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Systematic review protocol to determine the most effective pharmacological and non-pharmacological interventions for the management of acute methamphetamine toxicity

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ABSTRACT

Introduction This study describes the protocol for a systematic review. The systematic review will address experiences of managing methamphetamine intoxication, specifically violence and agitation related to intoxication, in the emergency department (ED).

Methods and analysis This study uses the Grading of Recommendations Assessment, Development and Evaluation system to guide the methods in this section. The primary objective of the review is to identify experimental studies assessing the effectiveness of both pharmacological and non-pharmacological strategies to manage acute methamphetamine intoxication in patients presenting violently in the ED. Our secondary objectives will be to assess the impact of specific strategies on the time it takes to achieve de-escalation and/or sedation, the length of stay in the ED, frequency of admission, mortality and provider satisfaction with the intervention.

Ethics and dissemination Ethics approval has been obtained from the Conjoint Health Research Ethics Board REB21-1387. Results will be published in a peer-reviewed journal and presented at healthcare conferences in Canada.

Trial registration number The protocol is registered through the International Prospective Register of Systematic Reviews (identification number: CRD42020157938) and will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extensions for systematic review protocols.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Search strategy developed with a medical librarian and peer reviewed by another medical librarian.
⇒ Search strategy was developed with assistance from patients with lived experience of methamphetamine use as well as hospital protective services personnel who care for these patients in crisis.
⇒ Search strategy includes grey literature to capture all available community experiences that have been shared on the management of methamphetamine-related behavioural disturbances.
⇒ Search was limited by heterogeneity in the definitions of both the intervention (non-pharmacological and pharmacological strategies) as well as the definition of what qualifies as methamphetamine intoxication.

INTRODUCTION

Description of the issue

Amphetamine-type stimulants, with methamphetamines being the predominant compound, are among the most widely used illicit substances in the world. Seizures of methamphetamine by law enforcement, hospitalisations, emergency department (ED) utilisation and treatment seeking have all increased for methamphetamines.[1–4] Once inhaled, snorted or injected, methamphetamines rapidly achieve high concentrations in the brain where they block the reuptake of, and promote the release of, catecholamines, stimulating the central and sympathetic nervous systems.[5] Its use is associated with significant agitation, violence and psychosis in addition to the rapid development of addiction and other serious societal and personal harms.[3 6 7]

Description of the existing intervention data

Currently, there are no specific pharmacotherapies for treating methamphetamine use disorders, and management has focused on efforts to limit the effects of methamphetamines including agitation, violence and psychosis in acute care settings.[3] Unfortunately, there is a wide range of approaches among practitioners in the management of methamphetamine intoxication, resulting in significant variability in time required to achieve adequate sedation, increasing risk to patients and staff.[7 8]

Rationale

Many EDs have protocols to guide clinicians in the management of acute behavioural disturbances and associated risks including over-sedation, but they are not specific to methamphetamine intoxication.[7] A recent Alberta Health Services rapid review provides an overview of the management of methamphetamine intoxication, but there is no specific protocol recommended beyond suggestion that benzodiazepines be used as a first-line therapy with the addition of atypical antipsychotics if benzodiazepines are insufficient.[8]

This systematic review aims to address the current lack of consistent evidence-based approaches to methamphetamine intoxication in the ED and create evidence-based protocols, using broad stakeholder input, that will improve outcomes for both patients with acute methamphetamine intoxication and the staff treating and supporting them.

METHODS AND ANALYSIS

Objectives

This systematic review's primary objective is to identify experimental studies assessing the effectiveness of both pharmacological and non-pharmacological strategies to manage acute methamphetamine intoxication in patients presenting violently in the ED in North America and internationally, defined as the time it takes to achieve de-escalation and/or sedation. If data are available, our secondary objectives will be to assess the impact of specific strategies on the length of stay in the ED, frequency of admission, mortality and provider satisfaction with the intervention including perceptions of patient and staff safety. The protocol is registered through the International Prospective Register of Systematic Reviews (identification number: CRD42020157938) and will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) extensions for systematic review protocols.[9] It uses the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide the methods in this section. The review began July 2023 and is anticipated to be completed June 2024.

Study inclusion factors

We will include both interventional and observational studies (cohort, case-control, cross-sectional) as randomised control trials will likely be very few. We will also include quasi-experimental study designs, case series and quality improvement studies that report quantitative or qualitative outcomes. Other inclusion factors are listed in table 1.

Search methods

Our search strategy was developed with the assistance of a medical librarian in collaboration with the larger research team.

Electronic search

The medical librarian (JK) conducted comprehensive searches in Ovid Medline, Ovid Embase, APA PsycInfo, CINAHL, Scopus, Cochrane Library (via Wiley), ProQuest Dissertations & Theses Global and Sociological Abstracts (via ProQuest) on 19 July 2023. To capture all relevant literature pertaining to methamphetamine management, relevant keywords and controlled vocabulary were carefully selected. The draft search was peer reviewed by a second experienced research librarian (MDW). Searches excluded paediatric populations, pregnant populations, were limited to English language and were restricted to the publication date range from 2011 to current to capture the more recent studies concerning the management of methamphetamine in diverse settings. Refer to the online supplemental appendix for full-text search strategies. A total of 4271 results were retrieved; after deduplication, 3383 unique results remained for the initial title and abstract screening in Covidence systematic review software (Veritas Health Innovation, Melbourne).[10] In addition to subscription databases, the research team will review the first 200 Google Scholar results. Bibliographies from included studies will also be reviewed. The reporting of this systematic review was guided by the standards of the PRISMA Statement.

