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Evaluating the impact of an emergency department protocol that guides management of methamphetamine-induced agitation and psychosis

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Abstract

Background: Methamphetamine is an addictive stimulant that may induce symptoms of agitation and psychosis. The estimated rate of methamphetamine use is 6.6 per 1000 people. Currently, no treatment guidelines exist to support the optimal management of patients presenting with methamphetamine-induced agitation. Emergency department (ED) providers may prescribe various benzodiazepines (BZDs) and antipsychotics (APs) as first-line agents to stabilize these agitated patients. This study aims to determine the effectiveness of a protocol to guide management of this condition.

Methods: This was a retrospective, pre- and poststudy conducted from July 2020 to March 2021 at a large academic medical center. A multidisciplinary protocol was designed to help manage methamphetamine-induced agitation in the ED. The primary outcome of the study was a reduction in the number of BZDs and APs used for the treatment of methamphetamine-induced agitation. This was measured by the incidence of overprescribing, defined as 3 or more APs or BZDs administered within 30 minutes. Secondary outcomes included the use of physical restraints, ED length of stay, and adverse events.

Results: We did not observe a significantly lower incidence of overprescribing, adverse events, or ED length of stay when comparing pre- and postprotocol groups. A subgroup analysis demonstrated that when protocol was followed, there was a statistically significant reduction in overprescribing ($P = .001$).

Discussion: We did not find any differences among our primary and secondary outcomes, which may be attributed to protocol nonadherence. Full compliance to the protocol may reduce the rate of overprescribing APs or BZDs in patients with methamphetamine-induced agitation.

Keywords: methamphetamine induced agitation, methamphetamine psychosis, emergency room, acute agitation, antipsychotics, benzodiazepines, methamphetamine, substance use, agitation, stabilization

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Introduction

Methamphetamine is a highly addictive stimulant that acts through the trace amine associated receptor 1, and it can induce feelings of euphoria, increased energy, and excitability.[1] According to the US Centers for Disease Control and Prevention, the estimated rate of methamphetamine use is 6.6 per 1000 people.[2] Methamphetamine can also induce psychotic symptoms, such as paranoia,

