Pharmacological, psychosocial, and harm reduction interventions for the treatment of methamphetamine-related disorders

An overview of reviews

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Pharmacological, psychosocial, and harm reduction interventions for the treatment of methamphetamine-related disorders: An overview of reviews

Findings from a study led by the BC Centre for Disease Control
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Introduction

METHAMPHETAMINE USE DISORDER is a public health concern around the world. The United Nations Office on Drugs and Crime (UNODC) identifies methamphetamine as the second most common drug used worldwide — used by about 27 million people — and use is increasing in North America.[1] Adverse effects of methamphetamine include but are not limited to restlessness, headache, dry mouth, insomnia, hyperthermia, decreased appetite, convulsions, increased risk of HIV, and elevated risk of fatal overdose. Long-term use of methamphetamine can lead to paranoia, mood disorders, psychosis, and cognitive impairment. Following prolonged use, discontinuation of methamphetamine can result in withdrawal symptoms such as mood swings, violent behaviour, fatigue, sleep disturbances, depression, and memory loss.[2-4]

While opioids continue to dominate overdose-related deaths in Canada, the number of fatal overdoses that involve methamphetamine is rising. There are no nationwide data on the number of methamphetamine-attributable deaths in Canada; however, coroners estimate that methamphetamine was involved in about one-quarter of the 4,000 opioid-related overdose deaths in Canada in 2017.[5] Some provincial-level estimates also highlight an increase in methamphetamine-related deaths in recent years. For example, the BC Coroners Service indicates that methamphetamine was the third most commonly detected drug in overdose deaths in July 2020 to August 2022 (40%) after fentanyl (88%) and cocaine (46%).[6] Moreover, reports from Alberta also show that 42% of all fentanyl-related deaths in 2017 had methamphetamine involved as a contributing factor, a figure that is 2.6 times higher than in 2015 (16%).[7] Methamphetamine-related deaths have also increased in Manitoba from three cases in 2014, to 25 in 2016, and 17 in 2017.[8]

Given the health and societal costs of methamphetamine use disorder, there is an urgent need to identify effective pharmacological, psychosocial and harm reduction interventions.

Given the health and societal costs of methamphetamine use disorder, there is an urgent need to identify effective pharmacological, psychosocial and harm reduction interventions. Several systematic reviews of varying scope and quality have identified a range of interventions to reduce the use of and harms associated with methamphetamine use disorder.[3,4] These interventions include pharmacological (e.g., modafinil, methylphenidate, topiramate), psychosocial (e.g., contingency management, cognitive behavioural therapy, drug counseling,

motivational interviewing) treatments and harm reduction strategies (e.g., pipe distribution, supervised consumption, drug checking). While there is no agreement over what interventions work best in addressing methamphetamine use disorder in different sub-populations, existing reviews often suggest the use of different psychosocial interventions for methamphetamine as a first-line treatment, and provide little evidence supporting pharmacological treatments.

However, there is a lack of consensus over what combination and order of interventions leads to better mental and physical health outcomes. Moreover, the long-term impact of interventions is unclear. This overview of reviews therefore, aims to compare the benefits and harms of existing pharmacologic, psychosocial, and harm reduction interventions for methamphetamine use disorder in adults. We also assess the methodological quality of existing reviews and the overall strength of the evidence for existing practices to provide reliable recommendations.

Objectives

- **KEY QUESTION 1:** What are the comparative benefits, harms, and unintended impacts of pharmacological, psychosocial, and harm reduction interventions in adults with methamphetamine use disorder?
- **KEY QUESTION 2:** Are there known subpopulations for which different forms of pharmacological, psychosocial, and harm reduction interventions are most or least effective for methamphetamine use disorder?
- **KEY QUESTION 3:** What combinations of interventions are most effective in reducing and addressing methamphetamine use disorder?

This overview of reviews therefore, aims to compare the benefits and harms of existing pharmacologic, psychosocial, and harm reduction interventions for methamphetamine use disorder in adults.

