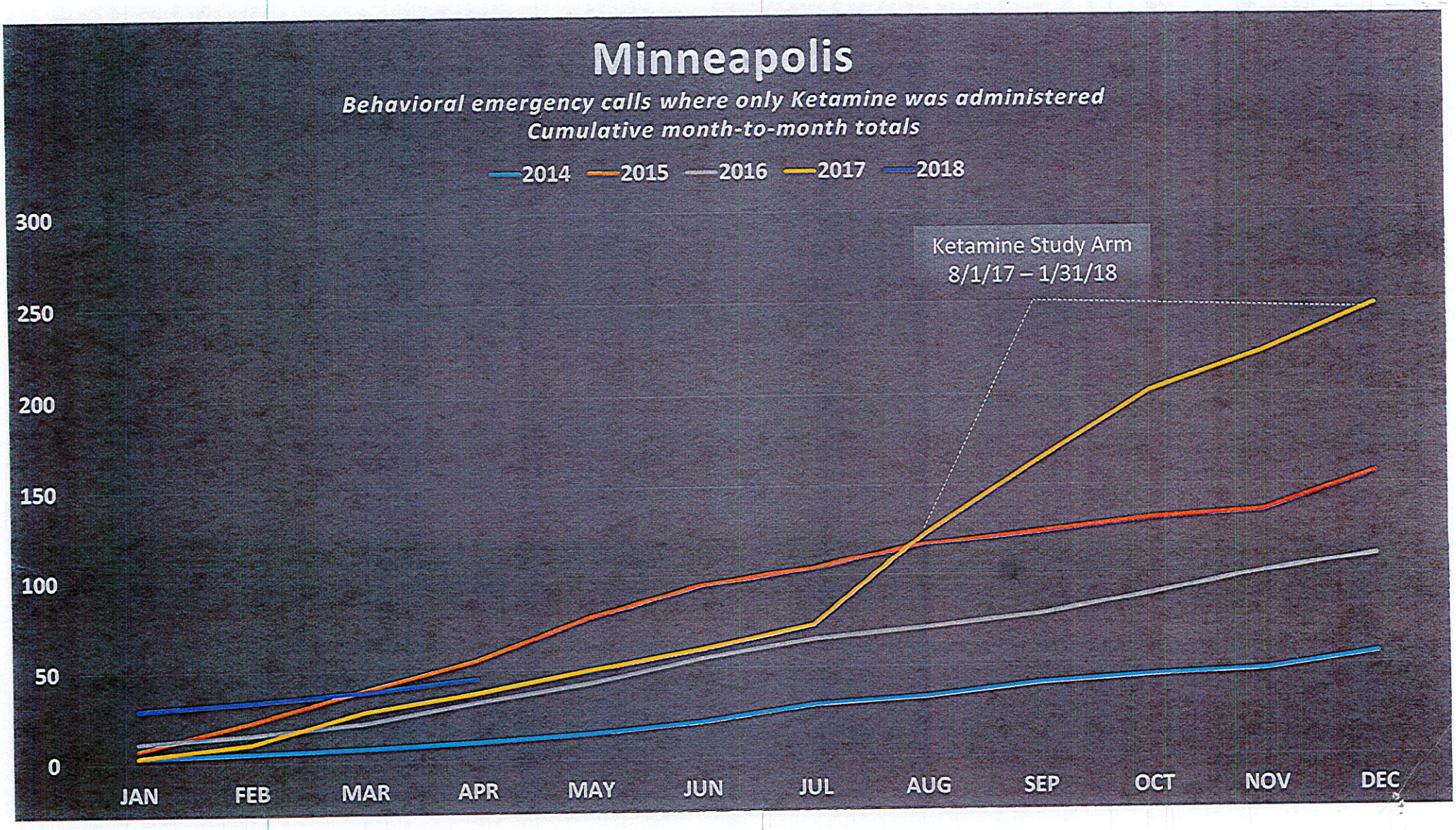
Cole JB, Klein LR, Nystrom PC, Moore JC, Driver BE, Fryza BJ, Harrington J, Ho JD. A prospective study of ketamine as primary therapy for prehospital profound agitation. Am J Emerg Med. 2018 May;36(5):789-796.


MINNEAPOLIS
Versed Only
Haldol Only
Ketamine Only
45
63
56
47
27
156
43
70
110
83
77
248
2014
2015
2016
2017


SUBURBS
Versed Only
Haldol Only
Ketamine Only
15
19
15
18
11
48
12
20
25
32
13
61
2014
2015
2016
2017


Minneapolis
Treatments as a % of EMS responses for entire service area
2014
2015
2016
2017
2018
0.60%
0.50%
0.40%
0.30%
0.20%
0.10%
0.00%
Ketamine Only
Versed Only
Haldol Only
Total


Minneapolis
Behavioral emergency calls where only Ketamine was administered
Monthly totals
2014
2015
2016
2017
2018
60
50
40
30
20
10
0
Ketamine Study Arm
8/1/17 – 1/31/18
Versed Study Arm
2/1/2018 - current
JAN
FEB
MAR
APR
MAY
JUN
JUL
AUG
SEP
OCT
NOV
DEC


Minneapolis
Behavioral emergency calls where only Ketamine was administered
Cumulative month-to-month totals
2014
2015
2016
2017
2018
Ketamine Study Arm
8/1/17 – 1/31/18
300
250
200
150
100
50
0
JAN
FEB
MAR
APR
MAY
JUN
JUL
AUG
SEP
OCT
NOV
DEC

APPENDIX 3: Ketamine Versus Midazolam for Prehospital Agitation Study Information

Ketamine Versus Midazolam for Prehospital Agitation

ClinicalTrials.gov Identifier: NCT03554915

Recruitment Status: Recruiting
First Posted: June 13, 2018
Last Update Posted: June 13, 2018

See **Contacts and Locations**

Sponsor:
Minneapolis Medical Research Foundation

Information provided by (Responsible Party):
Minneapolis Medical Research Foundation

Study Description

Go to

Brief Summary:
This research study is being done to figure out the best approach to treatment of pre-hospital agitation. It will compare two tiered dosing treatment protocols, one ketamine-based and one midazolam-based. Agitation is a state of extreme emotional disturbance where patients can become physically aggressive or violent, endangering themselves and those who are caring for them. Often chemical substances or severe mental illness are involved in this level of agitation. Specifically, the investigators are interested in studying agitation

that is treated in the prehospital setting by paramedics. This study's hypothesis is a ketamine-based protocol will achieve a faster time to adequate sedation than a midazolam-based protocol for treatment of agitation in the prehospital environment. This study will observe the natural history of an emergency medical services standard operating procedure change from a ketamine-based protocol to a midazolam-based protocol.

Condition or disease	Intervention/treatment	Phase
Agitation	Other: Ketamine-based protocol Other: Midazolam-based protocol	Phase 4

Study Design

Go to

Study Type:	Interventional (Clinical Trial)
Estimated Enrollment:	420 participants
Allocation:	Non-Randomized
Intervention Model:	Sequential Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Ketamine Versus Midazolam for Prehospital Agitation
Actual Study Start Date:	August 1, 2017
Estimated Primary Completion Date:	August 31, 2018
Estimated Study Completion Date:	August 31, 2018

Resource links provided by the National Library of Medicine

Drug Information available for: Ketamine Midazolam Midazolam maleate Midazolam hydrochloride

U.S. FDA Resources

Arms and Interventions

Go to

Arm	Intervention/treatment
Active Comparator: Ketamine-based Protocol The first 6 month period of the study will employ a ketamine-based protocol for prehospital agitation. There will be a tiered	Other: Ketamine-based protocol For profoundly agitated (physically violent) patients, intramuscular ketamine 5 mg/kg will be administered first line. For severely agitated

dosing protocol based on degree of agitation.	patients, intramuscular ketamine 3 mg/kg will be administered first line.
Active Comparator: Midazolam-based Protocol The second 6 month period of the study will employ a midazolam-based protocol for prehospital agitation. There will again be a tiered dosing protocol based on degree of agitation.	Other: Midazolam-based protocol For profoundly agitated patients, intramuscular midazolam 15 mg will be administered. For severely agitated patients, intramuscular midazolam 5 mg will be administered.

Outcome Measures

Go to

Primary Outcome Measures :

1. Time from injection of drug to adequate sedation, defined as a score of +1 or less on the AMSS [Time Frame: 2 hours]

   The Altered Mental Status Scale (AMSS) is an integral ordinal scale evaluating both agitation and sedation with scores from -4 to +4. It was developed at our institution and has been internally and externally validated. This scale is a modified version of the Behavioral Activity Rating Scale with additional data points from the Observer's Assessment of Alertness Scale. Effectiveness of sedation will be defined as an AMSS score less than or equal to +1.

   AMSS will be determined by the treating paramedic, who will undergo training as a research associate prior to commencement of the study. Participants will be followed for the duration of agitation, an expected average of 2 hours.

Secondary Outcome Measures :

1. Number of participants intubated [Time Frame: 2 hours]

   Participants will be followed for the duration of agitation, an expected average of 2 hours. Enrolling paramedics or research associates in the Emergency Department will record if the patient is intubated.

2. Number of participants experiencing hypersalivation [Time Frame: 2 hours]

   Participants will be followed for the duration of agitation, an expected average of 2 hours. Enrolling paramedics or research associates in the Emergency Department will record if the patient experiences hypersalivation.

3. Number of participants experiencing apnea [Time Frame: 2 hours]

   Participants will be followed for the duration of agitation, an expected average of 2 hours. Enrolling paramedics or research associates in the Emergency Department will record if the patient experiences apnea, defined as 6 seconds of absent EtCO2 waveform.

4. Number of participants experiencing nausea/vomiting [Time Frame: 2 hours]

   Participants will be followed for the duration of agitation, an expected average of 2 hours. Enrolling paramedics or research associates in the Emergency Department will record if the patient experiences nausea/vomiting

5. Number of participants experiencing laryngospasm [Time Frame: 2 hours]

   Participants will be followed for the duration of agitation, an expected average of 2 hours. Enrolling paramedics or research associates in the Emergency Department will record if laryngospasm occurs.

6. Number of participants needing rescue sedation [Time Frame: 2 hours]

   Participants will be followed for the duration of agitation, an expected average of 2 hours. Enrolling paramedics or research associates in the Emergency Department will record if additional sedatives are needed in the prehospital or ED environment.

Eligibility Criteria

Go to

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Age 18 or older
- Severe agitation (AMSS +2 or +3) or profound agitation (AMSS +4) requiring chemical sedation
- Transport to Hennepin County Medical Center

Exclusion Criteria:

- Obviously gravid women
- Patients known or suspected to be less than 18 years of age
- Patients in which stopwatch activation, for safety reasons, is unable to occur

Contacts and Locations

Go to

Information from the National Library of Medicine NIH NLM

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT03554915***

Contacts

Contact: Jon B Cole, MD 612.873.6000 jon.cole@hcmed.org

Locations

United States, Minnesota

Hennepin County Medical Center **Recruiting**
Minneapolis, **Minnesota**, **United States**, 55415
Contact: Jon B Cole, MD 612-873-6000 jon.cole@hcmed.org

Sponsors and Collaborators

Minneapolis Medical Research Foundation

More Information

Go to

Publications:

Cole JB, Klein LR, Nystrom PC, Moore JC, Driver BE, Fryza BJ, Harrington J, Ho JD. A prospective study of ketamine as primary therapy for prehospital profound agitation. Am J Emerg Med. 2018 May;36(5):789-796. doi: 10.1016/j.ajem.2017.10.022. Epub 2017 Oct 7.

Olives TD, Nystrom PC, Cole JB, Dodd KW, Ho JD. Intubation of Profoundly Agitated Patients Treated with Prehospital Ketamine. Prehosp Disaster Med. 2016 Dec;31(6):593-602. Epub 2016 Sep 19.

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Signs and Symptoms
Ketamine
Midazolam
Analgesics
Sensory System Agents
Peripheral Nervous System Agents
Physiological Effects of Drugs
Anesthetics, Dissociative
Anesthetics, Intravenous
Anesthetics, General
Anesthetics
Central Nervous System Depressants
Excitatory Amino Acid Antagonists
Excitatory Amino Acid Agents
Neurotransmitter Agents
Molecular Mechanisms of Pharmacological Action
Adjuvants, Anesthesia
Hypnotics and Sedatives
Anti-Anxiety Agents
Tranquilizing Agents
Psychotropic Drugs
GABA Modulators
GABA Agents

APPENDIX 4: White Paper Report on Excited Delirium Syndrome

White Paper Report on Excited Delirium Syndrome

ACEP Excited Delirium Task Force

September 10, 2009

Report to the Council and Board of Directors on Excited Delirium at the Direction of Amended Resolution 21(08)

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American College of Emergency Physicians®
ADVANCING EMERGENCY CARE

Excited Delirium Task Force
White Paper Report to the Council and Board of Directors
September 10, 2009

PREAMBLE

The 2008 Council of the American College of Emergency Physicians (ACEP) adopted Amended Resolution 21(08), "Excited Delirium," which was then adopted by the ACEP Board of Directors:

"RESOLVED, that ACEP study:

1. The existence of "excited delirium" as a disease entity (or not);
2. Characteristics that help identify the presentation and risk for death; and
3. Current and emerging methods of control and treatment.

And be it further RESOLVED,
That ACEP develop and disseminate a white paper on findings to appropriate entities (e.g., EMS, law enforcement)."

INTRODUCTION

In response to this resolution, ACEP convened a Task Force of nineteen experts in what the Task Force has chosen to call Excited Delirium Syndrome (ExDS). Eighteen of these experts are emergency physician members of ACEP and one is a PhD researcher. The Task Force was charged to examine the available literature and existing data and use their expert experience and consensus to determine:

1. if the entity commonly referred to as "excited delirium" exists, and
2. if so, whether it could be better defined, identified, and treated.

It is the consensus of the Task Force that ExDS is a unique syndrome which may be identified by the presence of a distinctive group of clinical and behavioral characteristics that can be recognized in the pre-mortem state. ExDS, while potentially fatal, may be amenable to early therapeutic intervention in some cases.

The term "Excited Delirium" has been used to refer to a subcategory of delirium that has primarily been described retrospectively in the medical examiner literature. Over time, the concept of excited delirium has made its way into the emergency medicine, psychiatric, law enforcement, prehospital and medicolegal literature. It has generally been used to describe a small group of patients with a set of symptoms that has eluded a unifying, prospective clinical definition. The Task Force debated the merits of renaming the syndrome in a medically more descriptive way. However, it was decided that the literature and general understanding in the health care and law enforcement fields of the term "Excited Delirium" favored retention of the traditionally understood word for research and clinical purposes. It was incorporated into the described syndrome as "Excited Delirium Syndrome (ExDS)."

The difficulty surrounding the clinical identification of ExDS is that the spectrum of behaviors and signs overlap with many clinical disease processes. ExDS is not intended to include these diseases, except insofar as they might meet the definition of ExDS. Treatment interventions targeted at one of these alternate diagnoses may potentially alleviate or exacerbate ExDS, thus further confounding the diagnosis. Faced with the lack of a clear definition and cause, the decision to identify ExDS as a syndrome instead of a unique disease is similar to the dec-

ades-long controversy over the causes of Sudden Infant Death Syndrome.

Despite increased research, the exact pathophysiology of ExDS remains unidentified. Some recent research in the area of fatal ExDS points to dopamine transporter abnormalities. Eventually, there might be found a genetic susceptibility, an enzyme excess or deficiency, an overdose or withdrawal state, or some other multifactorial trigger, including a variety of medical and psychiatric conditions.

At present, physicians and other medical and non-medical personnel involved in personal interactions with these patients do not have a definitive diagnostic "test" for ExDS. It must be identified by its clinical features. This also makes it is very difficult to ascertain the true incidence of ExDS.

While not universally fatal, it is clear that a proportion of patients with ExDS progress to cardiac arrest and death. It is impossible at present to know how many patients receive a therapeutic intervention that stops the terminal progression of this syndrome. While many of the current deaths from ExDS are likely not preventable, there may be an unidentified subset in whom death could be averted with early directed therapeutic intervention.

In this paper, the Task Force provides a review of the history and epidemiology of ExDS, clinical perspectives, and a discussion of its potential pathophysiology, diagnostic characteristics, differential diagnoses, and clinical treatment. Ultimately, the goals are to raise awareness of the existence of this syndrome to medical and public entities, to aid law enforcement, Emergency Medical Service (EMS) personnel, physicians, health care providers, corrections officers and others in the recognition of ExDS, and to identify best practices to deal with this true medical emergency.

HISTORY

For more than 150 years, there have been case reports that do not use the exact term "excited delirium," yet describe a similar constellation of symptoms and features. These cases discuss clinical behavior and outcomes that are strikingly similar to the modern day concept of ExDS.

