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SUMMARY WITH CRITICAL APPRAISAL

Management of Acute Withdrawal and Detoxification for Adults who Misuse Methamphetamine: A Review of the Clinical Evidence and Guidelines

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Abbreviations

RCT	randomized controlled trial

Context and Policy Issues

Methamphetamine is a highly addictive drug that is created illegally in clandestine laboratories using a variety of household chemicals, including ephedrine or pseudoephedrine, that is extracted from over the counter medications.[1] There is no legally available alternative drug. Methamphetamine comes as a white powder or a crystal format and can be sniffed up the nose or mixed with water and injected.[1] The production of methamphetamine is dangerous and produces large volumes of toxic chemical waste.[1] In 2006, Canada introduced new regulations to limit access to the precursor chemicals needed to produce methamphetamine including the move to keep ephedrine-containing products behind the pharmacy counter.[1] The prevalence of methamphetamine use in Canada is low, with about 0.2% of the population reported to use the substance; however, it would appear that the availability of methamphetamine in Canada has recently increased.[1] There was a 590% increase in the number of methamphetamine-related drug offences and seizures between 2010 and 2017.[1]

Methamphetamine has a long half-life and the high experienced when using it can take effect in seconds[1] and last up to 12 hours.[1] Short-term effects associated with its use include elevated breathing, heart rate, and blood pressure, lack of appetite, weight loss, increased body temperature, headache, and dizziness.[1] Longer-term effects may include dental decay caused by extreme dry mouth, paranoia, psychosis or psychotic symptoms, itching, and sleeplessness.[1] The prevalence of long-term use is significantly higher for males than for females.[1] There has been an observed increase in the number of individuals seeking treatment for methamphetamine misuse across a number of Canadian jurisdictions.[1] When the drug wears off, people can experience anxiety and depression and may become agitated or violent and demonstrate unpredictable behaviour.[1] This aspect of behavior can make it difficult to safely care for people who are experiencing methamphetamine withdrawal and detoxification symptoms.

The objective of this report is to summarize the clinical evidence and evidence-based guidelines regarding methods to manage acute withdrawal for adults who misuse methamphetamine.

Research Questions

1. What is the clinical evidence regarding methods to manage acute detoxification or withdrawal for adults who misuse methamphetamine?
2. What are the evidence-based guidelines regarding the management of acute detoxification or withdrawal for adults who misuse methamphetamine?

Key Findings

Good quality evidence from one systematic review suggested that aripiprazole, haloperidol, and quetiapine may be effective for the management of methamphetamine-induced psychosis. Intravenous lorazepam and droperidol may be effective for the management of agitation associated with acute methamphetamine toxicity in the emergency department and isradipine may be effective for the treatment of methamphetamine-induced high blood pressure. The results of two randomized controlled trials suggested that pexacerfont and buprenorphine may be effective for managing methamphetamine craving during methamphetamine withdrawal. One evidence-based guideline recommends benzodiazepines should be considered as a first line treatment option for the management of severe agitation, aggressiveness, or psychosis stemming from methamphetamine intoxication.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and January 11, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults who misuse methamphetamines
Intervention	Acute detoxification, withdrawal, or management protocols (e.g., medication-assisted, evidence-based assessment, chemical sedation, etc.)
Comparator	Acute detoxification, withdrawal or management without a defined protocol, different protocols compared with each other
Outcomes	Q1. Clinical evidence (e.g., examples of protocols or strategies) Q2. Evidence-based guidelines (e.g., best practice, specific treatment protocols, recommended length of stay, follow-up measures)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, were analyzed as part of in included systematic review, or were published prior to 2014. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using Assessing the Methodological Quality of Systematic Reviews 2 (AMSTAR 2) tool,[2] randomized studies were critically appraised using the Scottish Intercollegiate Guidelines Network tool (SIGN50)[3] and guidelines were assessed with the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.[4] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 432 citations were identified in the literature search. Following screening of titles and abstracts, 405 citations were excluded and 27 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full text review. Of these potentially relevant articles, 23 publications were excluded for various reasons, and five publications met the inclusion criteria and were included in this report. These comprised one systematic review (SR), two randomized controlled trials (RCTs), and two evidence-based guidelines. Appendix 1 presents the PRISMA[5] flowchart of the study selection.

Additional references of potential interest that did not meet the inclusion criteria for this review are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

One SR[6] was identified that included 81 publications including RCTs, prospective observational studies, case series and case reports. The population included in the SR was broader than that of this CADTH review. Of the 81 publication included in the SR, three RCTs, two observational studies, four case series, and five case reports included people who misused methamphetamine.[6] The literature search results included publications identified from the inception of the searched databases to September 10, 2014.[6] Interventional studies examining methamphetamine that were included in the SR were published between 1997 and 2014.[6]

Two double-blind RCTs[7,8] were identified; one placebo-controlled[7] and one active controlled.[8] Morbbi et al.[7] conducted their study at two addition health services camps in Tehran, Iran. The study by Ahmadi et al.[8] was conducted at a university hospital-affiliated psychiatric ward.

Two evidence-based guidelines were identified.[9,10] The 2017 guideline regarding the pharmacological management of acute methamphetamine-related disorders and toxicity was developed by a group from Germany.[9] The 2015 guideline regarding the management of non-tobacco substance use disorders was developed by the US Department of Veterans Affairs and the Department of Defense (VA/DoD).[10] Both guideline groups conducted SRs to identify SRs[9] and RCTs[9,10] to support their guideline development. Wodarz et al.[9] used the Oxford Centre for Evidence-based Medicine (OCEBM) tool to assess methodological quality and grade evidence. To assess the included evidence they also used the Cochrane Risk of Bias tool to assess RCTs, the AMSTAR tool to assess SRs, and the Deutsches Instrument zur methodischen Leitlinien-Bewertung (DELBI) instrument to assess guidelines.[9] The VA/DoD group used Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess the quality of the included evidence.[10] Wodarz et al.[9] developed recommendations using the nominal group technique. The VA/DoD developed their recommendations through an iterative process involving internal and external peer review.[10] Detailed explanations of the methods of rating the evidence and recommendations are provided in Table 4.