We also assess the methodological quality of existing reviews and the overall strength of the evidence for existing practices to provide reliable recommendations.

Methods

Research approach

Our approach was guided by a conceptual framework, which was developed in consultation with knowledge users and community members (see Appendix A), and methodologically guided by the Cochrane Collaboration and Lunney et al.[9,10]

Study selection

SEARCH STRATEGY

The Population, Interventions, Comparisons, Outcomes, and Study designs (PICOS) elements considered for this overview of reviews are listed in Table 1. Published reviews in English or French from inception to January 4th 2021 were searched in MEDLINE (Ovid platform), CINAHL, Cochrane Database of Systematic Reviews, PsycInfo, Web of Science, and Embase (Ovid platform). A validated search filter for the retrieval of reviews in combination with search terms and Boolean operators relevant to methamphetamine use literature were used. Grey literature, including Google Scholar (first 200 citations), Grey Literature Report, PROSPERO and reference lists of included reviews were also searched to identify unpublished or non-peer-reviewed studies. Systematic reviews of randomized and non-randomized studies were included.

A combination of the following concepts were searched for in each database: Methamphetamine (e.g., amphetamine OR methamphetamine) AND pharmacological/psychological/harm reduction interventions (e.g., adrafinil OR amfebutamone OR amfepramone OR aminorex OR benzphetamine OR bufylline OR cathinone OR dexamphetamine OR dexanfetamine OR etamiphylline OR brief psychotherapy OR counseling OR cognitive therapy OR motivational interviewing OR pipe distribution OR supervised consumption OR drug checking) (see Appendix B for a sample search strategy).

Table 1. Population, intervention, comparison, outcomes, and study (PICOS) design elements

Inclusion Criteria	Definition
Population[a]	i) Adults (aged 18 years or older) with methamphetamine use disorder diagnosed by any set of criteria. This includes both Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD-10) criteria, as well as any other explicit methamphetamine dependence diagnostic system. ii) People with methamphetamine use disorder in combination with other substances (polysubstance use). Participants may be in an inpatient unit (drug and alcohol rehabilitation or hospital setting), residing in the community, engaging in psychotherapy or persons residing in a prison setting.
Intervention[b]	i) Harm reduction interventions (e.g., methamphetamine pipe distribution, drug checking) ii) Pharmacological treatment interventions (e.g., mirtazapine, modafinil, topiramate) iii) Psychosocial treatment interventions (e.g., contingency management, cognitive therapy, motivational interviewing)
Comparators	i) Interventions may be compared with active controls (e.g., 12-step program), no intervention, treatment as usual and/or inactive controls (e.g., wait-list control or standard care).
Outcomes[c]	**Primary:** i) Efficacy (defined as the proportion of individuals abstinent) and the acceptability (defined as the proportion of individuals who dropped out from the study due to any cause) of the interventions at the end of treatment ii) Harms (defined as the proportion of serious adverse events) **Secondary:** i) Change in overall mortality and morbidity post-intervention ii) Blood-borne virus risk reduction (injecting drugs/sexual risk behaviour) post-intervention iii) Change in aspects of quality of life post-intervention iv) Change in employment outcomes and legal outcomes post-intervention
Study designs[d]	Reviews with or without meta-analysis, systematic reviews with network meta-analysis of intervention studies

a. Reviews focused solely on children and adolescents under the age of 18 years were excluded.

b. Interventions can be of any duration, delivery, frequency and intensity.

c. Outcomes may reflect short-term or long-term time frames and can be rated by clients or clinicians, in the form of an assessment by objective (e.g., urine, blood) or subjective measures (e.g., questionnaire). Drug use was measured as: amount of drug use, frequency of drug use, continuous using days or other measures of actual drug-using behaviour.

d. Letters, commentaries, expert opinion, theoretical and unstructured reviews without a clearly described research question, search strategy, and selection criteria were excluded.