These historical cases occurred primarily within institutions that housed mentally disturbed individuals in protective custody largely because of the lack of effective pharmacologic treatment available during that time period. The behavior seen in these cases has been called "Bell's Mania," named after Dr. Luther Bell, the primary psychiatrist at the McLane Asylum for the Insane in Massachusetts. Dr. Bell was the first to describe a clinical condition that took the lives of over 75% of those suffering from it. Based on the clinical features and outcomes of the institutionalized cases from the 1800s when compared to the presently accepted criteria known to accompany ExDS, it is believed that Bell's Mania may be related to the syndrome of ExDS that we witness today.

Historical research indicates that the worrisome behaviors and deaths following uncontrolled psychiatric illness described in the 1800s seemed to decline drastically by the mid-1950s. This is largely attributed to the advent of modern antipsychotic pharmaceutical therapy that changed psychiatric practice from one of custodial patient control to a goal of de-institutionalization and patient placement within normal community settings.

There is only one reference before 1985 known to mention the exact term "Excited Delirium." In this reference, the words "excited" and "delirium" were combined to describe the condition of a patient just prior to death following a hemorrhoid operation by an accomplished surgeon. At the time, it was felt that the operation somehow damaged the patient's nervous system, and lead to acute psychiatric decompensation and death.

In the 1980s, there was a dramatic increase in the number of reported cases with behavior similar to an uncontrolled psychiatric emergency. While some seemed to be unchecked psychiatric disease, most of these cases were found to be associated with the introduction and abuse of cocaine in North America. Since then, this connection between ExDS and co-

caine has continued. Additionally, ExDS has now been recognized to occur in association with other illicit drugs of abuse, as well as with certain types of mental illness and their associated treatment medications.

Before 1985, there was no single unifying term to describe the clinical pattern seen in these patients. In 1985 a subset of cocaine deaths was described by Wetli and Fishbain in a seminal paper which for the first time used the term "excited delirium."

The typical course of a published ExDS patient involves acute drug intoxication, often a history of mental illness (especially those conditions involving paranoia), a struggle with law enforcement, physical or noxious chemical control measures or electrical control device (ECD) application, sudden and unexpected death, and an autopsy which fails to reveal a definite cause of death from trauma or natural disease.

As a consequence of the circumstances surrounding the death and the lack of a definitive cause on autopsy, there has been continued debate about the validity of the term "excited delirium." This debate continues today. There are those who believe it to be a convenient term used to excuse and exonerate authorities when someone dies while in their custody. It is articulated by some that ExDS is a term or concept that has been "manufactured" as a law enforcement conspiracy or cover-up for brutality.

This argument mainly centers on the fact that most organized medical associations (e.g., American Medical Association) and medical coding reference materials (e.g., International Classification of Diseases, Ninth Revision, or ICD-9) do not recognize the exact term "excited delirium" or "excited delirium syndrome." The countering argument is that there are organized medical associations that do recognize ExDS as an entity (e.g., National Association of Medical Examiners) and references such as the ICD-9 contain several codes that can be used to describe the same entity as ExDS, albeit with different wording such as:

- 296.00S Manic Excitement
- 293.1J Delirium of Mixed Origin
- 292.81Q Delirium, drug induced
- 292.81R Delirium, induced by drug
- 307.9AD Agitation
- 780.09E Delirium
- 799.2AM Psychomotor Excitement
- 799.2V Psychomotor Agitation
- 799.2X Abnormal Excitement

This issue of semantics does not indicate that ExDS does not exist, but it does mean that this exact and specific terminology may not yet be accepted within some organizations or references.

EPIDEMIOLOGY

The exact incidence of ExDS is impossible to determine as there is no current standardized case definition to identify ExDS. In addition, since ExDS is mainly discussed in the forensic literature and is a diagnosis of exclusion established on autopsy, there is little documentation about survivors of the syndrome. A published observational study suggests that the incidence of death among patients manifesting signs and symptoms consistent with ExDS is 8.3%. Some Task Force members have cared for multiple individual patients with ExDS who have survived.

Stimulant drug use, including cocaine, methamphetamine, and PCP, demonstrates a well established association with ExDS and is usually associated with cases of ExDS death.

A review of the literature reveals common characteristics among patients identified post-mortem as suffering from ExDS. More than 95% of all published fatal cases are males with a mean age of 36. These subjects are hyperaggressive with bizarre behavior, and are impervious to pain, combative, hyperthermic and tachycardic. There is typically a struggle with law enforcement that involves physical, noxious chemical, or ECD use followed by a period of quiet and sudden death. The majority of

cases involve stimulant abuse, most commonly cocaine, though methamphetamine, PCP, and LSD have also been described. At least in the setting of cocaine use, the episode of ExDS usually appears to occur in the context of a cocaine binge that follows a long history of cocaine abuse.

Persons with psychiatric illnesses comprise the second largest but a distinctly smaller cohort of ExDS cases and deaths. The literature on ExDS frequently cites abrupt cessation of psychotherapeutic medications as a cause. This raises the question of whether the behavioral changes seen in this context represent withdrawal syndromes characteristic of the medications involved, central nervous system adaptations to medications, or recrudescence of underlying disease. Since medication noncompliance is common in psychiatric patients, health care providers should be aware of this potential cause of delirium-like behavior. Less commonly, persons with new-onset psychiatric disease (mania or psychosis) will present with ExDS. In most cases, the underlying disease will be untreated at the time of presentation, but in some cases the disease may be partially treated or mistreated.

Over a two-year period, presence or absence of 10 potential clinical features of ExDS was recorded by Canadian police for over 1 million police-public interactions (C. Hall, personal communication).

Of the 698 encounters involving use of force, 24 probable cases were identified, based upon the presence of perceived abnormal behavior and at least 6 of 10 potential clinical criteria for ExDS. These represent 3.4% (or 2-5%) of the use of force cohort. For the individuals manifesting 7 or more features including tactile hyperthermia, **Table 1** lists the occurrence of all 10 potential features with their frequencies and 95% confidence intervals. (Note that the oft-reported mirror or glass attraction is rather infrequent). These represent 2.7% (or 1-3.5%) of the use of force cohort, a not inconsequential number given the potential for sudden unexpected death.

Although no deaths occurred in this collection period, the 97.5% one sided confidence interval for the absence of death still implies that up to 14% of these individuals could experience sudden death, a number in line with the previously mentioned and published observational study.

Table 1: ExDS Prehospital Potential Features and Frequencies with 95% Confidence Intervals

FEATURE	FREQUENCY % (95% CI)
Pain Tolerance	100 (83-100)
Tachypnea	100 (83-100)
Sweating	95 (75-100)
Agitation	95 (75-100)
Tactile Hyperthermia	95 (75-100)
Police Noncompliance	90 (68-99)
Lack of Tiring	90 (68-90)
Unusual Strength	90 (68-90
Inappropriately Clothed	70 (45-88)
Mirror/Glass Attraction	10

PATHOPHYSIOLOGY

The pathophysiology of ExDS is complex and poorly understood. The fundamental manifestation is delirium. There are several different potential underlying associations or causes, including stimulant drug abuse, psychiatric disease, psychiatric drug withdrawal, and metabolic disorders. Unknown mechanisms lead from these conditions to the overt ExDS state. Specific manifestations vary among different cases. We do not fully understand why some cases progress to death and why some do not.

Although our knowledge concerning the etiology and pathophysiology of ExDS is limited, basic science and clinical studies have provided some insight. Stimulant drug use, especially cocaine, is associated with ExDS. Of note, post-mortem toxicological analysis of fatal cocaine-associated ExDS patients demonstrates cocaine concentrations similar to those found in recreational drug users and less

than those noted in acute cocaine intoxication deaths, suggesting a different mechanism of death.

Subsequent anatomic and molecular characterization of this group of fatal ExDS patients has focused primarily on postmortem brain examination. Results from this increasingly robust body of work demonstrate a characteristic loss of the dopamine transporter in the striatum of chronic cocaine abusers who die in police custody from apparent ExDS. This suggests that one potential pathway for the development of ExDS is excessive dopamine stimulation in the striatum, but the significance of this in the larger context of ExDS unrelated to chronic cocaine abuse remains unknown.

Making a central dopamine hypothesis more appealing is the fact that hypothalamic dopamine receptors are responsible for thermoregulation. Disturbances of dopamine neurotransmission may help explain the profound hyperthermia noted in many ExDS patients. Post-mortem studies in these patients have demonstrated elevated levels of heat shock proteins (HSP). The central dopamine hypothesis also provides a link to psychiatric etiologies of ExDS.

While the specific precipitants of fatal ExDS remain unclear, epidemiologic and clinical reports provide some understanding of the underlying pathophysiology. When available, cardiac rhythm analysis demonstrates bradyasystole; ventricular dysrhythmias are rare, occurring in only a single patient in one study. The majority of lethal ExDS patients die shortly after a violent struggle. Severe acidosis appears to play a prominent role in lethal ExDS-associated cardiovascular collapse.

While attention has focused largely upon cases of fatal ExDS in humans, it must be noted that a similar syndrome, termed capture myopathy, has been reported in the veterinary literature. Clinically, it is characterized by prolonged neuromuscular activity, acidosis, and rhabdomyolysis.

CLINICAL PERSPECTIVES

Law Enforcement

In modern times, a law enforcement officer (LEO) is often present with a person suffering from ExDS because the situation at hand has degenerated to such a degree that someone has deemed it necessary to contact a person of authority to deal with it. LEOs are in the difficult and sometimes impossible position of having to recognize this as a medical emergency, attempting to control an irrational and physically resistive person, and minding the safety of all involved.

Given the irrational and potentially violent, dangerous, and lethal behavior of an ExDS subject, any LEO interaction with a person in this situation risks significant injury or death to either the LEO or the ExDS subject who has a potentially lethal medical syndrome. This already challenging situation has the potential for intense public scrutiny coupled with the expectation of a perfect outcome. Anything less creates a situation of potential public outrage. Unfortunately, this dangerous medical situation makes perfect outcomes difficult in many circumstances.

It is important for LEOs to recognize that ExDS subjects are persons with an acute, potentially life-threatening medical condition. LEOs must also be aware that remorse, normal fear and understanding of surroundings, and rational thoughts for safety are absent in such subjects.

ExDS subjects are known to be irrational, often violent and relatively impervious to pain. Unfortunately, almost everything taught to LEOs about control of subjects relies on a suspect to either be rational, appropriate, or to comply with painful stimuli. Tools and tactics available to LEOs (such as pepper spray, impact batons, joint lock maneuvers, punches and kicks, and ECD's, especially when used for pain compliance) that are traditionally effective in controlling resisting subjects, are likely to be less effective on ExDS subjects.

When methods such as pain compliance maneuvers or tools of force fail, the LEO is left with few op-

tions. It is not feasible for them to wait for the ExDS subject to calm down, as this may take hours in a potentially medically unstable situation fraught with scene safety concerns.

Some of the goals of LEOs in these situations should be to 1) recognize possible ExDS, contain the subject, and call for EMS; 2) take the subject into custody quickly, safely, and efficiently if necessary; and 3) then immediately turn the care of the subject over to EMS personnel when they arrive for treatment and transport to definitive medical care.

LEOs should be trained to recognize and manage subjects with ExDS. Officers should attempt to ensure that the tactile temperature of these subjects is documented and request EMS to measure it. In fatal cases, a significantly elevated temperature may suggest that a life-threatening disease or condition was present, and that the death was independent of the police intervention.

Emergency Medical Services

EMS dispatch personnel need to recognize clues from calls or radio traffic that personnel may be responding to a case of ExDS. This should trigger multiple law enforcement personnel responding in addition to EMS.

EMS personnel need to be trained in the recognition of the signs and symptoms of ExDS. They are in a difficult position because they need to recognize the heightened personal safety risks that ExDS subjects represent to them but they also have a duty to provide timely care. They need to understand and practice their expected interaction with LEOs.

It is the role of LEOs to control the person with potential ExDS. However, as soon as control has been obtained, it is the role of EMS to recognize that this is a medical emergency and to assume responsibility for assessment and care of the patient.

Emergency Department (ED)

Emergency Physicians (EP's) should be educated about the clinical features of ExDS and should include this in the differential diagnosis of any patient with altered mental status and agitation (either at the time of presentation or by history). There should be an increased index of suspicion for ExDS in agitated patients that present in the custody of law enforcement; however, this is a clinical entity that can enter the ED from any source (EMS, Law Enforcement, ED triage, etc).

EP's should recognize that this syndrome seems to be a multifactorial interaction of delirium and agitation, leading to hyperthermia and profound acidemia, often in the setting of stimulant drug abuse. Regardless of etiology, ExDS may be fatal in some patients. EP's should consider the possibility of ExDS in the evaluation of younger patients that present in cardiac arrest, especially in the setting of profound metabolic acidosis and hyperthermia. The physician should also initiate the documentation of clinical signs and the collection of specimens for research and diagnosis.

Medical Examiners

Medical Examiners are often required to render a decision as to the cause of death in cases that involve patients in police custody with multiple confounding variables such as pre-existing health conditions, concomitant illicit substance use, and underlying psychiatric conditions. Lack of complete prior medical information, especially underlying cardiac and metabolic pathology, hampers the ascertainment of the actual cause of death when only autopsy results are interpreted.

For example, an unknown case of Brugada syndrome (a genetic abnormality of sodium ion channels leading to sudden death from ventricular fibrillation) may be the actual cause of cardiac arrest in an individual under the influence of cocaine, even absent excessive LEO force. Without prior electrocardiograms, this condition would be entirely missed. Likewise, premortem potassium and glucose levels, and even basic vital signs (temperature and blood pressure) cannot possibly be investigated via autopsy.

The importance of a skilled investigation of the

scene of death cannot be overestimated. Crucial information such as subject behavior, drug use history, a history or presence of psychosis, or the presence of hyperthermia, can facilitate the determination of whether the clinical features of ExDS were present.

The time, quantity, and chronicity of drug ingestion cannot always be reliably determined by toxicology alone. Significant postmortem redistribution of drugs makes interpretation of blood levels found at autopsy fraught with speculation. Tolerance to many drugs of abuse can confound interpretation of blood or tissue levels. Specific drug levels may not correlate with acute drug toxicity or poisoning. While the majority of cases of ExDS appear to occur in the presence of or with a history of cocaine or other stimulants, their presence is not required for this syndrome to occur. Psychiatric cases not involving drugs of abuse have been reported. There is no current gold standard test for the diagnosis of ExDS. The presence of the hallmark clinical findings along with the presence of some type of centrally acting stimulant strongly suggests the diagnosis. Current understanding of pathophysiology suggests that the collection of various specimens (particularly brain tissue in fatal cases) is beneficial both for potential diagnosis confirmation and research.

CLINICAL CHARACTERISTICS

Because ExDS resulting in death does not currently have a known specific etiology or a consistent single anatomic feature, it can only be described by its epidemiology, commonly described clinical presentation, and usual course. The minimum features for ExDS to be considered include the presence of both delirium and an excited or agitated state. As described in the DSM-IV-R, the features of delirium are constant and defined by a disturbance of consciousness (reduced clarity of the awareness of the environment) with reduced ability to focus, sustain or shift attention. The perceptual disturbance develops over a short period of time (usually hours to days), may fluctuate during the course of a day, and is not accounted for by underlying dementia.

Because of varied underlying medical conditions that may generate ExDS, there is also variation in the specific symptom cluster. As in any disorder that affects mental status, there is no assumption that each subject's presentation will occur as a completely discrete entity with absolute boundaries. The consistency lies with subjects who are delirious with evidence of psychomotor and physiologic excitation.

The combination of delirium, psychomotor agitation, and physiologic excitation differentiates ExDS from other processes that induce delirium only. Similarly, subjects who are agitated or violent but who do not also demonstrate features of delirium simply do not meet the definition of ExDS.

Until wider recognition of ExDS began, most publications about it were found in the forensic pathology literature and there was little publication interest in cases of ExDS that did not end catastrophically. The high reported frequency of death is likely increased by measurement and reporting bias since pathologists who first identified the unifying prodrome of ExDS that leads to sudden unexpected death necessarily encountered only those subjects who died. At least one author (a forensic pathologist) describes the combination of a prodrome of excited delirium plus unanticipated sudden death as "excited delirium syndrome," with invocation of the term syndrome only if the subject died.

When death occurs, it occurs suddenly, typically following physical control measures (physical, noxious chemical, or electrical), and there is no clear anatomic cause of death at autopsy. In cases in which a subject dies following the application of control measures, many or most of the following features are found:

- male subjects, average age 36
- destructive or bizarre behavior generating calls to police,
- suspected or known psychostimulant drug or alcohol intoxication,
- suspected or known psychiatric illness,
- nudity or inappropriate clothing for the environment,

- failure to recognize or respond to police presence at the scene (reflecting delirium),
- erratic or violent behavior,
- unusual physical strength and stamina,
- ongoing struggle despite futility,
- cardiopulmonary collapse immediately following a struggle or very shortly after quiescence,
- inability to be resuscitated at the scene, and
- inability for a pathologist to determine a specific organic cause of death,
- attraction to glass or reflective surfaces (less frequent than all others per the Canadian data).