Country of Origin

The identified SR was conducted by a group in the United States.[6] Two RCTs[7,8] were conducted in Iran. The included guidelines were produced by groups from Germany[9] and the United States.[10]

Patient Population

The SR by Richards et al.[6] included adults presenting for treatment of agitation, psychosis, or hyperadrenergic symptoms resulting from the use of amphetamine, related derivatives, and analogues. They author identified which drug was used in each primary study but not further information describing the patient populations was provided.

Morabbi et al.[7] included 50 male participants with substance use disorder who were voluntarily referred to two addiction health services residential camps. Participants used heroin, methamphetamine, or both substances. Twenty-six participants were randomized to the treatment group with a mean age of 29.73 years and 10.5 years of substance use. Six used heroin and 20 used both heroin and methamphetamine. Twenty-four participants were randomized to the placebo group with a mean age of 34.00 years and 10.92 years of substance use. Twelve used heroin, two used methamphetamine, and 10 used both.[7]

There were no statistically significant differences observed between groups except in the distribution of the types of misused substances. Three participants in the placebo group dropped out of the study at week two due to legal issues.

Ahmadi et al.[8] included 40 male patients diagnosed with severe methamphetamine dependence and withdrawal who were treated at inpatient psychiatric ward. Twenty participants with a mean age of 31.2 years were randomized to the methadone group and 20 participants with a mean age of 34.35 years were randomized to the buprenorphine group. No statistically significant differences were observed between groups for age, education, employment, marital status, or income. No participants dropped out or were lost to follow-up.[8]

The target population of the guideline by Wodarz et al.[9] is adults who misuse methamphetamine. The intended users include doctors and staff in hospitals, medical practices, and addiction treatment centres.[9] The VA/DoD guideline[10] is intended to target adults with non-tobacco substance use disorders (including methamphetamine) who are eligible for care in the VA/DoD healthcare delivery system. The intended users are healthcare providers within the VA/DoD healthcare system.

Interventions and Comparators

Interventions included in the SR for participants who misused methamphetamine included aripiprazole, haloperidol, droperidol, benzodiazepines, zuclopenthixol, risperidone, olanzapine, quetiapine, and lorazepam.[6] The comparator treatments in these studies were not clearly reported.

Morabbi et al.[7] compared pexacerfont with placebo over a three week time period. Participants received one 300 mg capsule per day for the first week. This was reduced to a 200 mg capsule daily in the second week and 100 mg daily in the third week. No other interventions were administered during the trial.[7] Ahmadi et al. compared daily doses of 8 mg of sublingual buprenorphine with 40 mg of oral methadone over a period of 17 days.

The guideline by Wodarz et al.[9] considered a variety of pharmacological interventions for the management of acute methamphetamine-related disorders and toxicity including benzodiazepines, tricyclic antidepressants, dexamphetamine, and N-acetylcysteine. The VA/DoD guideline considered methods of healthcare delivery that might be effective for managing people who misuse substances. This included both pharmaceutical and psychosocial interventions.[10]

Outcomes

The SR examined the effectiveness of pharmacological interventions for psychotic symptom control or treatment of overdose.[6] They also included any available adverse event information.

The primary outcomes examined by Morabbi et al.[7] were the difference in the distribution of positive urine tests between groups at the end of the trial and the mean difference in the change in visual analogue scale (VAS) for craving from baseline to the end of the study. Secondary outcomes included: time × treatment interaction effect and mean difference in changes in scores for VAS for temptation severity to use the substance and frequency of temptation episodes, the Clinical Opiate Withdrawal Scale, the Amphetamine Withdrawal Questionnaire, the Beck Anxiety Inventory, and the Beck Depression Inventory II.[7] A

decrease in VAS scores indicated as an improvement and no information was provided regarding what was considered to be a clinically meaningful difference in scale score

Ahmadi et al.[8] assessed methamphetamine craving score using a validated VAS ranging from 0 (no craving) to 10 (severe craving and temptation all the time). A reduction in the VAS score indicated an improvement in the severity of craving. Urine drug tests were administered twice weekly to assess current methamphetamine use during the trial.[8]

The two guidelines[9,10] aimed to identify an optimal and evidence-based approach to management interventions that would result in a positive change to the management of people who misuse methamphetamine.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Reviews

The SR by Richards et al.[6] was generally well conducted. The research questions, inclusion criteria, review methods, and search strategy were all well described. Grey literature and hand searching were done and the full search strategy was provided in an appendix. The authors also indicated that they followed the PRISMA guidelines and that information was also provided in an appendix. The characteristics of the included primary studies included the number of participants and the intervention of interest; however, the population data was not well described and the authors did not describe whether there were any fundamental differences in the patient population between the primary studies. Without this information, it is difficult for the reader to determine whether the effects observed in the primary studies were a result of the intervention or were related to fundamental differences in the patient populations in each treatment groups. The potential risk of bias of the primary studies was assessed and the articles were graded using the Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence. The heterogeneity between primary studies was described and, due to the heterogeneity that was observed, a meta-analysis was not conducted. Sources of funding for the primary studies included in the review were not reported. The review authors reported no competing interests or conflicting funding sources.