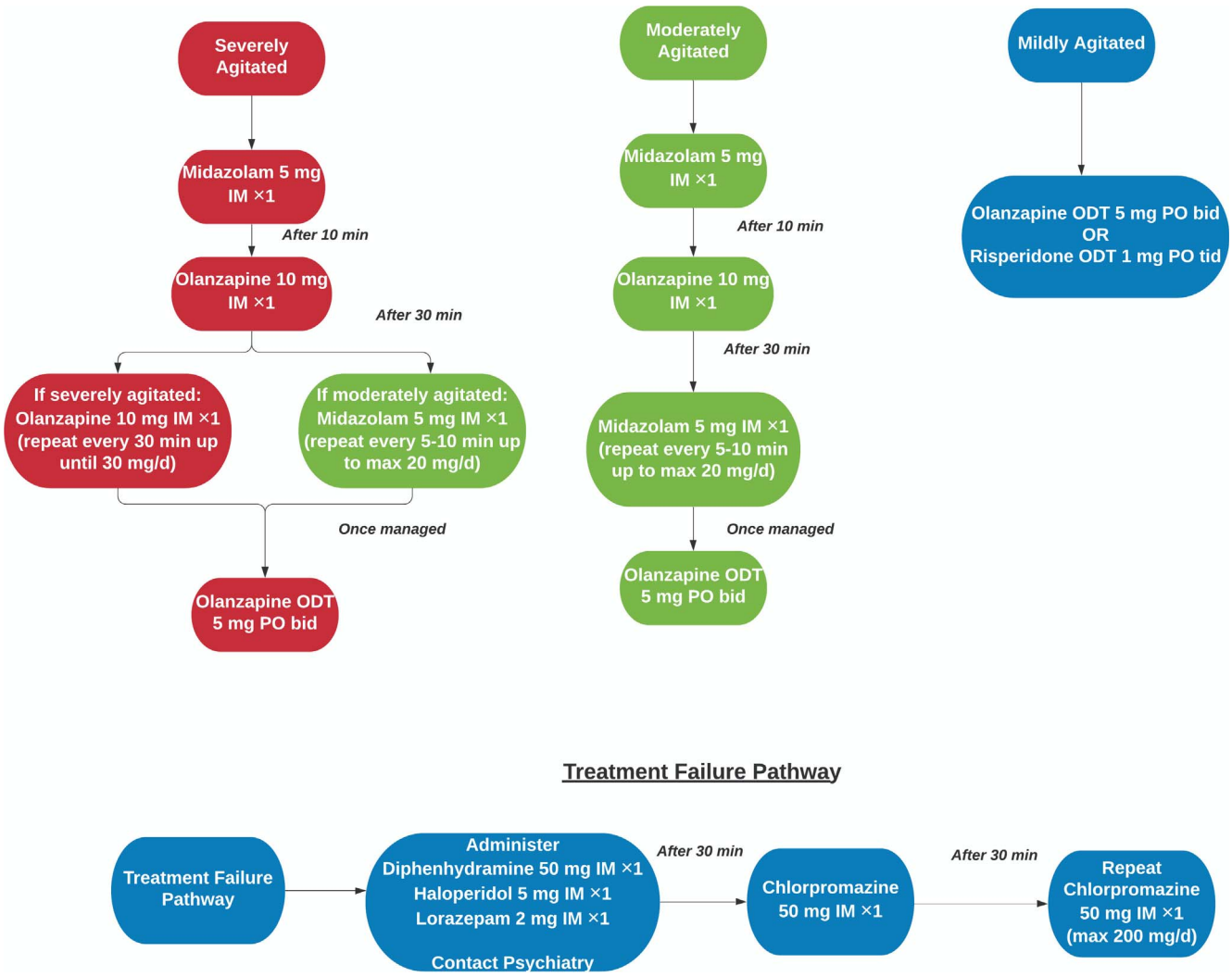

FIGURE 1: Our institution's methamphetamine protocol (bid = twice a day; ODT = oral disintegrating tablet; tid = three times a day)

delusions, hallucinations, and aggression.[3] These psychotic symptoms may lead to severe agitation and aggression, possibly requiring emergency medical management.

According to the *Journal of the American Medical Association*,[4] the number of methamphetamine-related emergency department (ED) visits has increased 245% since 2003. Despite this, there still are no guidelines to support the optimal treatment of patients presenting with methamphetamine-induced psychosis or agitation. Standard of care for treating this condition generally involves an intramuscular antipsychotic (AP; eg, haloperidol 5 mg, olanzapine 10 mg), benzodiazepine (BZD; eg, lorazepam 2 mg or midazolam 5 mg), or a combination of both.[5] Without an established guideline, ED physicians may prescribe multiple BZDs and APs during a short duration of time, which may lead to oversedation, hypotension, or a prolonged ED length of stay.

At our institution, we developed and implemented a protocol to help guide our ED providers in managing methamphetamine-induced agitation and psychosis. Our protocol included intramuscular midazolam 5 mg, to decrease agitation, and the addition of an intramuscular olanzapine 10 mg, to target the underlying psychosis (Figure 1).[5-7] We hypothesized that this protocol would reduce the number of BZDs and APs used to stabilize a patient, incidence of oversedation, ED length of stay, use of restraints, and risk of hypotension (defined as systolic blood pressure <100 mm Hg) in patients presenting with methamphetamine-induced agitation and psychosis.

Protocol Design

The protocol included 3 separate treatment algorithms based on the severity of methamphetamine induced agitation. We defined mild agitation as having paranoia

and expressing delusions but willing to take oral medications. We defined moderate agitation as being disruptive but not an immediate danger to self or others and refusing oral medications. We defined severe agitation as being an immediate threat to self or others, requiring physical restraints, and refusing oral medications. After acutely managing the agitation, a scheduled oral AP was recommended to be prescribed daily to treat the patient's underlying psychosis.