Subjects are incoherent and combative, and the struggle is more severe than anyone anticipates. Many have already sustained traumatic injuries before the arrival of law enforcement and still exhibit intense struggling even when a struggle is futile and self mutilation is a result.

Table 2 lists the features of excited delirium syndrome based on a review of the medical literature including 18 articles. The table is divided to indicate features based on the medical history of the subject, features that are observed in the company of the subject, features that are evident upon physical contact, features that are only evident with clinical assessment (i.e. vital signs), features that are described if the subject dies, and finally, features that are described on autopsy. A limitation of this analysis is that not all of these publications are observational studies and there is significant overlap of publications that reference each other to derive the most common clinical presentation.

Table 2: ExDS Features by Literature Review (n=18)

Features in History	# Articles
Male gender	**16**
Mean age ~30's	**16**
Sudden onset	**4**
History of Mental Illness	**8**
History of Psychostimulant abuse	**11**
Features evident at scene	**# Articles**
Call for disturbance/psychomotor agitation/excitation	**18**
Violent/combative/belligerent/assault call	**11**
Not responding to authorities/verbal commands	**1**
Psychosis/delusional/paranoid/fearful	**13**
Yelling/shouting/guttural sounds	**7**
Disrobing/inappropriate clothing	**5**
Violence toward/destruction of inanimate objects	**7**
Walking/running in traffic	**3**
Subject Obese	**5**
Features evident on contact	**# Articles**
Significant resistance to physical restraint	**11**
Superhuman strength	**8**
Impervious to pain	**3**
Continued struggle despite restraint	**7**
Profuse sweating/clammy skin	**3**
Features with clinical assessment	**# Articles**
Tachypnea	**1**
Tachycardia	**7**
Hyperthermia	**12**
Hypertension	**3**
Acidosis	**3**
Rhabdomyolysis	**5**

Features of death	# Articles
Period of tranquility/"giving up"	**4**
Sudden collapse after restraint	**12**
Respiratory Arrest described	**5**
Cardiac rhythm brady-asystole or PEA	**4**
Aggressive Resuscitation unsuccessful	**5**
Features on autopsy	**# Articles**
Drug screen Positive for psychostimulants	**9**
Drug levels lower than anticipated	**3**
No anatomic correlate for death	**6**
Dopamine transporter disregulation	**2**

Emergency clinicians and prehospital care providers are anecdotally aware that not all ExDS cases end in death. However, publication of nonfatal case reports or cohort studies remains infrequent. There is currently a paucity of literature to describe the epidemiology of ExDS if it is not accompanied by sudden death.

In the previously described Canadian data, 24 individuals demonstrated 6 or more of the clinical features found in **Table 1**. Prehospital ExDS may be reasonably presumed in subjects displaying 6 or more features of excited delirium (perhaps excluding attraction to reflective surfaces), thereby providing a potential case definition for future investigations. It is particularly likely if the subject displays constant or near constant physical activity, pain tolerance, superhuman strength, sweating, rapid breathing, tactile hyperthermia, and a failure to respond to police presence.

In summary, the clinical picture is one of an agitated and delirious state with autonomic dysregulation. It manifests through sympathetic hyper-arousal with frequent hyperthermia, vital sign abnormalities, and metabolic acidosis. For some, the clinical syndrome progresses to death.

Differential Diagnosis

Overview of delirium and altered mental status

Almost any drug, toxin, extraneous substance, psychiatric or medical condition, or biochemical or physiologic alteration in the body can cause acute changes in behavior or mental status. The general public, law enforcement, EMS, and even highly trained medical personnel may not be able to readily discern the cause of an acute behavioral disturbance, or differentiate a specific organic disease from ExDS.

Conditions that cause altered mental status

Altered mental status may be associated with a wide range of clinical signs and symptoms. The condition can range from coma to mild or profound confusion to uncontrolled agitation and delirium. A limited differential diagnosis of altered mental status is provided by the mnemonics AEIOU TIPS (**Table 3**), or SMASHED 2 (**Table 4**). Some etiologies may be suggested by clinical observation, obvious toxidromes, past medical history, patient age, or circumstances surrounding the acute event. Extensive testing and protracted evaluation and observation are often required to fully unravel the etiology of the acutely altered sensorium. As such, lifesaving interventions should be initiated prior to obtaining a specific diagnosis.

Table 3: AEIOU TIPS Mnemonic for Abbreviated Differential Diagnosis of Altered Mental Status

Letter	Description
A	Alcohol
E	Endocrine, Encephalopathy, Electrolytes
I	Insulin (hypoglycemia)
O	Oxygen (hypoxia), Opiates (drugs of abuse)
U	Uremia
T	Toxins, Trauma, Temperature
I	Infection
P	Psychiatric, Porphyria
S	Stroke, Shock, Subarachnoid Hemorrhage, Space-Occupying CNS Lesion

Table 4: SMASHED 2 Mnemonic for Differential Diagnosis of Altered Mental Status

Letter	Title	Description
S	**Substrates**	glucose (high/low), thiamine deficiency
	Sepsis	
M	**Meningitis**	all CNS infections, AIDS dementia, encephalitis, brain abscess or toxoplasmosis
	Mental illness	acute psychosis, medication noncompliance, mania, depression, malingering, rage, suicide intent (via police)
A	**Alcohol**	Intoxication, withdrawal
	Accident	head trauma, CVA, cerebral contusion, subdural or epidural hematoma
S	**Seizing**	or postictal
	Stimulants, hallucinogens, anticholinergics	Cocaine, amphetamines, caffeine, PCP, LSD, ketamine, psilocybin, antihistamines, atropine, scopolamine, jimson weed
H	**Hyper**	hypertension, hyperthyroidism, hypercarbia, hyperthermia
	Hypo	hypotension, hypothyroidism, hypoxia, hypothermia
E	**Electrolytes**	hyper/hyponatremia, hypercalcemia
	Encephalopathy	hepatic, HIV, uremic, hypertensive, lead, Reye's syndrome, CNS tumor
D	**Drugs**	Intoxication or withdrawal
	Don't forget other drugs	carbon monoxide, lithium, steroids, salicylates, designer/street drugs, theophylline, MDMA, antipsychotics, toxins not on routine drug screen, others

Several specific entities which cause altered mental status and may mimic ExDS deserve specific mention:

● Diabetic hypoglycemic reactions have been associated with outbursts of violent behavior and an appearance of intoxication. Diagnosis may be rapidly and conclusively made by determination of blood glucose and response to glucose administration.

● Heat stroke may manifest as tactile hyperthermia, rhabdomyolysis, and delirium, and may be associated with neuroleptic use and mental illness. A profound acidosis is often not present.

● Serotonin syndrome and neuroleptic malignant syndrome (NMS) may share some clinical characteristics with ExDS. However, they usually do not share the aggressive violent behavior manifested by patients with ExDS.

● Psychiatric issues may mimic ExDS. Some patients experience behavioral disturbances directly due to psychotropic drug withdrawal or noncompliance. Substance abuse is also very common in psychiatric patients. Many psychiatric conditions themselves, including acute paranoid schizophrenia, bipolar disorder, and even emotional rage from acute stressful social circumstances, may mimic an ExDS-like state. Untreated or poorly controlled psychiatric illness may also result in poor compliance with management of acute or chronic medical conditions. In *Phillips v Milwaukee*, a man who died in police custody of apparent ExDS was found at autopsy to have untreated thyrotoxicosis, as well as being noncompliant with his psychiatric medications.

Conditions that cause sudden death

Sudden unexpected death is the hallmark of fatal ExDS. The differential diagnosis for sudden death includes ischemic or drug induced sudden cardiac death, stress (Takotsubo) cardiomyopathy, inherited or acquired Long QT Syndrome, Brugada syndrome, and less common entities such as Cannon's Voodoo Death, Lethal Catatonia, and sudden unexplained death in epilepsy (SUDEP).

Treatment and Protocols

In the absence of clearly stated case definitions and prospective clinical studies, treatment of ExDS remains largely speculative and consensus-driven, directed towards supportive care and reversal of obvious clinical and laboratory abnormalities. The specific circumstances under which medical interventions will provide benefit are currently unclear. Nonetheless, there are current medical approaches that have consensus support. Most authorities, including this Task Force, posit the beneficial use of aggressive chemical sedation as first line intervention. As with any critically ill patient, treatment should proceed concurrently with evaluation for precipitating causes or additional pathology.

In subjects who do not respond to verbal calming and de-escalation techniques, control measures are a prerequisite for medical assessment and intervention. When necessary, this should be accomplished as rapidly and safely as possible. Recent research indicates that physical struggle is a much greater contributor to catecholamine surge and metabolic acidosis than other causes of exertion or noxious stimuli. Since these parameters are thought to contribute to poor outcomes in ExDS, the specific physical control methods employed should optimally minimize the time spent struggling, while safely achieving physical control. The use of multiple personnel with training in safe physical control measures is encouraged.

After adequate physical control is achieved, medical assessment and treatment should be immediately initiated. Indeed, because death might occur suddenly, EMS should ideally be present and prepared to resuscitate before definitive LEO control measures are initiated.

Initial assessment should include assessment of vital signs, cardiac monitoring, IV access, glucose measurement, pulse oximetry and supplemental oxygen, and careful physical examination. While the need for LEO control measures may initially preclude some or all of these interventions, they should be performed as soon as safely possible.

Agitation, hyperthermia, and acidosis are all major components of ExDS which can be effectively managed using traditional medical interventions. The approach to each of these components is described below.

Agitation

LEO control measures should be rapidly supplemented with sedation in the setting of acutely agitated, combative patients displaying signs of ExDS. While the intravenous (IV) route is preferred if available, intramuscular (IM) or intranasal (IN) transmucosal administration of sedative agents may be needed initially in order to facilitate IV placement. Commonly used agents and their doses are listed in **Table 5** and include benzodiazepines, antipsychotics, and the dissociative agent ketamine. Suggested doses are based upon consensus opinion. The actual effective dose of all suggested medications is unknown due to a paucity of research.

Because these agents have respiratory and cardiovascular effects, continuous monitoring of both should be performed as soon as feasible whenever parenteral sedation is administered. When appropriate safety systems are in place, one should be aware of manufacturers suggested dosing recommendations for other uses, but be prepared to use clinically effective doses for the management of this condition.

Table 5. Sedation Agents for ExDS–type symptoms

Class	Agent (Trade Name)	Available Routes	Dosing (mg)*	Onset (min)	Duration (min)
Midazolam (Versed)		IN	5	3-5	30-60
		IM	5	10-15	120-360
		IV	2 - 5	3-5	30-60
Lorazepam (Ativan)		IM	4	15-30	60-120
		IV	2 - 4	2-5	60-120
Diazepam (Valium)		IM	10	15-30	15-60
		IV	5 - 10	2-5	15-60
†Haloperidol (Haldol)		IM	10– 20	15	180-360
		††IV	5 – 10	10	180-360
†Droperidol (Inapsine)		IM	5	20	120-240
		IV	2.5	10	120-240
Ziprasidone (Geodon)		IM	10– 20	10	240
Olanzapine (Zyprexa)		IM	10	15-30	24 hrs
Ketamine (Ketaset, Ketalar)		IM	4-5 mg/kg	3-5	60-90
		IV	2 mg/kg)	1	20-30

IN: Intranasal; IM: Intramuscular; IV: Intravenous

* Typical adult dosing for severe agitation.

† The Food and Drug Administration has issued "Black Box" warnings regarding potential serious adverse effects (QT prolongation and torsades de points) with these agents. Clinicians should use their clinical judgment regarding the risk / benefit ratio on a case by case basis.

†† Though widely used in clinical practice, Haloperidol is not FDA approved for intravenous administration.

(*For adequate control of ExDS, the above doses are conservative and describe a reasonable starting point. Clinical effect in ExDS may require doses greatly in excess of those for traditional medical use in other conditions*).

Benzodiazepines are familiar, commonly available sedative agents which can be administered by the IM or IV routes. Midazolam is also available and rapidly absorbed by the intranasal route, making it attractive for use in situations such as ExDS when rapid treatment is essential but IV access may not be available. Benzodiazepines are often preferred if stimulant drug overdose is suspected. Potential disadvantages include relatively slow onset and unpredictability of action if not given IV, the need for repeat doses in many cases to achieve adequate sedation, and the potential for respiratory suppression. Often benzodiazepine doses many times the traditional suggested dose for sedation are required, and there is likely no maximum dose limit for benzodiazepines when facilities for respiratory and blood pressure support are available.

Antipsychotic agents are commonly used for sedation of agitated psychiatric patients, and can be administered by the IV or IM route. There is some concern for potential rare cardiac conduction effects such as QT prolongation with all of these agents, which may result in ventricular dysrhythmias such as torsades de pointes. These concerns, combined with a preexisting risk for sudden death among ExDS patients, official "black box" warnings from the FDA regarding QT prolongation with haloperidol and droperidol, and a slower onset of action than benzodiazepines by the IV or IM route, have led some clinicians to avoid this class of agents in suspected ExDS. Others have noted the potential for anticholinergic effects producing hyperthermia, and a mechanism of action involving central neurotransmitter systems (which may be markedly abnormal in some patients presenting with ExDS) as reasons to consider other agents.

The dissociative agent ketamine can also be administered by the IV or IM route and appears advantageous due to very rapid onset (especially by the IM route when compared to other medications), and lack of significant respiratory and cardiovascular effects. Case reports have indicated excellent results and safety when used in ExDS patients. Potential disadvantages include rare side effects such as increased oral secretions, laryngospasm, hypertension, and distress from emergence phenomena.

In some circumstances, sedation and paralysis with rapid sequence intubation and respiratory support may be necessary to control agitation in patients with ExDS. In these cases, standard techniques and medications may be utilized at the clinician's discretion.

Hyperthermia

Empiric treatment for hyperthermia may be initiated based on qualitative assessment (i.e. tactile hyperthermia) when needed, though core temperature measurement is preferred when available and practical. Basic cooling methods include removal of clothing and placement in a cool environment. Active external cooling may be initiated, with misting of water on exposed skin, providing air flow to enhance evaporative cooling, and placement of ice packs at the neck, axillae, and groin. Rapid cooling by infusion of cold saline IV has been shown to be effective in a number of other settings and can also be used. Care must be taken to avoid treatment "overshoot" leading to hypothermia.

Once the patient is stabilized in the ED or hospital setting, additional measures may be considered. In refractory or severe cases, immersion in cool water can rapidly reduce core body temperature, though this may present some difficulty with monitoring and treatment. A variety of external and internal temperature control devices are now available and may also be considered. If NMS or malignant hyperthermia is suspected, dantrolene may be indicated.

Acidosis

Metabolic acidosis and hypovolemia are thought to be common in ExDS. If suspected based on the clinical situation or physical exam, fluid resuscitation with intravenous fluids is prudent. In severe cases, sodium bicarbonate may be used either empirically or based on laboratory results revealing significant acidosis. Controversy exists regarding empiric use of sodium bicarbonate; the efficacy of supplemental sodium bicarbonate is unknown, and has not been supported as routine therapy for the metabolic acidosis of cardiac arrest. It is approved by some EMS agencies, but not by others (**Table 6**). Sodium bicarbonate may be administered by bolus injections or as a continuous infusion. Hyperventilation is the body's normal compensatory mechanism for correcting acidosis. Control measures that might interfere with ventilation should be avoided.

Other

Other components of ExDS may include rhabdomyolysis and hyperkalemia. Rhabdomyolysis is initially managed by fluid administration and urine alkalinization with sodium bicarbonate. These interventions may have already been initiated empirically for other components of ExDS before laboratory results allow confirmation of rhabdomyolysis. Hyperkalemia may also be treated with traditional ACLS interventions based on characteristic EKG changes and laboratory results.

Many EMS systems already have protocols in place that incorporate these recommendations, allowing treatment of the clinical signs and symptoms of ExDS in the prehospital setting. While some agencies have adopted specific ExDS protocols, others place the interventions within traditional headings such as agitation and hyperthermia. Several prehospital protocols are summarized in **Table 6**.