Randomized Controlled Trials

Both of the included RCTs addressed a clear and focused research question.[7,8] Assignment of participants was randomized using computerized random number generation.[7,8] Morabbi et al.[7] described allocation concealment through the use of sequentially numbered sealed opaque envelopes but details of allocation concealment for Ahmadi et al.[8] were not available in the main publication. Subjects and investigators were blinded to the intervention in both studies.[7,8] and both studies measured treatment outcomes using urine drug tests and validated visual analogue scales. The treatment and control groups were not statistically significantly different from each other in either study.[7,8] The similarity between the groups allows for the observed effect to be attributed to the intervention rather than to chance. The participants the RCT by Morabbi et al.[7] included people who misused heroin, methamphetamine, or both drugs; however, due to the study's small sample size, the authors were not able to perform sub-analyses of each user group. Intention-to-treat analysis was conducted in both studies.[7,8] No participants dropped out of the Ahmadi study.[8] Three participants (12.5%) in the placebo group had to drop out of the Morabbi

study due to legal issues and their last observed test results were carried forward for analysis.[7] The authors of both studies declared no conflicts of interest.[7,8]

Evidence-based Guidelines

Two evidence-based guidelines were identified.[9,10] Both guidelines clearly described their overall objective, the target population of the guideline, and the intended user group.[9,10] The VA/DoD guideline[10] clearly outlined specific and defined research questions while these were lacking in the guideline by Wodarz et al.[9] Neither guideline indicated that it had sought out the view or preferences of the target population of people who misuse substances.[9,10] Both guidelines were developed using rigorous systematic methodology and were based on a systematically reviewed and critically appraised body of clinical evidence gives more confidence that the recommendations are based on the body of evidence and not only on studies that support the views of the guideline groups.[9,10] Recommendations in both guidelines were accompanied by a grading of the associated evidence and a measure of strength of the recommendation.[9,10] Detail regarding the exact methods used to form the recommendations and information regarding external peer review and guidelines for updating were somewhat lacking in the Wodarz publication; however, this information was taken from an English summary as the complete guideline document was published only in German.[9] The VA/DoD guideline[10] provides some information regarding barriers and facilitators to its application. Potential resource implications, implementation guidance, and monitoring or auditing criteria were not described in either guideline.[9,10] Conflicts of interest were addressed in the VA/DoD guideline.[10]

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Evidence Regarding Methods to Manage Acute Detoxification or Withdrawal from Methamphetamine

The SR by Richards et al.[6] examined treatments for agitation and psychosis resulting from the misuse of a variety of substances. Five studies reported on interventions for people who misused methamphetamine. Statistical significance of the results were not reported. Aripiprazole was found to be superior to placebo for the control of psychotic symptoms.[6] Haloperidol was compared with quetiapine and both drugs were found to be equally effective in controlling symptoms of methamphetamine-induced psychosis but more motor system events were observed in the haloperidol group.[6] Intravenous lorazepam was compared with droperidol for the management of acute methamphetamine toxicity in the emergency department.[6] Both drugs were effective for controlling agitation but the time to sedation was faster with droperidol and repeated dosing of intravenous lorazepam was required to achieve sedation.[6] One dystonic reaction was observed in the droperidol group and no adverse events (AEs) were reported in the haloperidol group.[6] Two studies examined the use of isradipine for the treatment of methamphetamine-induced rise in blood pressure and the authors found that, while isradipine reduced both systolic and diastolic blood pressure, the beneficial effect was offset by a reflex increase in heart rate.[6] Overall, Richards et al.[6] concluded that butyrophenones and later-generation antipsychotics may be an appropriate option for the control of agitation and psychosis associated with the use of methamphetamine and other substances, although motor system events may occur.

Morabbi et al.[7] compared pexacerfont with placebo for the treatment of withdrawal symptoms in men with heroin and/or methamphetamine dependence. At baseline, urine drug test results were positive for all participants in both treatment groups and, at the end of

the study (week three), no positive tests were reported in the treatment group and two positive tests in the placebo group.[7] Symptoms were measured using a number of validated symptom scales. There were statistically significant differences observed between the two groups in favor of pexacerfont in terms of changes in scores from baseline to the three week endpoint in VAS for craving, VAS for temptation severity, temptation frequency, and Beck Depression Inventory II.[7] No statistically significant differences were reported between groups in terms of AEs.[7] The most commonly reported AEs were increased appetite, dry mouth, fatigue, muscle twitches, and bradykinesia.

Ahmadi et al.[8] compared buprenorphine with methadone to reduce methamphetamine craving over a period of 17 days. All participants in both treatment groups had positive urine drug tests for methamphetamine at baseline and all participants had negative urine drug test results at the end of the study.[8] At the end of 17 days, the change in methamphetamine craving score was significantly reduced from baseline in both groups; however, the reduction in mean craving score was significantly greater in the buprenorphine group.[8] No significant AEs were observed during the study. The authors concluded that, while both treatments reduced methamphetamine craving, the craving in the buprenorphine group was significantly lower than that of the methadone group and they suggested that buprenorphine was the more effective treatment.[8]

Evidence-based Guidelines Regarding Methods to Manage Acute Detoxification or Withdrawal from Methamphetamine

Wodarz et al.,[9] from Germany, produced a set of recommendations regarding the pharmacological management of acute methamphetamine-related disorders and toxicity. See Table 4 for further explanation regarding how the levels of evidence and strength of recommendations were determined. The recommendations include that:

- Individuals presenting with methamphetamine intoxication be treated in a quiet and low stimulus environment (Level of evidence (LOE) 5 / positive recommendation),
- When pharmaceutical management is required, benzodiazepines should be used as the first-line treatment for individuals presenting with severe agitation, aggressiveness or psychotic symptoms resulting from methamphetamine intoxication (LOE 5 / strong positive recommendation),
- Benzodiazepines can be considered as a temporary addition to antipsychotic medications for the management of methamphetamine-induced psychosis (LOE 5 / open recommendation),
- Methamphetamine withdrawal treatment should last for at least three weeks, especially when the individual has reported regular consumption of high levels of methamphetamine (LOE 5 / strong positive recommendation),
- Bupropion or a tricyclic antidepressant may be considered for the management of methamphetamine withdrawal when the main symptoms include exhaustion, hypersomnia, or depressive-anxious symptoms (LOE 5 / open recommendation),
- First generation antipsychotic medications should not be used to alleviate the acute symptoms of methamphetamine withdrawal (LOE 2 / negative recommendation),