SCREENING AND DATA EXTRACTION

Screening and data extraction was guided by the TIDieR (template for intervention description and replication) framework.[11] Two reviewers (SM, KZ) independently screened titles and abstracts in duplicate. Data was extracted on review characteristics (e.g., question or aims, types of primary studies included), participants' characteristics (e.g., target population, age, gender), outcomes (e.g., reduction/increase in methamphetamine use) and interventions characteristics (e.g. mode of delivery).

Two reviewers (SM, KZ) independently and in duplicate assessed the methodological quality of included reviews using the ROBIS (risk of bias in systematic reviews) tool,[2] a recently developed tool for assessing the risk of bias in systematic reviews. ROBIS evaluates four main domains through which bias may be introduced into a systematic review: i) study eligibility criteria; ii) identification and selection of studies; iii) data collection and study appraisal; and iv) synthesis and findings.

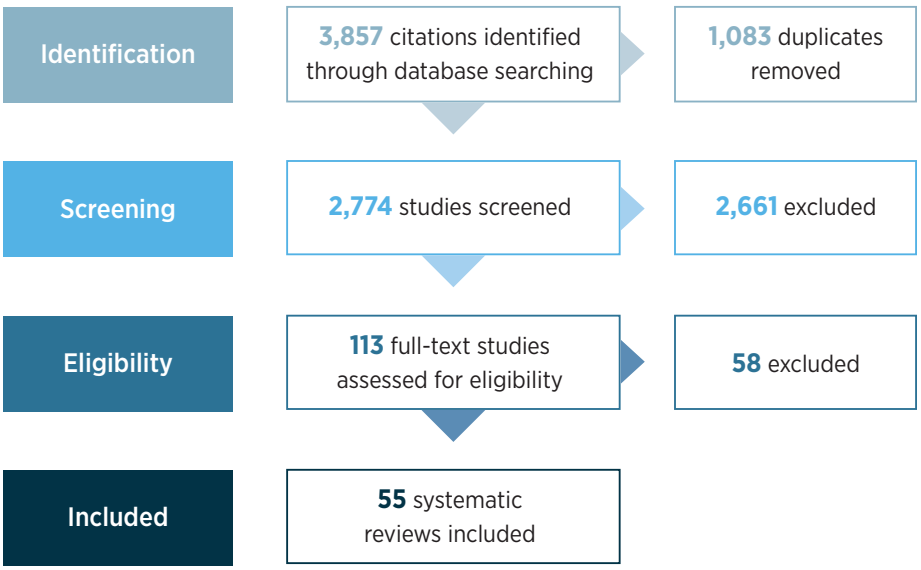
Findings

OUT OF THE 2,774 STUDIES SCREENED, we included 55 systematic reviews (Figure 1). Of the intervention types (i.e., pharmacological, psychosocial, and harm reduction), little to no effect has been reported for pharmacological interventions, most of which are based on low-quality and small sample size RCTs with high rates of dropouts.

Psychostimulants (e.g., methylphenidate, dextroamphetamine, and dexamphetamine), as well as opioid antagonist (e.g., naltrexone) and anticonvulsants (e.g., topiramate) have shown some promise in reducing methamphetamine use. However, the evidence is weak and inconsistent and often limited to certain sub-populations (e.g., men who have sex with men). The evidence around using antidepressants (e.g., bupropion, amineptine, mirtazapine) points to less consistent effectiveness.

Cognitive behavioural therapy and contingency management have been the most efficacious non-pharmacological interventions in reducing methamphetamine use and attending recovery-related appointments. Less consistent benefits have been reported for motivational interviewing, the matrix model, and structured physical exercise. No randomized studies on harm reduction interventions were found.