Table 6. Sample EMS Protocols for ExDS symptoms

City, State	Sedation	Fluids	Hyper-thermia	Other
Miami, FL	Midazolam (Versed) 5mg IN [max 20mg]	Normal Saline 1 liter bolus IV	Cold (<60°F) IV fluid Cold packs	Sodium Bicarb. 1 amp (50 mEq) per liter of Normal Saline
Nash-ville, TN	Midazolam (Versed) 2mg IV or 5mg IM [may repeat]	Normal Saline @ 500 cc/hr IV	Evapora-tive Cool-ing Cold packs	
Clark County (Las Vegas), NV	Midazolam (Versed) 2mg IV or 5mg IM / IN [may repeat]	Normal Saline	Evapora-tive Cool-ing Cold packs	
Colum-lum-bus, OH	Midazolam (Versed) 2- 5mg IN, IV, pr [max 10 mg]	Normal Saline 500cc over 20 min	Evapora-tive Cool-ing Cold packs	Sodium Bicarb. ½ amp (25 mEq) per liter of Normal Saline
Min-neapo-lis, MN	Ketamine 5 mg/kg IM or 2 mg/kg IV	Normal Saline up to 2 liter bolus IV	Evapora-tive Cool-ing Cold packs	Sodium Bicarb. 2 amps (100 mEq) IV push
Roche-ster, MN	Lorazepam (Ativan) 1-4 mg IV/IM or midazolam (Versed) 1-5 mg IV/IM	Normal Saline	Evapora-tive Cool-ing Cold Packs	Sodium Bicarbo-nate 1mEq/kg IV push in cardiac arrest

IV: Intravenous; IM: Intramuscular; IN: Intranasal; pr: per rectum; Normal Saline: 0.9% Sodium Chloride

LIMITATIONS OF CURRENT KNOWLEDGE AND RECOMMENDATIONS FOR FUTURE RESEARCH

The primary issues surrounding identifying and studying ExDS and subsequent therapeutic interventions are the lack of well-defined, consistent epidemiological case definition and overlap with other established diseases.

In those cases where a death occurs while in custody, there is the additional difficulty of separating any potential contribution of control measures from the underlying pathology. For example, was death due to the police control tool, or to positional asphyxia, or from ExDS, or from interplay of all these factors? Even in the situation where all caregivers agree that a patient is in an active delirious state, there is no proof of the most safe and effective control measure or therapy for what is most likely an extremely agitated patient. However, the existence of multiple EMS protocols as well as expert consensus suggests that there are practical and agreed-upon methods of therapy that are believed to lower morbidity or mortality. Sedative or dissociative agents such as benzodiazepines, major tranquilizers, and ketamine are suggested but there is no evidence yet to prove that these will result in a lower morbidity or mortality.

Future research should focus on several areas. Animal models should be developed to begin to better understand the pathophysiology of ExDS.

In humans, a consistent case definition should be developed and applied in a large epidemiologic prospective study or from a national or international database of all suspected cases, including those who survive. At a molecular level, and based upon post-mortem cocaine-associated ExDS brain tissue, a Genome Wide Association Scan may be performed to identify susceptibility genes.

Development of a national orphan case report registry is recommended. This registry would be important in beginning to define the course of ExDS, and might eventually provide for earlier recognition of individuals at risk. It would also allow the scientific community to begin the process of identifying common characteristics on a large scale as well as comparing therapies. Without including suspected cases and survivors, no meaningful conclusions can be reached that would allow the development of case definitions, etiologies, and treatments.

Studies should address the role of law enforcement control techniques and devices in the death of sub-

jects with ExDS. Finally, research is needed to establish field protocols and techniques that allow police, EMS and hospital personnel to interact with these agitated, aggressive patients in a manner safe both for the patients and the providers.

SUMMARY

Based upon available evidence, it is the consensus of the Task Force that ExDS is a real syndrome of uncertain etiology. It is characterized by delirium, agitation, and hyperadrenergic autonomic dysfunction, typically in the setting of acute on chronic drug abuse or serious mental illness.

Research suggests the pathophysiology may include genetic susceptibility and chronic stimulant-induced abnormalities of dopamine transporter pathways, along with elevation of heat shock proteins in fatal cases. There is insufficient data at this time to determine whether fatal ExDS is preventable, or whether there is a point of no return after which the patient will die regardless of advanced life support interventions.

The risk of death is likely increased with physiologic stress. Attempts to minimize such stress are needed in the management of these patients. Ideally, any necessary law enforcement control measures should be combined with immediate sedative medical intervention to attempt to reduce the risk of death.

There are well-documented cases of ExDS deaths with minimal restraint such as handcuffs without ECD use. This underscores that this is a potentially fatal syndrome in and of itself, sometimes reversible when expert medical treatment is immediately available.

For research and diagnostic purposes, thorough documentation of the patient's signs and symptoms along with appropriate testing should occur. This includes the presence of sweating or muscle rigidity, temperature, pulse, respiratory rate, blood pressure, venous blood gases, urine and serum toxicology, thyroid functions, and blood and (if fatal) anatomic brain specimens for genetic, heat shock proteins, and neurochemical analyses.

The ante-mortem diagnosis in the prehospital or emergency department setting depends upon clinical characteristics and the exclusion of alternative disease processes. It is our consensus that rapid and appropriate but limited control measures, and immediate administration of IV benzodiazepines or ketamine, IM ketamine, or intranasal midazolam, can be lifesaving.

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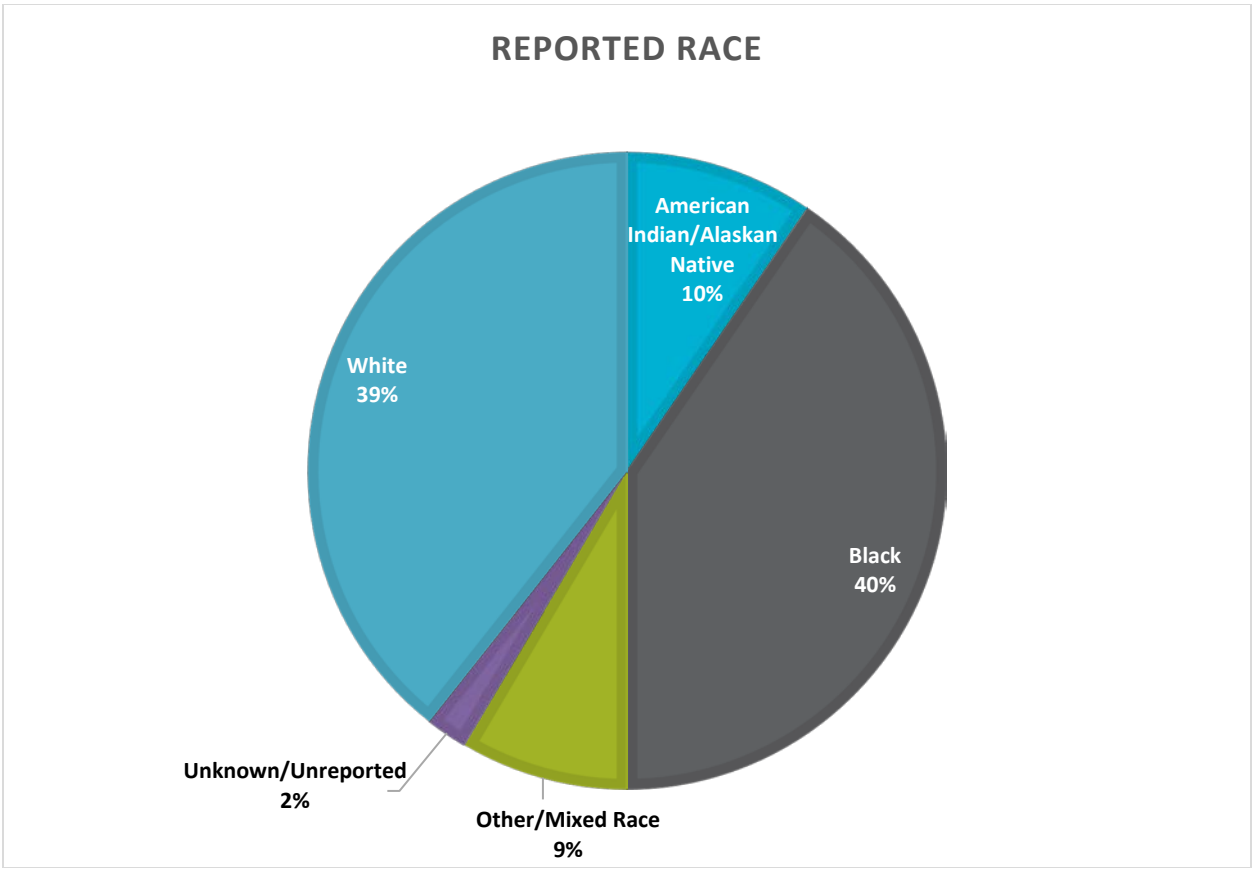
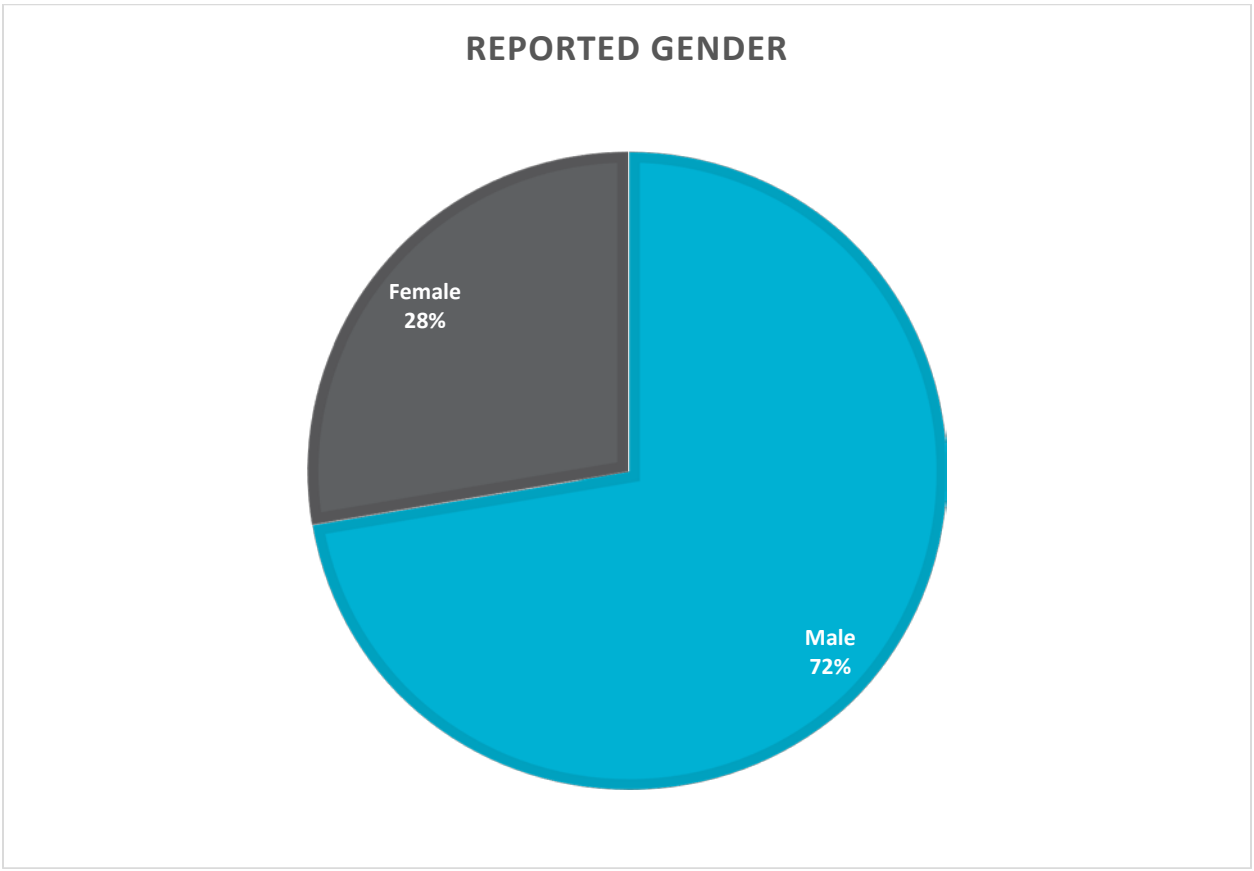
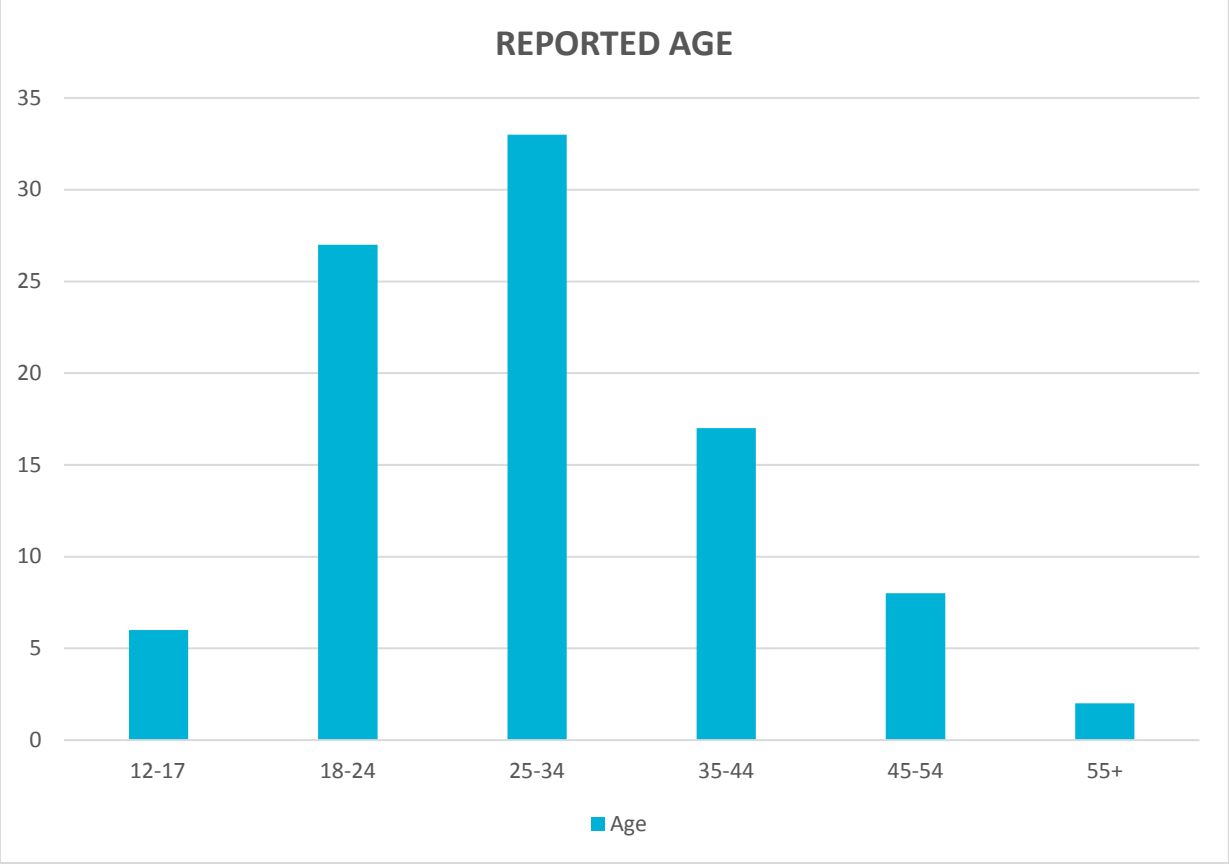
APPENDIX 5: Demographic Information for Incidents From 2016-2017



Race is reported by the officer. Ethnicity is not easily tracked, and as such, “White” may include people of Hispanic descent.




REPORTED AGE
35
30
25
20
15
10
5
0
12-17
18-24
25-34
35-44
45-54
55+
Age

APPENDIX 6: OPCR Research and Study Controls

Minneapolis
City of Lakes

OPCR Document Controls

Office of Police Conduct Review

The reports prepared as the result of OPCR research and study projects, program reviews, and program audits may contain sensitive and non-public information. While in draft form, they are considered non-public. To prevent unauthorized dissemination of non-public data or draft reports, the OPCR establishes the following procedures.

1. Workgroup
    a. The group performing the research and study project shall be defined by the director of civil rights or a designee (hereinafter "workgroup").
    b. The workgroup shall have access to the report and any materials (collectively "materials") used in its creation while the work is in progress.
    c. Any additional access to the materials shall be granted pursuant to sections 3-5.
2. Watermark
    a. Report drafts shall be watermarked DRAFT and contain the following disclaimer in the footer:

    "This report is a draft which may contain confidential and/or protected nonpublic data pursuant to Minn. Stat. Section 13.392 and is protected from disclosure and not for distribution. Any unauthorized acquisition, distribution, or copying of this draft report is strictly prohibited."