- Benzodiazepines may be considered to treat noticeable anxiety symptoms or to manage patient's treat of harm to themselves or others during inpatient methamphetamine withdrawal (LOE 5 / open recommendation),
- Benzodiazepines should be given at the lowest possible effective dose for the shortest period of time possible due to their addiction potential (LOE 5 / strong positive recommendation),
- Sustained-release dexamphetamine may be considered for inpatient methamphetamine withdrawal treatment where previous attempts at withdrawal have not been successful (LOE 5 / strong positive recommendation) and, if used, the dose should be determined specific to the individual, should be tapered before they are discharged from inpatient treatment, and should not be provided in an outpatient setting (LOE 5 strong negative recommendation),
- N-acetylcysteine may be useful for managing methamphetamine craving symptoms during the withdrawal period (LOE 2 / open recommendation).[9]

The authors of the VA/DoD guidelines are unable to recommend for or against any specific pharmacotherapy for the treatment of methamphetamine use disorder due to a lack of sufficient identified evidence.[10]

Limitations

The primary studies identified for inclusion in the SR and the two identified primary RCTs included a relatively small number of participants which could have an impact on the interpretation of the magnitude of the effect of the interventions studied.[6-8] Richards et al.[6] were not able to identify any large scale RCTs for inclusion in their SR and indicated that any bias present in the primary studies that were included could have influenced the results of their review. They also indicated that publication bias was a concern to them and that it was possible that not all AEs were reported in all of the included studies and this omission could have skewed the results of their analysis. The inclusion of case series and case reports in the SR and the use of broad search criteria were attempts to mitigate this type of bias in the review.[6]

The participant group in the Morabbi study[7] included people who misused methamphetamine, heroin, or both substances. Because of the small sample size of the study, the authors were not able to conduct subgroup analyses to explore the effects this heterogeneity might have had on their study results. The RCTs included only male participants due to the admission restrictions in place at the facilities where their studies were conducted.[7,8] The SR did not indicate whether the participants in the primary studies were male or female.[6] This may limit the ability to generalize the results of these studies to all people who misuse methamphetamine.

Both RCTs were conducted with voluntary inpatients.[7,8] The fact that these participants voluntarily took part in the research studies and were housed in inpatient facilities where they had limited or no access to methamphetamine might have contributed to the high rates of abstinence at the end of the study periods and may not be reflective of the effect these treatments would have in people who did not voluntarily present for treatment of methamphetamine misuse or who were being treated as outpatients and had easy access to methamphetamine. Morabbi et al.[7] also stated that, since many individuals who misuse substances participate in medication-assisted treatment programs rather than inpatient

programs, there is a limited population willing to participate in clinical research which undergoes severe enough methamphetamine withdrawal symptoms to study the true effect of drugs meant to mitigate the severity of those symptoms. Additionally, both of the RCTs were conducted in Iran.[7,8] It is possible that the Iranian healthcare system is different enough to limit the generalizability of their findings to the Canadian context.

The full guideline by Wodarz et al.[9] is published only in German. The information relating to this guideline that was included in the CADTH review was taken only from the English summary publication. Some reporting regarding the guideline development methodology is lacking in the English publication and this lack of detail may have had an impact on the critical appraisal of the guideline. The VA/DoD guideline[10] is intended to inform the care of those people participating in the VA/DoD healthcare system. The inclusion of primary research was not limited to studies conducted only in that setting so the recommendations in the guideline are likely generalizable to any healthcare setting; however, none were made specific to the management of people who misuse methamphetamine.

Conclusions and Implications for Decision or Policy Making

One SR,[6] two RCTs,[7,8] and two evidence-based guidelines[9,10] were identified regarding the management of acute withdrawal and detoxification for people who misuse methamphetamine.

Aripiprazole was found to be more effective than placebo and haloperidol and quetiapine were found to be equally effective for the management of methamphetamine-induced psychosis.[6] Intravenous lorazepam and droperidol were effective for the management of agitation associated with acute methamphetamine toxicity in the emergency department.[6] Isradipine was effective for the treatment of methamphetamine-induced high blood pressure.[6] Pexacerfont[7] and buprenorphine[8] were effective for managing methamphetamine craving during methamphetamine withdrawal. The authors of an included guideline recommend that benzodiazepines should be considered as a first line treatment option for the management of severe agitation, aggressiveness, or psychosis stemming from methamphetamine intoxication.[9]

There is a need for larger controlled studies of participants experiencing withdrawal from methamphetamine and also for longer term follow-up studies of individuals who had their withdrawal symptoms managed in an inpatient setting once they have been discharged from the controlled environment back to the community. Further research comparing the available pharmacotherapy methods with each other may help to reduce uncertainty in this area. It should be noted that no studies were identified regarding non-pharmacological strategies, including psychological and physical, for the management of acute withdrawal and detoxification and further study into these areas may also be helpful to inform clinical practice. None of the publications included in this CADTH review were conducted in Canada and, as such, the applicability of these findings to the Canadian healthcare setting may be limited.