Figure 1. PRISMA flowchart of included studies



Recommendations

IN THE ABSENCE OF EFFECTIVE AND APPROVED PHARMACOLOGICAL INTERVENTIONS for methamphetamine use disorder and that polysubstance use is the norm, addiction treatment services should be inclusive and not opioid-centric. Moreover, substance use treatment services should offer behavioural (e.g., contingency management, cognitive behavioural therapy) and harm reduction interventions (e.g., safer pipe and smoking supply distribution, supervised consumption facilities and overdose prevention services including sites where inhalation is allowed) tailored towards treating and reducing harms associated with methamphetamine use disorders.

The evidence for treating or reducing the harms associated with methamphetamine use disorder is limited in quantity and quality. Most of the existing studies suffer from methodological issues and limited generalizability. Large and long-term randomized clinical trials are required to compare the efficacy and safety of various interventions. Repeating small-scale trials/pilots on drugs and interventions that have been previously tested adds little to increasing the validity and reliability of the evidence. Moreover, studies need to take the polysubstance using nature of the population into account when it comes to defining their inclusion and exclusion criteria. Future research should also continue efforts at finding novel (i.e., not previously tested) pharmacological interventions for treating methamphetamine use disorders.

While several pharmacological and non-pharmacological interventions have been examined several times, very few studies have tried to assess the individual-level and population-level efficacy of available harm reduction interventions for methamphetamine use disorder.

Furthermore, the scarcity of data and studies focused on harm reduction interventions aimed at methamphetamine use disorder is concerning. While several pharmacological and non-pharmacological interventions have been examined several times, very few studies have tried to assess the individual-level and population-level efficacy of available harm reduction interventions for methamphetamine use disorder.

No randomized studies on harm reduction interventions were found. Potential harm reduction interventions to be assessed include but are not limited to strategies for safer injecting (e.g., needle syringe programs, use

of gelatine capsules); safer sex practices (e.g., condom promotion); safer smoking and snorting (e.g., free meth pipes, straws, lip balm); safer "booty-bumping" (e.g., access to sterile syringes and water); messaging around avoiding over-amping (e.g., eat, drink water, and sleep; "start low, go slow" approach); drug checking; and stimulant maintenance treatment.

British Columbia introduced risk mitigation guidance (pandemic prescribing) in 2020, in order to reduce the risk of overdose and COVID-19 transmission, which included prescribed oral stimulants methylphenidate (Ritalin) and dextroamphetamine (Dexedrine).[13] Outcomes of prescribed oral stimulants and proposed safer supply providing stimulants of known content, currently only available on the illicit market, should be assessed including unintended consequences.

We determined little to no impact of psychological and pharmacological interventions on methamphetamine use. However, these findings may in part be due to the selected outcomes (e.g., abstinence) and not being aligned to the reality of substance use.

The final phase of this study aims to re-conceptualize the outcomes of the interventions for methamphetamine use disorder to be more patient-oriented, and to conduct a Bayesian network meta-analysis to identify if combinations of interventions have meaningful benefits to people with methamphetamine use disorder.