3. Electronic Materials
    a. Materials shall be stored electronically whenever possible.
    b. Electronic material shall only be accessed with City-provided computers or mobile devices.
    c. Materials shall only be stored on secure locations.
        i. Materials shall be stored on a secure location accessible only to the workgroup, such as a network drive or SharePoint site.
        ii. Materials may be temporarily stored on an encrypted local drive, encrypted portable device, or encrypted flash drive.
    d. Locations housing the materials should not be indexed or available to enterprise search.
    e. The electronic files comprising the materials must be encrypted/password protected.
        i. Materials must be encrypted using a tool approved by the Director of Civil Rights or a designee, such as 7-Zip File Manager.
        ii. Password protection must prevent unauthorized access to the file as well as obscure the names of files.
    f. Passwords for the encrypted files and drives shall be separately stored.
    g. Passwords may only be shared amongst the workgroup when necessary.
    h. Materials shall not be emailed. Sharing materials amongst the workgroup shall be accomplished using a storage location with controlled access, such as SharePoint, or using an encrypted flash drive or other encrypted portable drive. Both the storage location and the files will be encrypted.
    i. Any flash drive or portable drive containing materials will be secured in a locked cabinet or office only accessible to the workgroup.
    j. All related materials will be permanently deleted from such drives upon completion of the project.
4. Printed Materials
    a. All printed materials will be kept in locked cabinets or offices only accessible to the workgroup.
    b. Any printed material that is not intended for dissemination is the responsibility of the person who prints it.
    c. When the document is no longer needed it shall be placed in the shredding bin.
    d. All printed materials will include a unique identifier in the document.
    e. Workgroup members shall maintain a log of printed copies created, including the unique identifier, printing date, document version, distribution, and final disposition.
5. Review of Draft Reports
    a. The Director of Civil Rights or a designee must approve any party outside the workgroup to review a draft report.

b. When the party is approved, they may review a printed copy of the report in a location designated by an approver.
c. If the director of Civil Rights or a designee deems it necessary for a party to take possession of printed materials, the party receiving the materials will initial each page of the printed materials before it is released to them.
d. When they finish reviewing materials, they shall return them to a member of the workgroup.
e. Any party taking possession of material shall sign an agreement stating that any subsequent dissemination of the materials they wish to make must be approved by the director of Civil Rights or a designee.

6. Review of statements by Contributors
    a. During a research project, outside contributors may provide statements to be included in the report.
    b. Before dissemination of a report outside of the workgroup, contributors will be provided an opportunity to review their statements used in the report.
    c. If possible, the contributors should be provided only the portion of the report where the statement is used. When this is not possible, approval for review shall follow the procedures contained in section 4.
7. File management after publication
    a. Upon publication of a report, prior drafts and supporting materials not included as attachments in the final report or required to support the findings will be deleted.
    b. Materials not included in the final report will be maintained according to section 2. Printed materials will be scanned and converted to electronic materials when possible.

Office of Police Conduct Review Release Agreement

Minneapolis
Office of Police
Conduct Review

I am being provided a draft which may contain confidential and/or protected nonpublic data pursuant to Minn. Stat. Section 13.392 and is protected from disclosure or distribution. Any unauthorized acquisition, distribution, or copying of this draft report is strictly prohibited. Upon receipt of the materials, I agree to the following:

- I will not disclose the materials to any additional parties unless I am approved to do so by the Director of Civil Rights or a designee.

- When I am not using the materials, I will keep them in a secure location, accessible only by me.

- I will return materials to staff from the Office of Police Conduct Review by: DATE

Report Name and Version:

Receiver:

_____ _____

Signature Date

Approver:

_____ _____

Signature Date

APPENDIX 7: PCOC Research and Study Process

Minneapolis
City of Lakes

PCOC Study Process

Office of Police Conduct Review

2017

Table of Contents

Introduction

The Police Conduct Oversight Commission (Commission) assures that police services are delivered in a lawful and nondiscriminatory manner and provides the public with meaningful participatory oversight of police policy and procedure. Commission members have a variety of responsibilities including shaping police policy, auditing cases, and engaging the community in discussions of police procedure. The Commission strives to be the citizen advisory group the community relies upon to openly discuss policy and procedures of the Minneapolis Police Department, to voice concerns regarding law enforcement/civilian interactions, and the organization that advances credible and meaningful feedback, without obligation to political influences, for the betterment of the City of Minneapolis. For more information about the work of the Commission, meeting times and locations, and meeting minutes, please visit the Commission website.

Additionally, in the Police Conduct Oversight Ordinance, the Commission has direction to conduct programs of research and study to achieve the mission of the ordinance. As such, the Commission conducts research and study related to problematic conduct recognized in complaints or matters of public concern raised by the community. By conducting research and study, the Commission aims to achieve an accurate picture of current practices, innovative procedures outside of Minneapolis, and/or community feedback related to the research question. Studies may lead to the issuance of recommendations to the MPD, City Council, or other appropriate body but relate directly to the results of research.

Experience combined with the review of misconduct cases serves as the basis for the generation of topics for research. However, commissioners are volunteers, and as such, they are not expected to perform the multitude of tasks associated with a project. To do so, commissioners work with analysts from the Office of Police Conduct Review (OPCR), supervised by the legal analyst. Commissioners create the ideas that lead to research and study, provide guidance to analysts throughout the project, and form final recommendations after the research concludes.

The research and study process is divided into four phases:

1. Project Formation and Initial Survey
2. Methodology Development
3. Fieldwork and Report Drafting, and
4. Final Report and Recommendations

Project Formation and Initial Survey

When commissioners have an idea for research and study, they may meet with analysts from the Office of Police Conduct Review to discuss it. Analysts may advise the commissioner on the feasibility of conducting the research[1] and assist in the creation of potential research questions that could address the underlying issue. If it is not clear whether the project is feasible, analysts may conduct an initial survey of the topic. Data may be accessed at this phase but is not retained for further analysis beyond assessing the feasibility of the study. The initial survey may also include meetings with relevant MPD parties, community stakeholders, or research partners.

Analysts may also advise the commissioner on the economy of conducting the research and study, primarily whether a research and study could be completed without expending a prohibitive amount of staff resources. OPCR analysts are responsible for conducting research for all commissioners as well as the OPCR. As such, analysts may not participate in a project if it aims to answer a meaningless question or expends a detrimental amount of resources.[2]

After the initial consult with OPCR analysts, the commissioner may put forth a motion and description of the project to the full commission for a vote. The project and research questions do not have to be fully realized at this stage, and the initial vote does not determine whether the study will be conducted. Commissioners vote on whether the study will be sent to the audit committee to develop the methodology to be followed during the research and study. If so, the methodology development phase begins.

[1] Ex. A study comparing MPD practices with nonpublic data held exclusively by another city.
[2] Ex. A study that examines of thousands of hours of body camera recordings to determine which model of a certain type of vehicle is most frequently stopped.

Methodology Development

If the Commission votes to refer a topic of research and study to the Audit Committee, OPCR analysts will create an initial draft methodology in consult with the sponsoring commissioner to be presented at the next committee meeting.

Methodologies typically include:

1. Background: description of the events that led to the motion for research and study
2. Study Goals: the broad categories of subjects to be analyzed
3. Research Questions: specific questions that the study will attempt to answer
4. Method of Analysis/Sample Collection: a description of the way in which research will be conducted (data to be collected[3], interviews, best practices surveys)
5. Limitations: Any known limitations on research that may impact the ability to complete the research and study
6. Appendix: Any documents related to the research and study that provide value at the initial stage

The Audit Committee typically receives an advance copy in preparation for the meeting and provides feedback on the proposed methodology. The methodology may be revised at the meeting or remanded to OPCR analysts for further work. If the methodology is acceptable, the Audit Committee may vote to refer it to the Commission. The Commission may vote to approve the methodology, modify it at the meeting, end the research and study with no further action, or refer it back to the Audit Committee for additional work.

If the Commission approves the methodology, relevant stakeholders are notified and the fieldwork phase begins.

[3] If nonpublic data will be accessed for the purposes of the study, the data to be accessed and the reasons for doing so will be stated in the methodology to ensure only essential data is collected.

Fieldwork and Report Drafting

During the fieldwork phase, the method of analysis is executed. Both the method and duration of fieldwork differs greatly depending on the nature of the study and the questions to be answered. While OPCR analysts will not work outside the scope of the study goals, the method of analysis may change when necessary to accurately answer research questions. OPCR analysts provide progress updates to the Audit Committee throughout the fieldwork phase and may provide draft updates to the Commissioner working on the project.

When nonpublic data is accessed for the purposes of research and study, OPCR analysts will ensure that no nonpublic data is released in discussions of the work outside of the analysis group unless a criminal act is suspected. In the event criminal activity is discovered, the matter will be referred to the City Attorney for review. Any nonpublic data will be converted to public summary data for inclusion in the final report. Analysts will observe § 172.85 of the Police Conduct Oversight Ordinance which requires compliance with all provisions of the Minnesota Government Data Practices Act.

Relevant parties may be interviewed during the course of the research and study process. This typically occurs after initial data analysis and research on the subject. The participants will know they are being interviewed relating to the research and study.

OPCR analysts will then draft the initial analysis and answer research questions when possible. Once fieldwork is completed, OPCR analysts will consult with the Commissioner who put forth the original motion that created the study or another Commissioner selected to monitor the work to discuss the results of the research and the initial draft of the report. If questions cannot be answered, analysts will note the limitations of the study and specific reasons for the missing information.

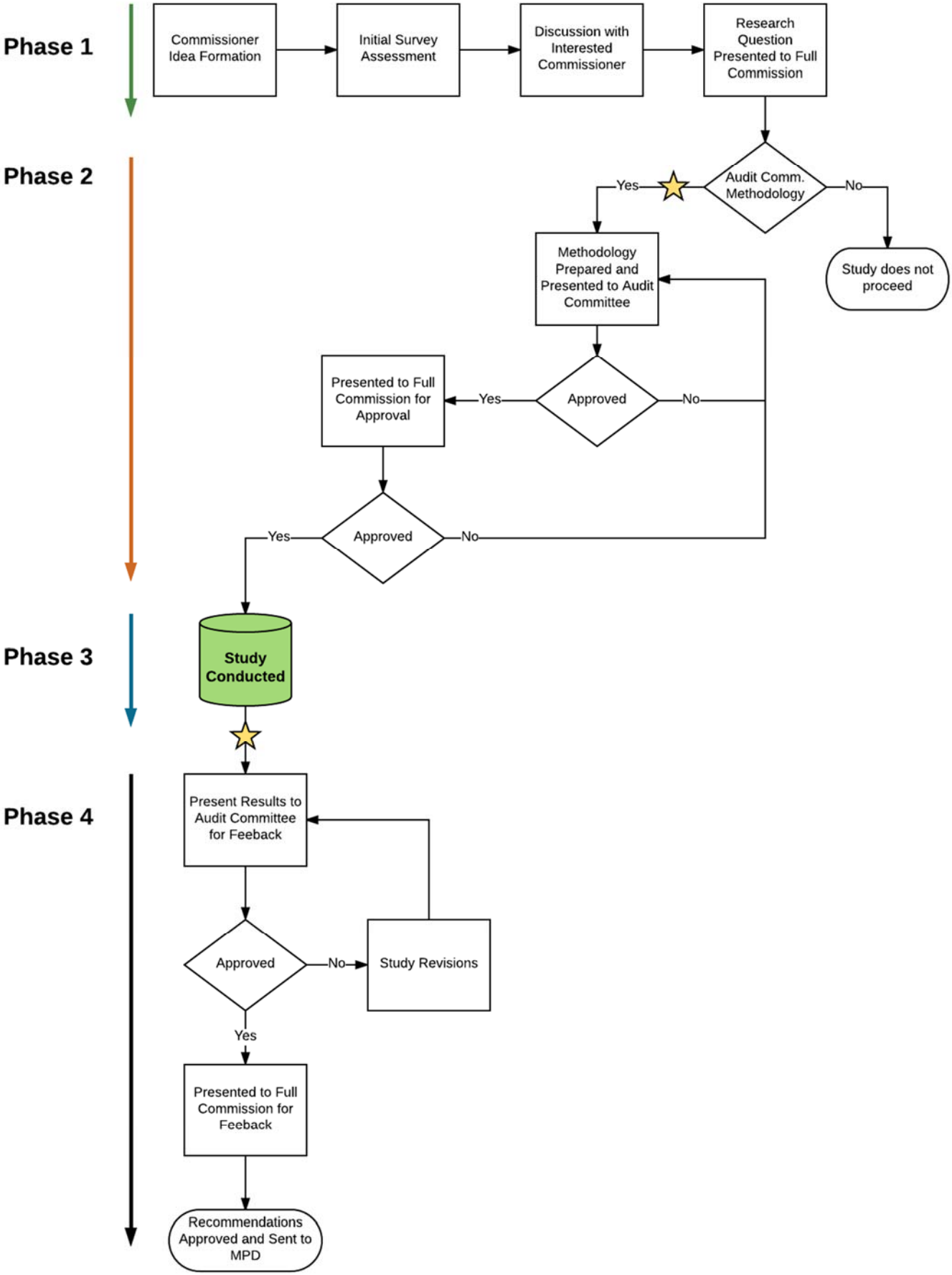
If participants were interviewed for the study, their comments that may be included in the report will be provided to them for approval. OPCR analysts will not publish comments or identifying information provided to them if the participant does not wish them to be available to the public.

The initial draft does not include recommendations without commissioner input. OPCR analysts may make suggested recommendations, but commissioners issue the recommendations. In the event that the Commission issues recommendations unsupported by the analysis, OPCR analysts may attach a letter explaining the opinion of the analysts.

Final Report and Recommendations

The initial draft of the completed study is first presented to the Audit Committee for input. Like prior parts of the research and study process, the Committee may revise, approve, or remand the study as well as attach recommendations to results. If recommendations involve changes to MPD Policy, the results may be referred to the Policy and Procedure Committee for further analysis. If the study is approved, it is presented to the Commission for final comment, revisions, and approval. If approved, the study and recommendations are typically submitted to the chief of police or the chief's designee with an offer to meet with the sponsoring commissioner and OPCR analysts to discuss the results.

When a study is approved that contains recommendations, OPCR analysts will typically create a recommendation implementation checklist to be included with the study. The Audit Committee is responsible for monitoring the progress of recommendations and, if recommendations are rejected, recording the reasons for doing so.


Phase 1
Commissioner Idea Formation
Initial Survey Assessment
Discussion with Interested Commissioner
Research Question Presented to Full Commission
Phase 2
Audit Comm. Methodology
Yes
No
Study does not proceed
Methodology Prepared and Presented to Audit Committee
Approved
Yes
No
Presented to Full Commission for Approval
Approved
Yes
No
Phase 3
Study Conducted
Phase 4
Present Results to Audit Committee for Feeback
Approved
No
Study Revisions
Yes
Presented to Full Commission for Feeback
Recommendations Approved and Sent to MPD

APPENDIX 8: Hennepin Health July 23 Response

Hennepin Healthcare Memorandum in Response to Minneapolis OPCR Draft Report on Ketamine

Hennepin Healthcare

Introduction

This memorandum provides a response to a May 2018 draft report from the Minneapolis Office of Police Conduct Review ("OPCR") on the use of ketamine ("Draft Report"). The actions of Hennepin EMS and its use of ketamine are one of the primary subjects of the Draft Report. Unfortunately, OPCR never informed Hennepin EMS of its investigation or sought any information from Hennepin EMS before creating this Draft Report.

In fact, Hennepin Healthcare was first made aware of the OPCR report in late May 2018. Hennepin Healthcare staff reviewed the Draft Report and immediately expressed concerns to City officials about the Draft Report's accuracy and soundness of its conclusions related to Hennepin EMS actions. On June 13, 2018, Hennepin Healthcare officials met with representatives of the City, including OPCR staff, and Hennepin Healthcare staff highlighted these concerns and pledged to work with OPCR to provide it with data and access to staff that could better inform OPCR staff about the proper use of ketamine in pre-hospital settings. The next day, the Star Tribune reported on the Draft Report. In the intervening weeks, OPCR has not sought any data or information from Hennepin Healthcare. It is Hennepin Healthcare's understanding that the Draft Report is being released this week by the City.

Hennepin Healthcare is providing this memorandum to the City because it believes that the Draft Report has many inaccuracies. Rather than try to highlight all the inaccuracies in the Draft Report, this memorandum highlights several significant categories of inaccurate information contained in the report. Hennepin Healthcare remains willing to discuss these matters with the City. Where appropriate, it will correct facts that have been misstated. From the outset, it is important to acknowledge that the comments herein should not be construed as an indication that Hennepin EMS has not benefited from certain insights derived from the Draft Report. However, it is vital that the record be set straight so that the public is accurately informed about the claims made in the draft report to the extent possible.

Point 1: Ketamine

The Draft Report contains an incomplete description of ketamine's uses, pharmacokinetics, and safety profile, to the point of grossly misrepresenting the medical utility of ketamine. Ketamine was approved by the FDA in 1970 and has been used by healthcare providers for decades, including Hennepin Healthcare. Ketamine has been used by Hennepin EMS paramedics since 2010, and is today used by all paramedic services in the Twin Cities. Ketamine has medical uses other than pre-hospital sedation, such as:

- Sedative for elective intubation of critically ill patients requiring airway management in both the prehospital and hospital settings. 33 percent of paramedics across the U.S. responding to a survey were authorized by protocol to use ketamine.
- Sedative for conscious sedation procedures, such as suturing lacerations or setting broken bones in children.
- Alternative to narcotics for effective pain management in acute traumatic injuries in the prehospital and hospital setting.
- Eliminating acute suicidal ideation in patients via a low-dose and prolonged infusion, supported by recent research around the world.