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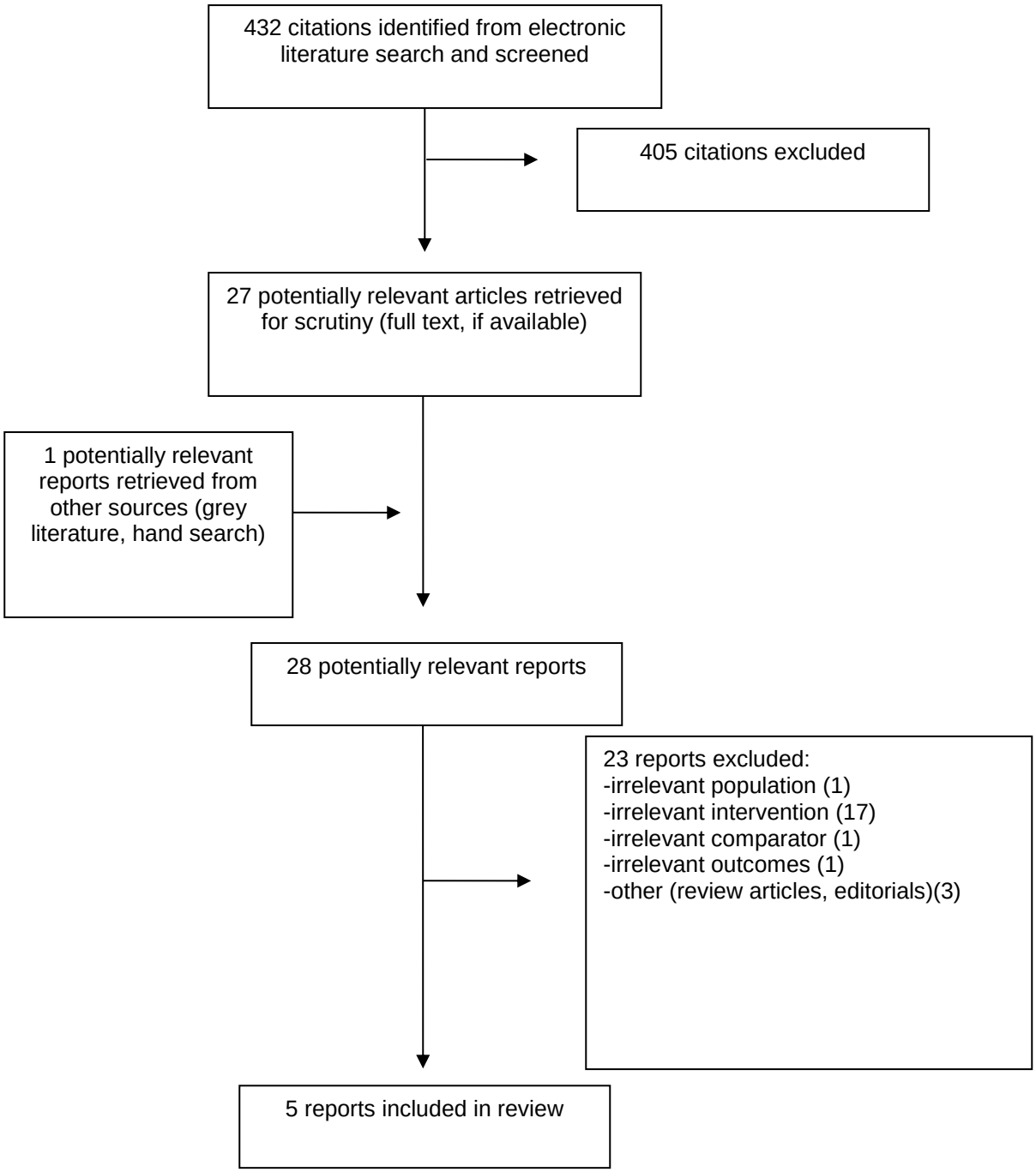
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up

Richards, 2015[6]
 	
United States
	81 publications (13 investigating methamphetamine)
	• Treatment of agitation and psychosis (47 papers, 10 investigating methamphetamine)
	  ○ 3 RCTs 2 case series
	  ○ 5 case reports
	• Treatment of overdose of amphetamines, hyperadrenergic state (34 papers, 3 investigating methamphetamine)
	  ○ 2 prospective observational studies (1 case series
	Literature search: inception to September 20, 2014
		Adults presenting for treatment of ADRA-related agitation, psychosis, or hyperadrenergic symptoms (hypertension, tachycardia)
		• No further description of the patient population was provided in the publication.
			Interventions[a]
			• Aripiprazole
			• Haloperidol
			• Droperidol
			• Benzodiazepines
			• Zuclopenthixol
			• Risperidone
			• Olanzapine
			• Quetiapine
			• Lorazepam
			
			Comparators were not clearly reported.
				• Psychotic symptom control
				• Treatment of overdose

ARDA = amphetamine, its related derivatives and analogues; RCT = randomized controlled trial

[a] = Only interventions listed for studies of methamphetamine included

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trials				
Morabbi, 2018[7] Iran	Double-blind, placebo-controlled RCT for the treatment of withdrawal symptoms in men with heroin or methamphetamine dependence	50 male participants with substance use disorder who were voluntarily referred to two addiction health services residential camps Pexacerfont (n = 26) • Age = 29.73 (SD = 9.57) • Years of substance use = 10.50 (SD = 7.03) • Type of substance	Pexacerfont vs placebo 3 weeks of treatment beginning with one 300 mg capsule/day in the first week, 200 mg/day the second week and 100 mg/day the third week.	Primary outcomes: • Difference in the distribution of positive urine tests at the end of the trial • Mean difference in the change in VAS for craving from baseline to endpoint