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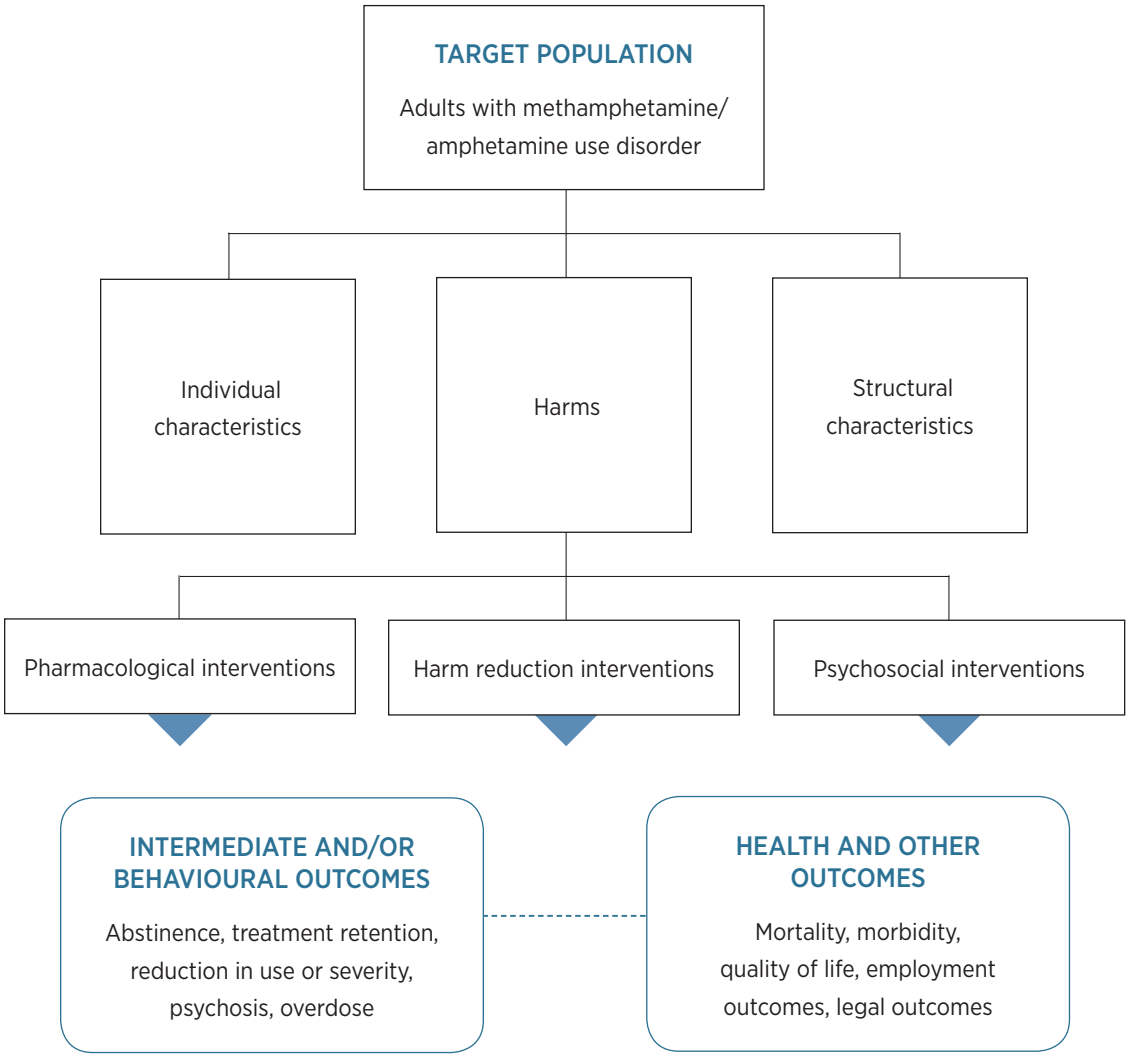
APPENDIX A

Conceptual framework



APPENDIX B

Sample search strategy

Database: Ovid MEDLINE <1946 to Present>

Search Strategy:

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1. ((amphetamine or amfetamine or methamphetamine or metamfetamine) adj5 (abuse* or addict* or chronic* or disorder* or depend* or habitual* or misuse* or overuse or users or withdraw*)).tw [5694]

2. exp amphetamine/ or amphetamine.tw [28592]

3. ((stimulant* or psychostimulant* or psycho-stimulant*) adj5 (abuse* or addict* or chronic* or disorder* or depend* or habitual* or misuse* or overuse or users)).tw [3871]

5. 1 or 2 or 3 or 4 [34092]

6. meta analysis.mp [169205]

7. review.pt [2554632]

8. search:.tw [425045]

9. 6 or 7 or 8 [2868369]

10. 5 and 9 [3297]

11. Limit 10 to humans [2658]

Note: mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms; exp (explode)= retrieves citations using the selected term and all of its more specific terms; tw: The text word index includes title and abstract; pt: Publication type

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