Hennepin Healthcare has been a national and international leader in researching the safe use of ketamine in the context of pre-hospital sedation. Ketamine has been widely accepted in the medical community over other sedatives in several situations due to its rapid onset, relatively short duration compared to other sedatives, and because unlike other sedatives, ketamine generally neither negatively impacts the patient's breathing nor does it cause unsafe drops in blood pressure. (However, this does not necessarily hold true in patients where intoxication may already be inhibiting their ability to breathe.)

References to ketamine alternatives in the Draft Report fail to explain and address the risks other options pose to the patient. Patients in the throes of a behavioral emergency, or those who are combative for myriad other reasons, may not be candidates for ketamine alternatives. The fast onset of ketamine and the relatively short action period often make it the safest way to gain control of these patients who require medical attention. Allowing a patient to continue to struggle against restraints, especially restraints that force the patient into a position that impedes the physiology of breathing greatly increases the patient's risk for developing metabolic acidosis and possible death. In other words, the fact that a person is being physically restrained does not obviate the medical necessity of using ketamine.

While Hennepin Healthcare recognizes that ketamine can be abused, this is true for many pharmacological agents that are of great benefit to patients when administered by medical professionals. Therefore, Hennepin Healthcare believes that referring to ketamine as a "date rape drug" is particularly misleading and inflammatory, especially where ketamine is being used under the direction of medical professionals as in the situations contained in this draft report.

In short, ketamine - when abused - can have harmful consequences, but when administered under the supervision of trained professionals, ketamine can and does save lives. Paramedics, physicians, and nurses have been trained as to what to look for and how to manage any adverse event of ketamine administration, as well as how to intervene and manage the patient to a high standard.

Point 2: First responder roles and responsibilities

Relying soley only on body camera footage, the Draft Report suggests that Hennepin EMS has improperly administered ketamine based on the request of police officers or to study the effects of ketamine. Sedation should never be administered based on a request from police officers or to further medical research as alleged in the Draft Report. The decision to use sedation has always been a medical decision made by paramedics providing the care, regardless of comments or statements made by police officers at the scene or the existence of an active medical study. In other words, only medical necessity has dictated the use of sedatives. The existence of a medical study or suggestions from police officers had no influence on the use of sedatives by Hennepin EMS paramedics.

In addition, sedation was never administered to patients because they have committed a crime. EMS does not control the interactions between law enforcement and individuals being detained for suspicion of committing a crime. If these interactions turn physical and law enforcement determines that it has become a medical emergency, EMS is called to the scene and intervenes to address the medical emergency. It is sometimes possible that successful intervention may be achieved through verbal de-escalation techniques, simple physical restraint procedures, or sedation. The medical decision to use

sedation is vested solely with the paramedic. Hennepin EMS never transports patients requiring pharmacological intervention or medical evaluation to jail. Patients in need of medical care or who have received prehospital treatment are always transported to an emergency department.

Before being made aware of the Draft Report, Hennepin EMS learned of an issue within the Minneapolis Police (MPD) regarding its officers' role during certain interactions with Hennepin EMS paramedics at scenes where patients require pre-hospital sedation for uncontrolled agitation. Specifically, Hennepin EMS paramedics had alerted Hennepin EMS leadership that on some occasions MPD offices were requesting Hennepin EMS administer ketamine. Hennepin EMS leadership brought this issue to the attention of MPD and on May 18, 2018, MPD issued an Administrative Announcement (Appendix) advising its officers of the appropriate roles of EMS personnel and MPD officers, respectively, in situations requiring prehospital sedation for uncontrolled agitation. This prompted Hennepin EMS to issue similar memos on May 25, 2018 and May 31, 2018 (Appendix) to its paramedic staff.

Point 3: Medical Expertise

The Draft Report draws conclusions about whether particular instances of pre-hospital sedation are appropriate; however, the report highlights that OPCR staff do not have the medical expertise to make such conclusions and these conclusions are only based on review of body cam footage. Hennepin Healthcare and Hennepin EMS have now had an opportunity to review the eight cases identified in the Draft Report that involve HEMS paramedics. In all eight, Hennepin Healthcare and Hennepin EMS believe that paramedics acted appropriately in determining that ketamine use was appropriate.

Neither Hennepin Healthcare nor Hennepin EMS can provide pertinent patient data due to privacy restrictions that prohibit public disclosure of medical records or patient information. However, the Draft Report contains multiple statements amounting to medical diagnoses or condition descriptions which are not accurate. Hennepin Healthcare cannot provide specifics without violating patient privacy laws.

The OPCR has authority to conduct investigations of police misconduct (Minneapolis Ordinance 172.90). Despite this limited authority, the Draft Report goes beyond review of police officer conduct and contains opinions and conclusions regarding Hennepin EMS medical care that are neither informed by qualified health professionals nor meet the standard of evidence-based medicine.

Inaccuracies in this report include misidentification of providers, agencies, policies, protocols, and diagnoses. For example, HCMC is referred to 12 times and Hennepin County Medical Center is referred to 6 times. Based on Hennepin Healthcare's review, of these 18 references, half do not appear to refer to patients who were cared for by Hennepin EMS or according to the Hennepin EMS protocol. One reference did not even involve the use of ketamine.

Point 4: Protocols and Policies

The Draft Report does not accurately describe the relevant protocols and policies, nor does it correctly identify the scope of these protocols and policies. The Draft Report repeatedly refers to protocol 3420 as "the HCMC policy" for use of ketamine. This misstates both the nature and source of 3420, which is a protocol (not a policy) (see definitions below) of the Hennepin County EMS System. The protocol was approved by the Hennepin County EMS Advisory Council, which oversees five services including Allina Health EMS, Edina Fire Department, Hennepin EMS, North Memorial Ambulance Service, and Ridgeview Ambulance Service.

Moreover, this protocol, like others, does not definitively dictate a course of action in every situation. Protocol 1000 of the Hennepin County EMS System Advanced Life Support (ALS) states:

> Each of the ambulance services operating in the Primary Services Area (PSA) within Hennepin County has an ambulance service medical director. Per MN Statute 144E.265, Subd. 2, "responsibilities of the medical director" shall include, but are not limited to...(6) establishing procedures for the administration of drugs...
>
> The policies and protocols [of Hennepin County EMS System] represent the collective medical expertise and authority of the medical directors for the five ALS ambulance services operating PSAs within Hennepin County. If any conflict exists between a service policy or protocol and a system policy or protocol, paramedics should follow their service policy.

Furthermore, ALS Protocol 2000, "Guidelines," states in relevant part as follows:

> E. In all circumstances, physicians have latitude in the care they give and may deviate from these Medical Protocols if it is felt that such deviation is in the best interest of the patient. Nothing in these protocols shall be interpreted as to limit the range of treatment modalities available to medical control physicians to utilize, other than the modalities and the medications used must be consistent with the paramedic's training.
>
> F. The specific conditions listed...in this document...are operational diagnoses to guide the paramedic in initiating appropriate treatment. This document is to be used as consultative material in striving for optimal patient care. It is recognized that specific procedures and/or treatments may be modified depending on the circumstances of a particular case.... [emphasis added]

In contrast to presumptions underlying the Draft Report, ALS Protocols 1000 and 2000 make it clear that Protocol 3420 is neither a policy nor does it bind the actions of Hennepin EMS paramedics. Rather, it is simply a guideline that is subject to modification based upon the paramedics' and the Hennepin EMS' medical director's professional judgment.

In addition, the Draft Report's interpretation of Hennepin County EMS System ALS Protocol 3420 is narrow and fails to consider all circumstances that may be present when providers make the decision to sedate a patient and the agent to be used. The authors of the Draft Report often opined as to the level of agitation or threat of agitation, without having any knowledge whatsoever of the medical standard that informed the paramedics' decision to administer sedation. Active physical violence by a patient may or may not be continuous. Because of that, the provider has to consider the potential for a patient to become violent in the confines of an ambulance during transport to the hospital. Also, the use of chemical or physical restraints are entirely situation-dependent, and may include the patients' medical condition, the time needed to achieve appropriate sedation, and the resources available.

It is widely understood by medical providers that restrained patients are not a contraindication for sedation. Restrained patients can be a threat to the safety of responders due to spitting, biting, scratching, grabbing and other similar behavior. Additionally, restrained patients are a threat to themselves due to the fact that they can cause themselves significant injury when fighting against restraints. Restrained patients may also become severely ill by exhausting themselves to the point of suffering respiratory arrest due to a medical condition known as metabolic acidosis, which can lead to death.

The Draft Report claims that Hennepin EMS violated Protocol 3420 when, in fact, the protocol allows for appropriate modification at the discretion of the Medical Director and/or the paramedic on the scene, as established in ALS Protocol 2000.

Conclusion

Through this memorandum, Hennepin Healthcare has highlighted some of the areas where the Draft Report is inaccurate. In addition, it provides the medical context for the use of sedatives, including ketamine, in the situations highlighted in the Draft Report. The use of ketamine has increased over the past several years. This is not due to any study of ketamine or inappropriate actions on the part of Hennepin EMS. Instead, it is due to a number of factors, including an increase in illicit use of certain street drugs (namely synthetic cannabinoids that cause significant and unpredictable swings in behavior,) as well as an increase in behavioral emergencies.

Hennepin Healthcare and others in the medical community acknowledge that sedatives can be misused. However, when they are safely administered by trained medical professionals, sedatives have saved many lives.

Hennepin Healthcare recognizes that the convergence of issues raised in the Draft Report creates a situation that is difficult to explain without a complete understanding of each of the issues. It is committed to providing answers and facilitating understanding of the care Hennepin EMS paramedics provide and the benefits that medical studies produce. As a public entity, Hennepin Healthcare holds itself to a higher level of public accountability and pledges to continue to be transparent and proactive on the issues of sedation in agitated patients, research, and the interaction with law enforcement. Hennepin Healthcare maintains that the Draft Report is not accurate and its conclusions are not sound with respect to Hennepin EMS. However, Hennepin Healthcare does understand that the underlying concerns need to be seriously and comprehensively addressed. Thus, independent external reviews have been sought. In the final analysis, Hennepin Healthcare is confident that the community will be reassured that it acts in the best interest of people who find themselves in crisis situations and to meet their needs for comprehensive, evidence-based care that ensures their recovery.

Definitions

Hennepin Healthcare : Refers to the full system, which includes Hennepin EMS and HCMC.

Hennepin EMS: Refers to the ambulance service operated by Hennepin Healthcare.

Hennepin County EMS System: Refers to the Hennepin County Department that provides planning support and regulatory oversight for Hennepin County's county-wide emergency medical services

system. The systems include Allina Health EMS, Edina Fire Department, Hennepin EMS, North Memorial Ambulance Service, and Ridgeview Ambulance Services.

Protocol: May be used synonymously with guideline and means a document that is to be used as consultative material which allows for certain latitude and autonomy based on the circumstances of a situation that is within the scope of practice, knowledge, and training of the employee for whom the protocol or guideline was written.

Policy: Refers to a course of action adopted and pursued, and that is used as a basis for making decisions and/or what to do in a particular situation.

Appendix

MINNEAPOLIS POLICE DEPARTMENT
BY ORDER OF THE CHIEF OF POLICE

ADMINISTRATIVE ANNOUNCEMENT

DATE ISSUED:	DATE EFFECTIVE:	NUMBER:	PAGE:
5/18/18	5/18/18	AA18-013	1 of 1
ISSUED BY:		ASSIGNMENT LOCATION:	
Commander Todd Sauvageau		Leadership & Organizational Development Division	
TO:			RETENTION DATE:
ALL MPD			Until Rescinded
SUBJECT:			APPROVED BY:
EMS Sedation			*DC Halvorson*

MP-3407

We are seeing an increase in MPD incidents ending with EMS sedation and subjects being transported to hospitals for care. This AA is a reminder to MPD Employees regarding the roles and responsibilities of EMS Personnel and MPD Officers on these scenes.

EMS Responsibilities: To evaluate the overall situation *(patient's current condition and behaviors)* and determine the proper medical action. EMS must follow their policies and training when determining whether administering a chemical sedation drug, like Ketamine, is the best option.

MPD Officer Responsibility: To provide arriving EMS with information related to the subject's observed/known conditions and behaviors so EMS can conduct a quick and accurate assessment and determine the best course of medical action. MPD Officers shall never suggest or demand EMS Personnel "sedated" a subject. This is a decision that needs to be clearly made by EMS Personnel, not MPD Officers.

As always, in situations where a subject is showing physical signs of a medical condition such as cocaine psychosis or excited delirium, EMS should always be requested early as a precaution. It's important to have EMS en-route as soon as possible to ensure timely medical assistance.

In those cases where EMS determines chemical sedation is not an option, MPD officers and paramedics should collaborate to stabilize the situation and control the subject. Transportation options can be determined once the subject has been controlled.

In situations not requiring EMS response *(i.e. subject is physically resisting, combative/ aggressive, but does not show signs of a medical condition or distress requiring EMS)*, Officer should utilize their training and experience to attempt de-escalation and/or physical controlling tactics to stabilize the situation. One physical option available to MPD Officers is the Maximal Restraint Technique.

Maximal Restraint Technique (MRT): Used to secure a subject's feet to their waist in order to prevent the movement of legs and limit the possibility of property damage or injury to him/her or others. The MRT shall only be used in situations where handcuffed subjects are combative and still pose a threat to themselves, officers or others, or could cause significant damage to property if not properly restrained.

Hennepin Emergency Medical Services
701 Park Avenue South, MC 825
Minneapolis, MN 55415
612-873-5678

INTER OFFICE MEMORANDUM

TO: HENNEPIN EMS STAFF
FROM: ROSS CHÁVEZ, ASSISTANT CHIEF
SUBJECT: SEDATION FOR BEHAVIORAL EMERGENCIES
DATE: MAY 25, 2018

Please be aware that Hennepin EMS leadership is working on an issue that has come up in regards to how Minneapolis Police and Hennepin EMS interface on calls that may require sedating a patient experiencing a behavioral emergency. Look for more detailed communication to come out soon, but in the meantime please continue to follow your protocols, exercise your clinical judgement, and remain professional with all of our customers: patients, families, fire, law enforcement, hospital staff, and each other.

Please direct any questions to Ross.Chavez@hcmed.org.

Respectfully,

Ross A. Chávez
Assistant Chief

Hennepin Emergency Medical Services
701 Park Avenue South, MC 825
Minneapolis, MN 55415
612-873-5678

INTER OFFICE MEMORANDUM

TO: HENNEPIN EMS STAFF
FROM: DR. JEFF HO, CHIEF MEDICAL DIRECTOR | ROSS CHÁVEZ, ASST. CHIEF
SUBJECT: SEDATION FOR BEHAVIORAL EMERGENCIES
DATE: MAY 31, 2018

Please review the memo from Dr. Ho **in its entirety** at your earliest convenience. The following bullet points are what you need to know right now:

- Per the previous memo posted on May 25th, Hennepin EMS leadership and MPD leadership are working on clarifying expectations when responding to calls involving agitated/potentially violent patients who may require sedation. Your personal safety is paramount and you are not expected to enter into a situation before it is deemed Code 4 by Law Enforcement.
- Two-way communication between you and Law Enforcement on scene is essential for you to formulate an appropriate plan for the patient, except in emergent situations where clinical intervention may take precedence over information-gathering.
- The decision to use chemical sedation ultimately rests with you, the clinical expert on scene, and not with Law Enforcement.
- Chemical sedation should be a final option unless your clinical judgement dictates otherwise. You are not required to exhaust all de-escalation techniques if it is not appropriate for the situation.
- It is expected that your decision to use chemical sedation be supported by documentation.
- Continuous monitoring of the agitated patient is essential, even if de-escalated, as the need for chemical sedation may arise during transport, restraint application, personal safety precautions, and/or the need for additional resources.

All HEMS Paramedic Staff,

Within the past several months, there has been a notable, unintentional shift in our interactions with the Minneapolis Police Department (MPD) on calls involving agitated/potentially violent patients. Several of you have made me aware of this and it involves MPD personnel at these scenes strongly urging us to use chemical sedation to manage these cases immediately upon our arrival on scene. I know that this puts you in an awkward situation of feeling as if you are being ordered to do something without the benefit of understanding the totality of the situation.

In discussing this with the MPD and HEMS executive command, we are on the same page with our expectations of our respective personnel. This is a reminder summary of what your official roles/responsibilities/expectations are on these types of calls:

1. Your personal safety is paramount. You are not expected to enter into a situation before it is deemed Code 4 by Law Enforcement.