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		○ Heroin = 6 (23.08%) ○ Methamphetamine = 0 ○ Both = 20 (76.92%) Placebo (n = 24) • Age = 34.00 (SD = 9.85) • Years of substance use = 10.92 (SD = 5.76) • Type of substance ○ Heroin = 12 (50.00%) ○ Methamphetamine = 2 (8.33%) ○ Both = 10 (41.67%) • Three participants withdrew from the trial in the second week due to legal reasons No statistically significant difference observed between groups except in the distribution of the types of misused substances.	No simultaneous antidepressants, behavioral interventions, or substitution therapy were administered.	Secondary outcomes: • time × treatment interaction effect • mean difference in changes in scores for VAS for temptation severity to use the substance and frequency of temptation episodes, the Clinical Opiate Withdrawal Scale the Amphetamine Withdrawal Questionnaire, the Beck Anxiety Inventory and the Beck Depression Inventory II Length of follow-up: three weeks
Ahmadi, 2017[8] Iran	Double-blind RCT for the management of methamphetamine withdrawal craving	40 male patients diagnosed with severe methamphetamine dependence and withdrawal and treated at inpatient psychiatric ward Methadone (n = 20) • Age = 31.2 ± 9.04 Buprenorphine (n = 20) • Age = 34.35 ± 9.65 No statistically significant differences were observed between groups for age, education, employment, marital status or income. No participants dropped out or were lost to follow-up	8 mg sublingual buprenorphine vs 40 mg oral methadone daily	Primary outcome: • Changes in methamphetamine craving score • Negative urine drug screening test Length of follow-up: 17 days Effectiveness was evaluated by daily interview and precise assessment of craving by asking the subjects about their experience

mg = milligram; RCT = randomized controlled trial; SD = standard deviation; VAS = visual analogue scale; vs = versus

Table 4: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Wodarz, 2017[9]						
Intended users: Doctors and staff in hospitals, practices, and addiction treatment centres Target population: Adults who misuse methamphetamine	Pharmacological management of acute methamphetamine-related disorders and toxicity	NR	• Systematic literature search in multiple clinical data bases • Search dates: 2000 to June 2015 • Guidelines search conducted in April 2015 • Two reviewers • Included publications in German or English	• OCEBM tool used to assess methodological quality and grade evidence • Cochrane RoB tool used for RCTs • Guidelines assessed using DELBI instrument • AMSTAR score was used for SRs	• Recommendations on pharmacological treatment strategies created using nominal group technique • Level of evidence assigned using OCEBM ○ Level 1 – SRs and RCTs ○ Level 2 – RCTs or observational studies with dramatic effect ○ Level 3 – non-randomized, controlled cohort or follow-up study ○ Level 4 – case series, case-controlled studies, or historically controlled studies ○ Level 5 – mechanism-based reasoning • Grades of Recommendation ○ Strong recommendation ○ Recommendation ○ Open recommendation	NR
Department of Veterans Affairs / Department of Defense, 2015 [10]						
Intended users:	Framework by which to evaluate,	NR	• Update to the 2009	• GRADE was used to	• Guidelines were developed through an	NR

Table 4: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Health care providers any healthcare system Target population: Adults with substance use disorders who are eligible for care in the VA and DoD healthcare delivery system	treat, and manage the individual needs and preferences of patients with non-tobacco substance use disorders		guideline • Used internal Guideline for Guidelines document • Based on a SR • Literature search: November 2007 to January 2015	assess the quality of the evidence	iterative process and underwent internal and external peer review and comment • GRADE was used to assign a grade for the strength of recommendation ○ Strong for ○ Weak for ○ Weak against ○ Strong against	

AMSTAR = Assessing the Methodological Quality of Systematic Reviews; DELBI = Deutsches Instrument zur methodischen Leitlinien-Bewertung; GRADE = Grading of Recommendations Assessment, Development and Evaluation; NR = not reported; OCEBM = Oxford Centre for Evidence-Based Medicine; RCT = randomized controlled trial; RoB = risk of bias; SR = systematic review

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Review and Meta-Analysis using AMSTAR 2[2]

Strengths	Limitations
Richards, 2015[6]	
• Research questions and inclusion criteria include PICO elements • Explicitly stated that methods were established a priori • PRISMA guidelines were followed and information was provided in an appendix • Reviewers explained the selection of study designs • Comprehensive search strategy used (detailed in a supplement) and explained • Grey literature and hand searching was done • Selection and data extraction were done in duplicate • Included studies were described in adequate detail • RoB of primary studies was appropriately assessed and accounted for when discussing the results • Articles were graded using OCEBM levels of evidence The heterogeneity between studies was well described • The review authors reported no competing interests or conflicting funding sources	• Unclear from main publication details whether selection and data extraction were done in duplicate • Population data from the primary studies was not well described. Unable to tell whether there were fundamental differences in characteristics between groups • Sources of funding for the studies included in the review were not reported • Meta-analysis was not conducted due to heterogeneity in the primary study methods

OCEBM = Oxford Centre for Evidence-Based Medicine; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses

Table 6: Strengths and Limitations of Clinical Studies using SIGN50 Quality Assessment Instrument for RCT

Strengths	Limitations
Randomized Controlled Trials	
Morabbi, 2018[7]	
• The study addresses an appropriate and clearly focused question • The assignment of subjects to treatment groups was randomized using computerized random number generation • Adequate allocation concealment was used (sequentially numbered sealed opaque envelopes) and subjects and investigators were blinded to the intervention (identical active and placebo capsules were formulated for use in the study) • Treatment and control groups were not significantly different at baseline • Relevant outcomes were measured in a standard, valid and reliable way (positive or negative urine tests and validated symptom scales) • ITT analysis was conducted • 12.5% (3 of 24) of the placebo group dropped out • The authors declared no conflicts of interest	• Funding sources for the study were not described • The patient population included both people who misused both heroin and methamphetamine and sub-analyses could not be undertaken because of the study's sample size

Table 6: Strengths and Limitations of Clinical Studies using SIGN50 Quality Assessment Instrument for RCT

Strengths	Limitations
Ahmadi, 2017[8]	
• The study addresses an appropriate and clearly focused question • The assignment of subjects to treatment groups was randomized using a computer generated random sample set • Subjects and investigators were blinded to the intervention • Pills were manufactured to be the same shape and color to maintain blinding • Treatment and control groups were not significantly different at baseline • Relevant outcomes were measured in a standard, valid and reliable way (using a validated VAS and urine drug tests) • No participants dropped out or were lost to follow-up in either treatment group • ITT analysis was conducted • The authors declared no conflicts of interest	• Methods of allocation concealment were not described in the publication but a completed consort statement indicated it was described on another page • Funding sources were not described