Patient vital signs were collected and closely monitored. Hold parameters were set if systolic blood pressure dropped below 100 mm Hg, heart rate dropped below 60 beats/min, or respiratory rate dropped below 12 breaths/min. Regarding treatment selection, midazolam was chosen for its fast onset and offset compared with lorazepam, and olanzapine was chosen compared with haloperidol to avoid extrapyramidal side effects. A treatment failure pathway was also included to give ED providers guidance on which drug to select if the methamphetamine induced agitation algorithm did not sufficiently stabilize the patient (Figure 1).

After the methamphetamine protocol was approved, education was provided to the ED physicians via in-person and virtual sessions. Large printouts of the treatment algorithm were placed in the provider dictation room as a physical reminder to help increase protocol compliance. The ED pharmacists were also educated on the protocol pathway and served to encourage physicians to follow the algorithm when treating methamphetamine-induced agitated patients.

We originally planned to create an order set that would allow ED physicians to follow the new protocol; however, because of the nuances of the ED workflow, a general agitation preference list was developed instead. The main difference between order sets and a preference list is that an order set would populate a specific group of medications with defined doses; in contrast, a preference list itemizes medications for a condition in a systematic order, from which prescribers can select. The preference list would model our protocol (ie, midazolam and olanzapine listed at the top) but also include other medications for agitation.

Methods

This study was an IRB exempt-approved, retrospective, pre- and poststudy involving patients with methamphetamine-induced agitation at our ED. The methamphetamine protocol (Figure 1) was designed by the principal investigators in August 2020, vetted by the ED and psychiatry leadership, and approved by our institution's Pharmacy and Therapeutics committee in November 2020. The protocol was implemented on November 15, 2020. Preprotocol group data were collected via chart reviews from July 1, 2020, through November 14, 2020. Postprotocol implementation data were collected via chart reviews from November 15, 2020, through March 31, 2021. Inclusion criteria consisted of patients at least 18 years of age, and either (1) with a history of methamphetamine use, (2) with an ICD-10 diagnosis of methamphetamine abuse or positive amphetamine urine drug screen upon admission, or (3) given oral or intramuscular BZDs and/or APs for stabilization. Patients were included in our study if they met the age criteria and at least 1 of the listed inclusion criteria. Patients were excluded if they failed to meet any inclusion criteria, if they were older than 65 years, or if recent methamphetamine use was unclear. We identified 341 unique patient encounters with a diagnosis of methamphetamine intoxication, but only 170 patient encounters met our inclusion criteria for the study. Baseline demographics, vital signs, emergency medications used to stabilize the patient, use of physical restraints, and ED length of stay were collected via chart review following ED protocol implementation.

Study Outcomes

The primary outcome was the reduction in total number of emergency BZDs and APs administered to stabilize a patient's agitation following implementation of the protocol. This outcome was measured by the incidence of *overprescribing*, which we defined as receiving 3 or more APs or BZDs in total within 30 minutes. We recorded the total number of emergency medications administered from the patient's electronic health record. Secondary outcomes included the impact of the protocol on adverse events, ED length of stay, and use of physical restraints. Secondary outcomes were recorded by retrospectively reviewing patient encounters in the electronic medical record. Excessive somnolence was determined by identifying key phrases, such as *excessive somnolence*, *lethargic*, or *difficult to assess*, within the physician and nursing notes. Vital signs were collected before and after AP and BZD administration to assess hypotension. Lastly, use of physical restraints was determined by reviewing the patient's chart for an order for restraints while in the ED.