2. When you arrive to assume care of the patient, you have the right to receive full information about the situation, the patient, and MPD's ultimate goal (e.g. arrest vs. psychiatric hold vs. medical assessment, etc.). In emergent cases, deal with the emergency first and obtain the information later. Emergent cases may include, but are not limited to, an active fight and MPD is losing or the patient is clinically in the throes of Excited Delirium Syndrome and is at high risk of cardiopulmonary arrest and needs immediate medical intervention.

3. When dealing with an agitated subject, chemical sedation should be the final option if, in your judgment, other options (such as verbal de-escalation, situational and environmental de-escalation, etc.) are not appropriate. You are not required to exhaust all de-escalation tools prior to resorting to chemical sedation, but you will be expected to articulate to me and in your documentation why no other options would have been reasonable to use.

   ****I cannot stress this enough**: I am not asking you to try every option before using chemical sedation for a patient that needs it. In situations of imminent danger, you may need to use chemical sedation immediately. However, I am asking you to heavily weigh in your decision-making process whether chemical sedation is absolutely necessary in a particular scenario. I am asking you to consider if the patient really needs to receive chemical sedation. If the answer is "yes", the facts of the situation are clear, and you can document the basis for your decision, you will have my support every single time.**

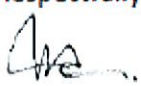
4. The decision to use chemical sedation on a patient for behavioral control rests ultimately with HEMS (meaning you as the on-scene paramedic) and not with MPD. Your decision-making process should take into account the totality of the situation including MPD's request, but there are many other variables involved. These factors may include, but are not limited to considerations such as:
    a. Size and gender of both the patient and yourself (e.g., if you are outweighed and outsized by the patient and will have to be in the back of the truck alone with them during transport, that may be a safety concern).
    b. Patient abilities or past history (e.g., the patient is a known martial arts or fighting expert or has been known to assault EMS staff in the past).
    c. Patient clinical condition (e.g., the patient has been significantly agitated and you are concerned that if they do not sufficiently calm down their level of metabolic acidosis places them at elevated risk for cardiopulmonary arrest).
    d. Other factors (e.g., there is a discretionary level of decision-making that goes into managing these types of situations and other factors that may impact your decision. In order to support those decisions you must document what those factors are and document why they compelled your decision.)

5. Once you have assumed patient care, regardless of whether or not chemical sedation was used, the patient's care and well-being becomes your full responsibility. You must constantly monitor each patient for basic ABC's and intervene when necessary. Additionally, you must consider how the patient will behave during transport. A patient's behavior can change rapidly and without warning. Even a de-escalated patient can become agitated and dangerous to you. Therefore, always consider the need for physical restraints, your proximity and position to the patient, and/or the need for additional assistance in the back of the ambulance during transport.

Ultimately, your personal safety, the outstanding care of our patients, and collaborative work with our partners are among the goals of Hennepin EMS. Feel free to stop in to see me if the instructions are not clear.

Thank you for all that you do.

Respectfully,



Jeffrey D. Ho, M.D., FACEP, FAAEM
MD1, Chief Medical Director
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APPENDIX 9: Letter to FDA and OHRP Regarding Prospective Clinical Trials Testing Ketamine for Agitation

PUBLICCITIZEN
1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

July 25, 2018

Scott Gottlieb, M.D.
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections
U.S. Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

RE: Prospective clinical trials comparing the safety and effectiveness of ketamine with those of other drugs for management of agitation were conducted without the informed consent of the subjects, in violation of federal human subjects protection regulations

Dear Drs. Gottlieb and Menikoff:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, and the undersigned individuals — with expertise spanning, among other things, bioethics, medicine, human subjects protections, human rights, and law — are writing to request that the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP) immediately launch formal compliance oversight investigations into the conduct and oversight of two prospective clinical trials that involved testing the safety and effectiveness of the general anesthetic ketamine in comparison with those of other potent sedative drugs for management of prehospital agitation. Based on our review of available documents describing these clinical trials — which were conducted by investigators at the Hennepin County Medical Center in Minneapolis, MN — the trials failed to (a) materially comply with key requirements of FDA and Department of Health and Human Services (HHS) regulations for the protection of human subjects at 21 C.F.R. Parts 50 and 56 and at 45 C.F.R. Part 46, respectively, and (b) satisfy the basic ethical principles upon which those regulations are founded.

Disturbingly, these clinical trials were incorrectly determined by the investigators and the Hennepin County Medical Center's institutional review board (IRB) to involve no more than minimal risk to the subjects and, based on that determination, the IRB waived the informed

consent requirements under HHS regulations at 45 C.F.R. § 46.116(d), when in fact these experiments clearly involved research-stipulated interventions that far exceeded the minimal risk threshold.

We note that both the FDA and OHRP have jurisdiction over these clinical trials. First, the trials were clinical investigations involving human subjects as defined by FDA human subjects protection regulations at 21 C.F.R. §§ 56.102(c) and (e). Second, the trials comprised research involving human subjects as defined by HHS human subjects protection regulations at 45 C.F.R. §§ 46.102(d) and (f), and the Hennepin County Medical Center holds an OHRP-approved Federalwide Assurance (FWA #6047) that applies to all non-exempt human subjects research regardless of sponsorship.[1]

The following is a detailed discussion of these trials and the serious regulatory and ethical lapses related to their oversight and conduct.

Overview of the clinical trials

Ketamine versus haloperidol trial for prehospital agitation

The first trial, a prospective clinical trial of ketamine versus haloperidol for purportedly severe prehospital agitation, was described by Cole et al in an article published in *Clinical Toxicology* in 2016.[2] The trial investigators enrolled adults age 18 or older who were managed by paramedics within the local emergency medical system (EMS) and had "severe acute undifferentiated agitation" prior to being transported to the Hennepin County Medical Center emergency department (ED).

For the purposes of the trial, agitation was scored using the Altered Mental Status Scale (AMSS), which appears to be a research tool that was "routinely used in agitation research" at Hennepin County Medical Center. The AMSS was an amalgam of previous scales[3] that had been developed to assess levels of alertness or sedation,[4] agitation,[5] or intoxication.[6] The AMSS score is a composite of ratings for the following four elements: responsiveness, speech, facial expressions, and eyes.

[1] Email communication with OHRP.
[2] Cole JB, Moore JC, Nystrom PC, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. *Clin Toxicol (Phila)*. 2016;54(7):556-562.
[3] Martel M, Sterzinger A, Miner J, et al. Management of acute undifferentiated agitation in the emergency department: a randomized double-blind trial of droperidol, ziprasidone, and midazolam. *Acad Emerg Med*. 2005;12(12):1167–1172.
[4] Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the observer's assessment of alertness/sedation scale: study with intravenous midazolam. *J Clin Psychopharmacol*. 1990;10(4):244–251.
[5] Swift RH, Harrigan EP, Cappelleri JC, et al. Validation of the behavioral activity rating scale (BARS): a novel measure of activity in agitated patients. *J Psychiatr Res*. 2002; 36(2):87–95.
[6] Miner JR, Biros M. A standardized intoxication scale vs breath ethanol level as a predictor of observation time in the emergency department [abstract]. *Acad Emerg Med*. 2003; 10(5):520.

For the purposes of the trial, "severe agitation" was defined as an AMSS score of +2 (Responsiveness-anxious, agitated; Speech-loud outbursts; Facial Expression-normal; and Eyes-normal) or +3 (Responsiveness-very anxious, agitated, mild physical element of violence; Speech-loud outbursts; Facial Expression-agitated; and Eyes-normal). The trial excluded any patient with "profound agitation," which was defined as an AMSS score of +4 (Responsiveness-combative, very violent, or out of control; Speech-loud outbursts; Facial Expression-agitated; and Eyes-normal), because the investigators' institution "deemed it unethical and unwise to withhold ketamine from the most profoundly agitated patients at any time for both patient and caregiver safety."

The investigators used a prospective, open-label, nonrandomized design in which each subject's clinical trial group assignment and selection of intervention with ketamine or haloperidol was determined by the time period in which the subjects were enrolled, not by the clinical judgment of the health care professionals caring for the subjects. Specifically, the research interventions were described by the investigators as follows:

> To minimize potential bias introduced by seasonal changes, data were collected throughout an entire calendar year. **For the first three months of the study (October 2014–January 2015), the standard EMS operating procedure (SOP) for severely agitated patients was to treat acute undifferentiated agitation with 10 mg of IM haloperidol. For the next 6 months, haloperidol was removed from all ambulances in the system and the SOP for severely agitated patients was changed to 5 mg/kg of IM ketamine (dose calculation made by EMT-paramedic estimated weight in the field). For the final 3 months of the study, the SOP was returned to haloperidol 10 mg IM and haloperidol was reinstated on the ambulances**. [Emphasis added]

Thus, the clinical trial protocol dictated whether a particular subject with prehospital agitation would receive ketamine or haloperidol and precluded use of any other medication. Moreover, it appears that the care of all patients with agitation in the EMS system was potentially altered by the clinical trial protocol.

The primary outcome was the time to adequate sedation. Measurement of this outcome was done by the paramedics. The investigators described the training of the paramedics for the clinical trial as follows:

> All paramedics were trained in the AMSS, **a validated score of agitation routinely used in agitation research at the study institution**. Training was completed both online and at in-person training sessions led **by the primary investigator**. All paramedics were required to pass a quiz containing example patients where a correct AMSS score must be assigned. Upon encountering a patient with severe agitation requiring chemical sedation, paramedics activated a stopwatch immediately after injection of the sedative. Patients were excluded if stopwatch activation did not occur. AMSS scores were recorded every 5 minutes, or until adequate sedation was reached. Adequate sedation was defined clinically by the treating paramedic; however during training it was emphasized that adequate treatment of agitation would be an AMSS score < +1. Paramedics were specifically instructed to stop the stopwatch prior to 5 minutes if the patient appeared to

> have reached adequate sedation. **Paramedics also recorded prospectively if a legally authorized representative was present at the scene to give consent.** [Emphasis added]

Remarkably, despite the above description of the research procedures, the investigators asserted that "[t]his was a Waiver of Consent (45 CFR 46.116) prospective observational study."

The investigators also noted the following:

> Though this study was approved by the institutional IRB as a Waiver of Consent study, given the particularly vulnerable nature of this patient population a community consultation was performed in accordance with federal guidelines for Exception From Informed Consent (21 CFR 50.24) research. Both the caregivers affected by this study as well as a select group of patients at a local homeless shelter's inpatient chemical dependency program were consulted.

Between October 2015 and September 2016, 146 unwitting subjects were reportedly enrolled in the trial, 64 (57 with an initial AMSS score of +3 and seven with an initial score of +2) in the ketamine group and 82 (60 with an initial AMSS score of +3 and 22 with an initial score of +2) in the haloperidol group. Notably, adverse events, which included hypersalivation, emergence reactions, vomiting, dystonia, laryngospasm, akathisia, and death (one in the haloperidol group), were much more frequent in ketamine group subjects than in haloperidol group subjects (49 percent versus 5 percent, respectively; $p < 0.0001$). The rate of intubation was also significantly higher in ketamine group subjects than in haloperidol group subjects (39 percent versus 4 percent, respectively; $p < 0.0001$).

Ketamine versus midazolam trial for prehospital agitation

Even though the results of the first clinical trial clearly demonstrated that ketamine is significantly more dangerous than haloperidol for managing prehospital agitation as defined by an AMSS score of +2 or +3, some of the same investigators at Hennepin County Medical Center subsequently initiated a prospective clinical trial comparing ketamine with midazolam for purportedly severe or profound prehospital agitation. Details of the trial are available at ClinicalTrials.gov (NCT03554915).[7]

The trial, which began on August 1, 2017, and was suspended last month, appears to be using a design that is nearly identical to the ketamine versus haloperidol trial. The trial investigators enrolled adults age 18 or older who were managed by paramedics within the local emergency medical EMS and had purportedly severe agitation (an AMSS score of +2 or +3) or profound agitation (an AMSS score of +4) prior to being transported to the Hennepin County Medical Center ED. They had planned to enroll approximately 420 subjects between August 2017 and August 2018.

[7] U.S. National Library of Medicine. ClinicalTrials.gov. Ketamine versus midazolam for prehospital agitation. Updated July 2, 2018. https://clinicaltrials.gov/ct2/show/NCT03554915. Accessed July 6, 2018.

The investigators again used a prospective, open-label, nonrandomized design in which each subject's clinical trial group assignment and selection of intervention with ketamine or midazolam was determined by the time period in which the subjects were enrolled, not by the clinical judgment of the health care professionals caring for the subjects. Specifically, the research interventions were described by the investigators as follows:

> Active Comparator: Ketamine-based Protocol
>
> The first 6 month period of the study will employ a ketamine-based protocol for prehospital agitation. There will be a tiered dosing protocol based on degree of agitation… For profoundly agitated (physically violent) patients, intramuscular ketamine 5 mg/kg will be administered first line. For severely agitated patients, intramuscular ketamine 3 mg/kg will be administered first line.
>
> Active Comparator: Midazolam-based Protocol
>
> The second 6 month period of the study will employ a midazolam-based protocol for prehospital agitation. There will again be a tiered dosing protocol based on degree of agitation… For profoundly agitated patients, intramuscular midazolam 15 mg will be administered. For severely agitated patients, intramuscular midazolam 5 mg will be administered.

Similar to the first trial, the ketamine versus midazolam clinical trial protocol dictated whether a particular subject with prehospital agitation would receive ketamine or midazolam and precluded use of any other medication, such as haloperidol, which was demonstrated in the first trial to be safer than ketamine. Moreover, it appears that the clinical care of all patients with agitation in the EMS system was potentially altered by the clinical trial protocol.

The primary outcome of the trial is the time from injection of drug to adequate sedation, defined as a score of +1 or less on the AMSS. The AMSS score was to be "determined by the treating paramedic," who was to "**undergo training as a research associate** prior to commencement of the trial" [emphasis added]. Subjects were to be followed for the duration of agitation, an expected average of 2 hours. Secondary outcome measures included the number of subjects who were intubated and the number of subjects who experienced each of the following: hypersalivation, apnea, nausea and vomiting, laryngospasm, and the need for rescue sedation.

A "NOTIFCATION OF ENROLLMENT" form that was provided to subjects (or subjects' caregivers) after their involvement in the research (copy enclosed) stated the following:

> You are receiving this form because you or someone you care for was included in a research study examining patients with agitation. This research study is being done to find out if one of two drugs, ketamine or midazolam is better for treating agitation… The Hennepin EMS System is undergoing a standard protocol change from one drug to the other; to compare which drug may be better the study doctors are collecting data on patients before and after the protocol change… Previous studies from our hospital suggest both drugs have similar risks…

> **Because this study involves collection of data in a setting where usual care was conducted, you were not consented prior to enrollment. This is permitted under federal regulations for Waiver of Consent Research (45 CFR 46.116(d)).** [Emphasis added]

Hennepin County Medical Center suspended the clinical trial on June 25, 2018, after troubling details about the conduct of the study — including the failure to obtain informed consent from the subjects for this greater-than-minimal-risk research and the apparent use of ketamine in patients who may not have been severely agitated — were exposed by the *Star Tribune*.[8,9] Following the trial's suspension, the institution issued a question and answer document defending the trial that stated the following, in part:[10]

> This study was considered observational (i.e. only collecting data) and "low risk" by the Institutional Review Board (IRB) that oversees patient safety in research studies at our institution. This means our research was not intended to intervene in the routine care or treatment of patients or the decision-making process of our clinicians or EMS staff. Instead, the intent was to review the effects of those patients already receiving a sedative, like ketamine, to determine which sedative, if required in the field, would be the safest for our patients.
>
> **What is your response to community concern about having a waiver of consent?**
>
> The federal requirements from the IRB approval process for this study were completely followed – including the waiver of consent to review data. This met all the ethical standards under which we conduct research, and we take this very seriously.

Assessment of risk in these prospective ketamine clinical trials: Both experiments involved far greater than minimal risk

FDA regulations at 21 C.F.R. § 56.102(i) and HHS human regulations at 45 C.F.R. § 46.102(i) define minimal risk as follows:

> *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

[8] Mannix A. Patients sedated by ketamine were enrolled in Hennepin Healthcare study. *Star Tribune*. June 23, 2018. http://www.startribune.com/patients-sedated-by-ketamine-were-enrolled-in-hennepin-healthcare-study/486363071/. Accessed July 6, 2018.
[9] Mannix A. Ketamine study at Hennepin Healthcare suspended after criticism from politicians. *Star Tribune*. June 26, 2018. http://www.startribune.com/ketamine-study-at-hennepin-healthcare-suspended-after-criticism-from-politicians-minneapolis-police-sedate/486507021/. Accessed July 6, 2018.
[10] Hennepin County Medical Center. Frequently asked questions about the use of sedatives. https://hennepinmedical.files.wordpress.com/2018/06/faqs-2018-6-262.pdf. Accessed July 7, 2018.