Discrepancies and disagreements regarding a research abstract will be adjudicated by a third reviewer to mitigate the risk of selection bias. Studies relevant to emergency medicine and substance-induced agitation will have their full-text paper downloaded and will be reviewed. We will use the GRADE methodology[11] to evaluate the quality of evidence related to outcomes and will invite a panel of clinical experts to join our GRADE panel, as well as an advisory group consisting of representatives from emergency medicine, security services and those with lived experience to review the recommendations to ensure accuracy and relevance. We will use the GRADE methodology to evaluate the level of evidence and recommendations from the literature.[12]

Additionally, two independent reviewers will evaluate the risk of study bias using a formal tool. In the case of an interventional study, reviewers will apply the Cochrane Risk of Bias 2 tool.[13] Non-interventional studies will be evaluated using the Ottawa-Newcastle Scale.[14] Both tools are validated by the Cochrane Collaboration. Any discrepancies in risk-of-bias assessment will be decided on by a third reviewer.

Data extraction/analysis

Data extraction will be completed by two expert investigators, collated in the GRADE PRO software and duplicated in an excel spreadsheet designed specifically for data abstraction.

The following data will be extracted from each unique study:

1. Study aim or question.
2. Study characteristics (design, sample size, number of arms).
3. Intervention and control (type and characteristics of interventions and control, route of administration, total dose, medication rationale, changes in medication

Table 1 PICOST criteria for the inclusion of studies in the systematic review

Criteria	Description
Participants	Agitated patients 18 years or older in the ED, specifically agitated because of the effects of methamphetamine use. (Definition of agitation: Subjective/qualitative agitation; BARS; Activation/participation of Security Services/ Protective Services in the care of the patient)
Intervention	Pharmacological and non-pharmacological approaches (see medication list below) Pharmacological approaches (including brand, generic and international names) 1. Benzodiazepines 2. Ativan (lorazepam) 3. Valium (diazepam) 4. Zyprexa (olanzapine) 5. Haldol (haloperidol) 6. Risperdal (Risperidone) Non-pharmacological approaches 1. Verbal de-escalation 2. Reduce environmental stimulation 3. Removal of potential hazardous objects from surroundings 4. Presence of security and support staff
Control	Current standard of care
Primary outcome measures	Time to de-escalation of agitation and/or sedation
Secondary outcome measures	Length of stay in the ED, frequency of admission, mortality and provider satisfaction with the intervention including perceptions of patient and staff safety.
Study designs	Interventional (RCTs) and observational studies (cohort, case-control, cross-sectional) published in the English Language. Also included: quasi-experimental study designs, case series and quality improvement studies that report quantitative or qualitative outcomes.
Timing	January 2011 to 19 July 2023

BARS, Behavioral Activity Rating Scale; ED, emergency department; PICOST, Population, Intervention, Control, Outcome(s), Study Design(s), Timing; RCT, randomised control trial.

during study, adherence/compliance to medication use).
4. Study setting (country) and patient population (age, sex and gender).
5. Outcome measures (type of outcome, definition of outcome and time of assessment).
6. Results.

Descriptive statistics will be used to describe baseline results. Due to the predicted heterogeneity of the study designs and outcome measurements, we will employ narrative analysis to summarise the data. We will report mean differences for studies with continuous data and relative risks for dichotomous data, when available. Heterogeneity of the data (for the primary and secondary outcomes) will be measured by I2 while publication bias will be assessed using a funnel plot if more than 10 studies are included in the analysis. We do not anticipate enough robust studies to perform a meta-analysis on this topic. When each full-text article has been reviewed, we will review our findings with community experts and people with lived experience prior to finalising the recommendations in a publication for dissemination.

Subgroups and sensitivity considerations

We do not anticipate any specific subgroup analyses; however, we may include them for exploratory purposes depending on the heterogeneity of the studies included. If performed, subgroups will be based on characteristics relevant to the outcomes of the studies and will be mindful of vulnerable and disadvantaged populations.

Patient and public involvement

Both patients and the public were involved in the conceptualisation of this systemic review, which is part of a larger project to improve the care of people who use illicit methamphetamines and seek care in the ED. Security services personnel, people with lived experience and frontline health workers explored the topic initially through online surveys and qualitative interviews to understand the extent of the problem. Inpatient and community mental health providers and patients contributed by offering meaningful study outcomes.

Ethics and dissemination

Ethics approval has been obtained from the Conjoint Health Research Ethics Board. The ethics certification is REB21-1387. The results of this systematic review will be

submitted for publication in the *Journal of Emergency Medicine* (CJEM).

Strengths and limitations of this study

This is an innovative, multidisciplinary project aiming to enhance the care of ED patients and to support staff who care for patients presenting with acute violence/agitation secondary to their presumed crystal methamphetamine ingestion. It specifically addresses the needs of the ED patient population while also partnering with diverse stakeholder groups to apply the most up-to-date, evidence-based understanding of the best practices in methamphetamine agitation management. This project is novel in that it builds on work done forming relationships with both inpatient and community mental health supports by also including the perspectives of security services personnel, people with lived experience and frontline health workers in an effort to highlight and work towards equity, diversity and inclusion. It is limited by the lack of a standardised definition of methamphetamine behavioural disturbance and the heterogeneity of patient populations presenting in crisis for care.

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Contributors This systematic review was conceptualised by DC, LH, RT, DD, TA and EL. The medical librarian (JYK) conducted comprehensive searches based on input from SMG and SDV. SMG, SDV and GF reviewed abstracts and full-text articles. GF and SDV extracted data and applied quality of evidence assessment. EL provided guidance on the application of the GRADE method to the data. SDV is responsible for the overall content (as guarantor).

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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