We also recorded whether physicians were compliant, somewhat compliant, or not compliant with our protocol. We defined somewhat compliant as physicians who prescribed intramuscular midazolam first followed by an AP that deviated from our protocol, such as haloperidol or chlorpromazine; or if a physician prescribed intramuscular lorazepam followed by olanzapine.

Statistical Analysis

All analyses were conducted using IBM SPSS version 27. Baseline demographics, the rate of overprescribing,

TABLE 1: Demographics of the current study

Demographics	Preprotocol	Postprotocol	All
Age, y, mean	35.7	35.3	35.5
		No. (%)	
Patients	84 (49)	86 (51)	170
Male	63 (75.0)	63 (73.3)	126 (74.1)
Female	21 (25.0)	23 (26.7)	44 (25.9)
Hispanic	35 (41.7)	40 (46.5)	75 (44.1)
Non-Hispanic	49 (58.3)	46 (53.5)	95 (55.9)
Diagnosis of schizophrenia	32 (38.1)	22 (25.6)	54 (31.8)
Homeless	39 (46.4)	40 (46.5)	79 (46.5)
Mild agitation	33 (39.3)	30 (34.9)	63 (37.1)
Moderate agitation	17 (20.2)	20 (23.3)	37 (21.8)
Severe agitation	35 (41.7)	35 (40.6)	70 (41.2)
Protocol compliant		33 (38.4)	
Protocol somewhat compliant		19 (22.1)	
Protocol noncompliant		34 (39.5)	

TABLE 2: Primary and secondary outcome results

Outcomes	Preprotocol	Postprotocol	*P* Value
Overprescribed, No. (%)	28 (33.3)	21 (24.4)	.199
Excessive somnolence, No. (%)	25 (29.8)	18 (20.9)	.185
Restraints, No. (%)	33 (38.8)	44 (51.8)	.090
Length of stay, hr, mean	89.8	81.3	.259
Overprescribed, C vs NC		0 vs 15	.001
Overprescribed, NC vs SC		15 vs 6	1.000
Overprescribed, C vs SC		0 vs 6	.085

C = protocol compliant; NC = protocol noncompliant; SC = protocol somewhat compliant.

excessive somnolence, and hypotensive events were analyzed using χ^2 test. A Kruskal-Wallis test for independent samples was used to assess a subgroup analysis on the effect of protocol compliance on overprescribing. Mann-Whitney *U* tests for independent samples were used to compare change in ED hospitalization days before and after protocol implementation.

Results

Baseline Demographics

From July 1, 2020, to March 31, 2021, there were 170 patient encounters determined to be eligible for inclusion in this study. Of the 170 patient encounters we analyzed, 84 encounters were in the preprotocol cohort, and 86 encounters were in the postprotocol cohort. Baseline demographics were similar across both groups (Table 1).

Primary Outcome

There was no statistically significant difference in the rate of overprescribing when comparing both groups (28 preprotocol vs 21 postprotocol events; $P = .199$; Table 2). However, physicians were only compliant with the protocol 38.4% of the time (Table 1). A subgroup analysis was then performed to determine whether protocol compliance influenced overprescribing (Figure 2). Results demonstrate that when protocol was followed, overprescribing was reduced significantly when comparing patients who were being treated according to protocol versus those that were not (0 vs 15 events, respectively; $P = .001$; Figure 2). The treatment failure algorithm was not applied to any patients in this study.

Secondary Outcomes

There were no statistically significant differences in excessive somnolence, hypotension, or ED length of stay when comparing preprotocol versus postprotocol groups (Table 2). There was also an increase in the use of restraints in the postprotocol group when comparing both groups that was not statistically significant (Table 2).

Discussion

Our study's primary goal was to develop a protocol and evaluate its impact in standardizing the management of methamphetamine-induced agitation in the ED. In our study, we attempted to standardize treatment for this complex condition to improve patient outcomes.