Application of this definition is central to any decision to approve a waiver of informed consent for research. Under HHS regulations at 45 C.F.R. § 46.116(d), an IRB may waive the requirements for informed consent provided the IRB finds and documents, among other things, that the research involves no more than minimal risk to the subjects. Notably, when the ketamine versus haloperidol trial was conducted, the FDA regulations did not provide for a waiver of the informed consent requirements similar to the HHS waiver provisions at 45 C.F.R. § 46.116(d), so such a waiver was not permissible for any FDA-regulated clinical trial. Under guidance issued by the FDA in July 2017, just before the ketamine versus midazolam trial began, such a waiver is now permissible.[11]

However, whether the two trials involved no more than minimal risk is not in question: A prospective clinical trial in which human subjects were assigned by a research protocol to receive the general anesthetic ketamine or a different powerful sedative drug for agitation, rather than according to the clinical judgment of the health care professionals caring for the subjects, clearly exceeded minimal risk and therefore was **not** eligible for waiver of informed consent under HHS regulations at 45 C.F.R. § 46.116(d).

Reliance on the AMSS research tool to define "severe agitation" likely lowered the threshold for using ketamine or other potent sedatives compared with usual care

Importantly, for the purposes of these clinical trials the investigators utilized the AMSS, which appears to be a "validated" research tool that was "routinely used in agitation research" at Hennepin County Medical Center.[12] However, the AMSS apparently was not routinely used by paramedics within the Hennepin County EMS system at the time these clinical trials were conducted, given the need for the investigators to train paramedics in use of the tool for the purposes of both trials.

For both trials, the investigators arbitrarily defined "severe agitation" as an AMSS score of +2 or +3. This definition of "severe agitation" likely was overly broad and resulted in some patients — particularly those at the lower end of this AMSS score range — being labeled as severely agitated and subsequently receiving the general anesthetic agent ketamine (or another powerful sedative drug) that they otherwise might not have received as part of usual care outside of the clinical trials. We note that there may be little difference subjectively between someone who appears anxious and restless (a component of an AMSS score of +1, which presumably represents mild agitation) and someone who appears anxious and agitated (a component of an AMSS score of +2, the lower end of the protocol-defined severe agitation range). In addition, the AMSS scale as interpreted by the investigators for the purposes of these trials appears to exclude a category of "moderate agitation." Thus, a patient could have been anxious and mildly or moderately agitated, had an AMSS score of +2, and been enrolled in these trials.

[11] Food and Drug Administration. IRB waiver or alteration of informed consent for clinical investigations involving no more than minimal risk to human subjects; guidance for sponsors, investigators, and institutional review boards. July 2017. https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM566948.pdf. Accessed July 6, 2018.

[12] Cole JB, Moore JC, Nystrom PC, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. *Clin Toxicol (Phila)*. 2016;54(7):556-562.

Therefore, use of the AMSS research tool itself likely altered the interventions and risks to which the subjects were exposed in comparison to the usual care that they might have received had they not been enrolled in these clinical trials.

Risks of ketamine

Ketamine hydrochloride injection (sold under the brand name Ketalar and in generic versions) is a nonbarbiturate general anesthetic formulated for intravenous or intramuscular injection.[13] According to its FDA-approved product labeling, the drug is approved by the FDA only for the following indications:

- As the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation
- For the induction of anesthesia prior to the administration of other general anesthetic agents
- To supplement low-potency agents, such as nitrous oxide

The drug is not FDA-approved for management of agitation. The labeling cautions that the drug should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.

The product labeling for ketamine describes the following potentially serious adverse effects and risks of the drug:

- *Psychological*: Emergence reactions, which have occurred in approximately 12 percent of patients. The psychological manifestations of these reactions vary in severity between pleasant dream-like states, vivid imagery, hallucinations, and emergence delirium. In some cases, these states have been accompanied by confusion, excitement, and irrational behavior, which a few patients recall as an unpleasant experience. The duration of these reactions ordinarily is no more than a few hours; in a few cases, however, recurrences have taken place up to 24 hours postoperatively.
- *Cardiovascular*: Blood pressure and pulse rate are frequently elevated following administration of ketamine alone. However, hypotension and bradycardia have been observed. Arrhythmias also have occurred.
- *Respiration*: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of ketamine. Laryngospasms and other forms of airway obstruction have occurred during ketamine anesthesia.
- *Eye*: Diplopia and nystagmus have been noted following ketamine administration. It also may cause a slight elevation in intraocular pressure measurement.
- *Neurological*: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures.

[13] Par Pharmaceutical. Drug label: ketamine hydrochloride injection (KETALAR). April 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/016812s043lbl.pdf. Accessed July 6, 2018.

- *Gastrointestinal*: Anorexia, nausea, and vomiting have been observed.
- *General*: Anaphylaxis has been observed.

The drug also is contraindicated in patients in whom a significant elevation of blood pressure would constitute a serious hazard and in those who have hypersensitivity to the drug. Importantly, in contrast to the preoperative assessment of patients who are to receive ketamine as anesthesia for surgery or other invasive procedures, use of the drug by paramedics for agitation in most cases likely precludes an adequate assessment of whether a significant elevation of blood pressure would constitute a serious hazard in a particular acutely agitated patient and is therefore contraindicated.

Approximately two years prior to the initiation of the ketamine versus haloperidol trial, many of the investigators for these clinical trials had published a paper in *Prehospital Emergency Care* in 2013 that presented two case reports of the use of prehospital ketamine for the management of excited delirium syndrome, the most profound type of agitation.[14] In that paper, they explicitly warned that ketamine should be reserved for patients with excited delirium syndrome and should not be used in patients with lesser degrees (i.e., severe or less) of agitation because of the drug's known toxicities:

> **We would caution against using ketamine sedation in situations that do not warrant the immediate need for interruption of the severe, life-threatening, metabolic acidosis/catecholamine surge crisis seen in late-stage [excited delirium syndrome].** Clinicians should always consider the risk–benefit ratio of a possible intervention. In 2012, Burnett et al. described a case report of laryngospasm as a complication of prehospital ketamine administration in an agitated person. Laryngospasm is a known potential side effect of ketamine and can cause airway compromise. Although that person was labeled as an [excited delirium syndrome] patient, the details of that case (near normal pulse rate of 101 beats/min in the field with a respiratory rate of 18 breaths/min, normothermia, normal CK level, and a negative toxicology screen) make it unlikely to be late-stage [excited delirium syndrome] with an immediate threat to life. **Late-stage [excited delirium syndrome], where subjects are wildly agitated and violently exertional, should have marked tachycardia, hyperventilation secondary to metabolic acidosis, and hyperthermia with CK derangement. We would advocate that ketamine not be the chemical solution for every unruly or belligerent subjects [sic], as this would lead to overuse with unnecessary risk.** [Emphasis added]

The investigators further reported in their 2013 paper that Hennepin County's "EMS system standing-order protocol **reserves** the use of ketamine for profound agitation involving imminent risk of injury to patient or provider" [emphasis added]. The Hennepin County EMS system's standing-order protocol at that time thus appears to have precluded the use of ketamine in patients who did not have profound agitation.

[14] Ho JD, Smith SW, Nystrom PC, et al. Successful management of excited delirium syndrome with prehospital ketamine: Two Case Examples. *Prehosp Emerg Care*. 2013;17(2):274-279.

Nevertheless, disregarding their own advice, these investigators soon designed and conducted the ketamine versus haloperidol trial involving subjects who did not have excited delirium syndrome and instead had far less severe levels of agitation. And not surprisingly, their 2013 comments were prescient: As previously noted, adverse events, including laryngospasm, and the rate of intubation were significantly higher in ketamine group subjects than haloperidol group subjects, thus demonstrating that ketamine is significantly more dangerous than haloperidol for patients who have levels of agitation in the prehospital setting that are less severe than excited delirium syndrome.

In conclusion, the risks of exposure to ketamine obviously constituted the most substantial reasonably foreseeable risks to the subjects of both clinical trials, and those risks far exceeded the threshold of minimal risk, as defined by FDA and HHS human subjects protection regulations.

Risks of haloperidol and midazolam

Although the exposure of the research subjects to ketamine presented the greatest reasonably foreseeable risks to the subjects, exposure to either haloperidol or midazolam also exposed subjects to reasonably foreseeable risks of the clinical trials that exceeded minimal risk because the research protocols for these trials dictated when exposure to these drugs would occur for certain subjects, precluded other treatments, and likely resulted in some subjects receiving one of these potent sedatives when they otherwise might not have if they had been managed according to usual care.

The FDA-approved product labeling for haloperidol injection (sold under the brand name Haldol and in generic versions) indicates that the drug is approved only for the treatment of schizophrenia and the control of the tics and vocal utterances of Tourette's disorder.[15] The drug's many known risks include QT prolongation, cardiac arrhythmias, sudden death, tardive dyskinesia, and neuroleptic malignant syndrome.

The FDA-approved product labeling for midazolam (sold in generic versions only) indicates that the drug is approved only for preoperative sedation/anxiolysis/amnesia; sedation/anxiolysis/amnesia prior to or during diagnostic, therapeutic, or endoscopic procedures; induction of general anesthesia before administration of other anesthetic agents; sedation of intubated and mechanically ventilated patients as a component of anesthesia or during treatment in a critical care setting.[16] The drug's many known risks include respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest, cardiac arrest, permanent neurologic injury, and death.

[15] Janssen Pharmaceuticals Companies. Drug label: haloperidol injection (HALDOL). December 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/015923s092lbl.pdf. Accessed July 7, 2018.
[16] Akorn Drug label: midazolam hydrochloride injection. November 2017. https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=737361a0-8db1-4d3c-ba5e-44df3f49fa22&type=pdf&name=737361a0-8db1-4d3c-ba5e-44df3f49fa22. Accessed July 7, 2018.

Failure to satisfy the requirements for obtaining the informed consent of the subjects under FDA and HHS human subjects protection regulations

In summary, the two clinical trials were not eligible for a waiver of informed consent under HHS regulations at 45 C.F.R. § 46.116(d) or under the FDA's July 2017 guidance on waiver of informed consent for certain research involving no more than minimal risk because the research clearly involved reasonably foreseeable risks that far exceeded the threshold of minimal risk.[17] The shocking failure by the Hennepin County Medical Center's IRB to recognize that these prospective clinical trials would expose subjects to greater-than-minimal-risk research interventions resulted in inappropriate waivers of informed consent. The oversight and conduct of these clinical trials thus flagrantly violated the requirements for obtaining the legally effective informed consent of the subjects (or the subjects' legally authorized representatives) under FDA regulations at 21 C.F.R. §§ 50.20 and 50.25 and HHS regulations at 45 C.F.R. § 46.116, regulations that are founded on the Belmont Report's basic ethical principles of respect for persons.[18]

We acknowledge that the investigators and the IRB alternatively could have considered whether these clinical trials were eligible for the exception from informed consent requirements for emergency research under FDA regulations at 21 C.F.R. § 50.24. However, it is unlikely that all provisions of these regulations could have been reasonably satisfied for either trial as designed and conducted.

Other regulatory lapses

But the regulatory lapses regarding the conduct and oversight of this trial extend well beyond those related to the assessment of risk and the waiver of informed consent. By failing to recognize that these prospective clinical trials involved greater than minimal risk to the subjects, the Hennepin County Medical Center's IRB also could not possibly have appropriately determined that the research satisfied the following criteria, among others, required for approval of research under FDA regulations at 21 C.F.R. § 56.111 and HHS regulations at 45 C.F.R. § 46.111:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

[17] Food and Drug Administration. IRB waiver or alteration of informed consent for clinical investigations involving no more than minimal risk to human subjects; guidance for sponsors, investigators, and institutional review boards. July 2017. https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM566948.pdf. Accessed July 6, 2018.

[18] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Ethical principles and guidelines for the protection of human subjects of research. April 18, 1979. https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf. Accessed July 7, 2018.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

These regulatory requirements are founded on the Belmont Report's basic ethical principles of beneficence and justice.[19]

Finally, it seems likely that these trials required investigational new drug applications (INDs) under FDA regulations at 21 C.F.R. 21 Part 312. The FDA advised in guidance issued in 2013[20] that an IND is needed for a clinical investigation of a marketed drug unless *all* of the following criteria for an exemption under FDA regulations at 21 C.F.R. § 312.2(b) are met:

(1) The drug product is lawfully marketed in the United States.

(2) The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.

(3) In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.

(4) The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 C.F.R. § 312.2(b)(1)(iii)).

(5) The investigation is conducted in compliance with the requirements for review by an IRB (21 C.F.R. Part 56) and with the requirements for informed consent (21 C.F.R. Part 50).

(6) The investigation is conducted in compliance with the requirements of 21 C.F.R. § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

As already discussed, these trials did not meet criterion 5. Moreover, these clinical trials also did not meet criterion 4 because they involved patient populations that significantly increased the

[19] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Ethical principles and guidelines for the protection of human subjects of research. April 18, 1979. https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf. Accessed July 7, 2018.
[20] Food and Drug Administration. Guidance for clinical investigators, sponsors, and IRBs: Investigational new drug applications (INDs) — Determining whether human research studies can be conducted without an IND. September 2013. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm229175.pdf. Accessed July 7, 2018.

risk and decreased the acceptability of the risk associated with use of ketamine. Thus, an IND was required for these clinical trials.

Conclusions and requested actions

The unacceptable regulatory and ethical lapses in the oversight and conduct of these two prospective clinical trials that involved testing the safety and effectiveness of the general anesthetic ketamine compared with other potent sedative drugs for management of prehospital agitation reflect systemic breakdowns in the Hennepin County Medical Center's human subjects protection program. These breakdowns extend from the investigators to the IRB to senior institutional officials.

Evidence that these systemic breakdowns encompass senior institutional officials can be found in the awkward and troubling efforts of Hennepin County Medical Center's leadership to defend the conduct and oversight of these clinical trials. For example, in a June 27, 2018, email sent to all Hennepin Healthcare employees regarding the ketamine versus midazolam clinical trial after it was suspended, Hennepin Healthcare's Chief Executive Officer Dr. Jon L. Pryor, stated the following:[21]

> It is important that **you have the facts**, specifically about these issues [emphasis added]:
> …
> **Waiver of Consent** [emphasis in original]
>
> - There has been a lot in the press about doing a study without consent which is referred to as "waiver of consent." **The majority of Waivers of Consent "involve studies in which there are minimal risks to subjects" and this is the category of the Ketamine study under current scrutiny, since we were only reviewing data** [emphasis added]. To quality [sic] for waiver of consent with minimal risk we need to follow specific federally regulated ethical standards. We closely follow these standards and are currently doing nothing different at Hennepin Healthcare – we are just like hundreds of other academic medical centers in the U.S.

Likewise, in a public statement posted on the institution's website, the medical center characterized the ketamine versus midazolam clinical trial as being "observational (i.e. only collecting data)" and "low risk,"[22] representations that cannot be reconciled with the descriptions of the research protocol found in other publicly available documents. Also, in response to the question, "**Is ketamine use common and is it safe to use with agitated patients?**" the institution's public statement misleadingly stated that "Hennepin EMS has been using ketamine as the standard of care for patients safely since 2008." But as noted above, some of the investigators for these clinical trials themselves explained in 2013 that ketamine was *not* the

[21] Copy of email received in a personal communication.
[22] Hennepin County Medical Center. Frequently asked questions about the use of sedatives. https://hennepinmedical.files.wordpress.com/2018/06/faqs-2018-6-262.pdf. Accessed July 7, 2018.

standard of care and should *not* be used for managing the type of agitated patients with AMSS scores of +2 and +3 who were enrolled in these clinical trials.[23]

A critical question for the FDA and OHRP is how many other ongoing and prior clinical trials conducted by the Hennepin County Medical Center have or had similar serious regulatory and ethical lapses? To ensure the protection of human subjects enrolled in clinical trials conducted by this institution, it is imperative that the FDA and OHRP promptly learn the answer to this question.

We therefore urge the FDA and OHRP to immediately launch formal compliance oversight investigations into the conduct and oversight of the two prospective clinical trials that tested ketamine and into the Hennepin County Medical Center's human subjects protection program. These investigations should include (1) a rigorous FDA inspection of the institution's IRB and other clinical trials conducted by the same group of investigators that conducted the two ketamine clinical trials and (2) a comprehensive for-cause site visit by OHRP compliance oversight staff that examines IRB records for a wide array of clinical trials and other human subjects research.

We hope you share our concern regarding these troubling matters, and we look forward to a favorable response to our urgent request for investigations of the oversight and conduct of these clinical trials.

Please contact us if you have any questions or need additional information.

Sincerely,

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[23] Ho JD, Smith SW, Nystrom PC, et al. Successful management of excited delirium syndrome with prehospital ketamine: Two Case Examples. *Prehosp Emerg Care*. 2013;17(2):274-279.

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