ITT = intention-to-treat; VAS = visual analogue scale

Table 7: Strengths and Limitations of Guidelines using AGREE II[4]

Item	Guideline	
	Wodarz, 2017[9]	Department of Veterans Affairs / Department of Defense, 2015 [10]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	X	X
2. The health question(s) covered by the guideline is (are) specifically described.	-	X
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	X	X
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	-	X
5. The views and preferences of the target population (patients, public, etc.) have been sought.	-	-
6. The target users of the guideline are clearly defined.	X	X
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	X	X
8. The criteria for selecting the evidence are clearly described.	X	X
9. The strengths and limitations of the body of evidence are clearly described.	X	X

Table 7: Strengths and Limitations of Guidelines using AGREE II[4]

Item	Guideline	
10. The methods for formulating the recommendations are clearly described.	-	X
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	X	X
12. There is an explicit link between the recommendations and the supporting evidence.	X	X
13. The guideline has been externally reviewed by experts prior to its publication.	-	X
14. A procedure for updating the guideline is provided.	-	X
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	X	X
16. The different options for management of the condition or health issue are clearly presented.	X	X
17. Key recommendations are easily identifiable.	X	X
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	-	X
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	-	-
20. The potential resource implications of applying the recommendations have been considered.	-	-
21. The guideline presents monitoring and/or auditing criteria.	-	-
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	-	-
23. Competing interests of guideline development group members have been recorded and addressed.	-	X

X = yes; - = not described or specified, NA = not applicable

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings Included Systematic Review and Meta-Analysis

Main Study Findings	Authors' Conclusion
Richards, 2015[6]	
Statistical significance was not reported for any study results **Aripiprazole vs placebo (1 study)** • Aripiprazole was found to be superior to placebo for psychotic symptom control **Haloperidol vs quetiapine for methamphetamine-induced psychosis (1 study)** • Both treatments were found to be equally effective in controlling symptoms (values not reported) • More extrapyramidal events occurred with haloperidol vs quetiapine (5 vs 1) **IV lorazepam vs droperidol for acute methamphetamine toxicity in the ED (1 study) (n = 146)** • Both IV lorazepam and droperidol were effective for controlling agitation • Time to sedation was faster with droperidol • Repeated dosing of IV lorazepam was required to achieve sedation • One dystonic reaction was observed in the droperidol group **AEs reported in case series** • Two males who received zuclopenthixol, and haloperidol and subsequently developed rigidity without hyperthermia concerning for mild NMS which resolved over time **Isradipine for treatment of hyperadrenergic state (2 studies)** • Isradipine reduced methamphetamine-induced rise in SBP and DBP • The beneficial effect was offset by a reflex increase in HR.	"For control of agitation and psychosis from ARDA, butyrophenones and later-generation antipsychotics are a reasonable choice, with the understanding extrapyramidal side effects may occur." (page 10)

AE = adverse event; ARDA = amphetamines, related derivatives, and analogues; DBP = diastolic blood pressure; HR = heart rate; IV = intravenous; SBP = systolic blood pressure; vs = versus.

Table 9: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized Controlled Trials	
Morabbi, 2018[7]	
Comparison of positive urine test results **Pexacerfont (n = 26) – ITT and Complete Case** • **Baseline = 26 (100%)**	• "The distribution of the positive urine test results was similar in the pexacerfont and the placebo treatment arms during the trial, but the craving severity scores decreased considerably more in the pexacerfont arm compared with the placebo arm.

Table 9: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion

• **Week = 1 0 (0%)**
• **Week = 2 0 (0%)**
• **Week = 3 0 (0%)**
Placebo (n = 24) – ITT (LOCF)
• **Baseline = 24 (100%)**
• **Week 1 = 2 (8.33%)**
• **Week 2 = 2 (8.33%)**
• **Week 3 = 2 (8.33%)**
Placebo (n = 21) – Complete Case
• **Baseline = 21 (100%)**
• **Week 1 = 2 (9.52%)**
• **Week 2 = 2 (9.52%)**
• **Week 3 = 2 (9.52%)**
 	
Withdrawal symptoms
• "A significant time × treatment interaction was found for all the measured scales including the VAS for craving as a primary outcome as well as other secondary outcomes... In case of VAS for craving, VAS for temptation severity, temptation frequency, and Beck Depression Inventory II, there were significant differences in changes in scores from the baseline to the endpoint between the two treatment arms." (page 116)
 	
Adverse events - Pexacerfont (n = 26) / Placebo (n = 24) (%)
• No statistically significant difference in adverse events was observed between groups.
  ○ Daytime drowsiness = 1 (3.85) / 3 (12.50)
  ○ Morning drowsiness = 2 (7.67) / 4 (16.67)
  ○ Bradykinesia = 4 (15.38) / 4 (16.67)
  ○ Myalgia = 3 (11.54) / 4 (16.67)
  ○ Dizziness = 1 (3.85) / 0 (0)
  ○ Nervousness = 3 (11.54) / 4 (16.67)
  ○ Restlessness = 6 (23.08) / 8 (33.33)
  ○ Blurred vision = 3 (11.54) / 2 (8.33)
  ○ Increased appetite = 16 (61.54) / 14 (58.33)
  ○ Fatigue = 6 (23.08) / 5 (20.83)
  ○ Muscle twitches = 6 (23.08) / 6 (25.00)
  ○ Dry mouth = 7 (26.92) / 6 (25.00)
  ○ Sore throat = 1 (3.85) / 1 (4.17)
  ○ Palpitations = 1 (3.85) / 2 (8.33)
	Analysis also showed a greater improvement in the pexacerfont treatment arm in terms of temptation severity, frequency of temptation episodes, and depressive symptoms. Time × treatment interaction effects favored the efficacy of pexacerfont in all seven scales used." (page 116)
	• "This pilot study provides preliminary evidence for the potentially favorable effects of CRF1 receptor antagonists, that is pexacerfont, in the treatment of the withdrawal state in patients with substance dependence. Future studies are required to address both the limitations of this trial and consider the potential effects of CRF1 antagonists for the treatment of conditions that demonstrate withdrawal in neurobiology and symptomatology." (page 117)