In assessing the results of our primary outcome, we found that when protocol was followed, there was a significant reduction in the incidence of overprescribing. However, there was no difference in overprescribing when we considered the entirety of our primary outcome. Additionally, lack of education may also have attributed to the nonadherence of the protocol. Although we were able to provide multiple in-person and virtual educational sessions, the coronavirus pandemic limited provider availability and attendance. Furthermore, acute agitation is an emergent situation where quick management is necessary; therefore, providers may request nursing staff to override automated dispensing machines with familiar medications rather than using the protocol.

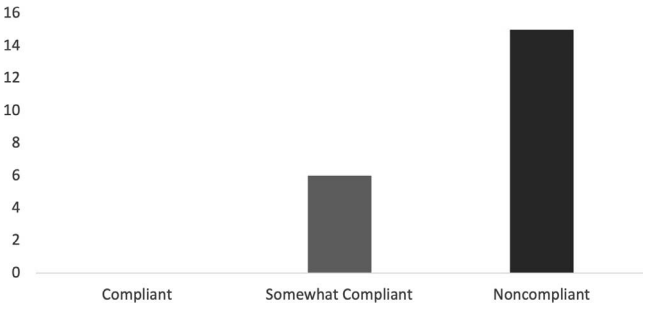

FIGURE 2: Influence of protocol on overprescribing

Not all patients had recorded documentation of their blood pressure readings. This fact could potentially have affected the results of our secondary outcome of hypotension. In addition, when implementing the protocol, there were concerns with coadministering intramuscular olanzapine and midazolam. The olanzapine medication labeling includes a FDA warning that concomitant administration of intramuscular olanzapine and a BZD may induce excessive sedation and cardiorespiratory depression[8]; however, data are lacking surrounding this warning. In the emergency room setting, this combination may be considered appropriate because patients' vital signs are closely monitored. In this study, no events of hypotension occurred following the coadministration of olanzapine and midazolam. Two hypotensive events occurred after administration of haloperidol, diphenhydramine, and lorazepam; 1 event occurred after several doses of chlorpromazine; and 1 hypotensive event occurred in a patient receiving a continuous infusion of midazolam. The results observed in this study along with other studies[9,10] that researched olanzapine and BZD coadministration are not consistent with the FDA warning.

Other limitations to our study included challenges in data collection supporting the excessive somnolence secondary outcome. Because of inconsistent documentation by medical staff and the retrospective nature of this study, it was difficult to accurately assess the level of somnolence for patients included in the study. Additionally, the use of a preference list by ED physicians may potentially have had a negative effect on our primary outcome. A preference list does not guide treatment choices as an order set would, but rather still allows physicians to select based on their personal choice. Lastly, our institution does not have a dedicated psychiatric emergency clinic or an around-the-clock psychiatrist in the emergency room.

We hypothesized that this protocol would reduce the use of restraints. Surprisingly, the study showed an increase in the use of restraints before versus after protocol implementation. The ED uses physical restraints when patients are severely agitated and behaving violently. This uncharacteristic finding may be attributed to the higher number of recorded moderate and severely agitated patients in the postprotocol group compared with the preprotocol group.

Going forward, we plan on providing more frequent education to all our ED staff in order to increase adherence to the treatment protocol. We also intend to create a hyperlink of the protocol in the hospital EMR for easier provider access. Finally, we aim to review the impact of the protocol during an extended duration of time. Larger-scale studies are warranted to determine the effectiveness of this protocol and determine barriers to compliance. Our protocol gives a brief snapshot of potential impacts of having a standardized methamphetamine induced agitation protocol.

Conclusion

A methamphetamine protocol in the ED would benefit patients and could improve clinical outcomes. Preprotocol and postprotocol implementation found no differences in medication overprescribing, incidence of hypotension, excessive somnolence, ED length of stay, or use of restraints. However, compliance with the protocol was low, which may have affected these results. When the protocol was followed, there was a reduction in the incidence of overprescribing. We conclude that full compliance with our protocol may reduce the rate of overprescribing APs or BZDs in patients with methamphetamine-induced agitation.

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