Ahmadi, 2017[8]	

Mean methamphetamine craving score over 17 days
• Buprenorphine
  ○ Day 1 = 7 ± 1.34
  ○ Day 17 = 0.15 ±0.37
  ○ Total = 2.92 ± 1.189
• Methadone
  ○ Day 1 = 7.2 ± 1.28
  ○ Day 17 = 0.8 ± 0.95
  ○ Total = 3.89 ± 1.517
• Methamphetamine craving score was significantly reduced in
	• "This study shows that although buprenorphine and methadone are both effective in treating methamphetamine craving during methamphetamine withdrawal, the craving in the buprenorphine group was significantly lower than that in the methadone group starting on the tenth day. Therefore, buprenorphine was more effective than methadone." (page 5)
	• "It is to be expected that craving decreases over time without any medication. Thus, the conclusion cannot be drawn that methadone and buprenorphine both reduce the craving.

Table 9: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
both groups • The reduction in mean craving score was significantly more in the buprenorphine group (P = 0.03) **Urine testing** • All participants had positive urine drug tests for methamphetamine at the beginning of the study and all participants had negative urine drug tests at the ends of the study **Adverse events** • No significant adverse events were observed during the study	Because buprenorphine is superior to methadone, only buprenorphine surely reduces the craving." (page 5) • "We suggest these opioids as short-term inpatient treatments to enhance retention or even as long-term maintenance treatment to minimize relapse." (page 5)

ITT = intention-to-treat; LOCF = last observation carried forward; VAS = visual analogue score

Table 10: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Wodarz, 2017[9]	
A person suffering from a methamphetamine intoxication ought to be treated in a quiet, low-stimulus environment if possible.	• Level of evidence 5 • Positive recommendation
In the case of methamphetamine intoxication with severe agitation, aggressiveness, or psychotic symptoms requiring pharmacological treatment, benzodiazepines should be given as first-line medication.	• Level of evidence 5 • Strong positive recommendation
A benzodiazepine may be considered temporarily as an add-on treatment to an antipsychotic medication of a methamphetamine-induced psychosis.	• Level of evidence 5 • Open recommendation ○ May be considered or no specific recommendation
Treatment of a methamphetamine withdrawal should be at least 3 weeks, particularly in the case of high and regular substance consumption.	• Level of evidence 5 • Strong positive recommendation
If, in the case of methamphetamine withdrawal, the prevailing signs are depressive-anxious symptoms, exhaustion, and/or hypersomnia, bupropion or a TCA with activating properties such as desipramine may be considered. (page 92)	• Level of evidence 5 • Open recommendation ○ May be considered or no specific recommendation
First-generation antipsychotic medication with high potency ought not to be used to alleviate withdrawal symptoms in the acute treatment of methamphetamine patients (page 92)	• Level of evidence 2 • Negative recommendation
Benzodiazepines may be considered in inpatient withdrawal treatment of methamphetamine-dependent users to attenuate an acute threat of harm to the patient himself/herself or others or to treat pronounced anxiety symptoms. (page 92)	• Level of evidence 5 • Open recommendation ○ May be considered or no specific recommendation
Given the addictive potential, benzodiazepines should be administered at the lowest possible dose and should be tapered off as soon as possible. (page 02)	• Level of evidence 5 • Strong positive recommendation
In justified individual cases and if previous withdrawal attempts	• Level of evidence 2

Table 10: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
have failed, sustained-release dexamphetamine may be considered in inpatient withdrawal treatment to alleviate withdrawal symptoms in methamphetamine-dependent users. (page 92)	• Open recommendation ○ May be considered or no specific recommendation
When sustained-release dexamphetamine is used in inpatient withdrawal treatment to alleviate withdrawal symptoms, the dose should be individually titrated and then tapered off no later than the time of discharge. (page 92)	• Level of evidence 5 • Strong positive recommendation
Sustained-release dexamphetamine should not be given to treat methamphetamine withdrawal in an outpatient setting.	• Level of evidence 5 • Strong negative recommendation
N-acetylcysteine may be considered for alleviating methamphetamine craving during withdrawal. (page 92)	• Level of evidence 2 • Open recommendation ○ May be considered or no specific recommendation
Department of Veterans Affairs / Department of Defense, 2015 [10]	
There is insufficient evidence to recommend for or against the use of any pharmacotherapy for the treatment of cocaine use disorder or methamphetamine use disorder. (page 27)	No recommendation made.

TCA = tricyclic antidepressant

Appendix 5: Additional References of Potential Interest

Systematic Reviews and Meta-Analyses – Alternative Intervention

Harada T, Tsutomi H, Mori R, Wilson DB. Cognitive-behavioural treatment for amphetamine-type stimulants (ATS)-use disorders. *Cochrane Database Syst Rev*. 2018 Dec 22;12:Cd011315.

PubMed: PM30577083

Lam L, Anand S, Li X, Tse ML, Zhao JX, Chan EW. Efficacy and safety of naltrexone for amfetamine and methamfetamine use disorder: a systematic review of randomized controlled trials. *Clin Toxicol (Phila)*. 2018 Nov 17:1-9.

PubMed: PM30451013

Lee NK, Jenner L, Harney A, Cameron J. Pharmacotherapy for amphetamine dependence: A systematic review. *Drug Alcohol Depend*. 2018 Oct 1;191:309-337.

PubMed: PM30173086

Bhatt M, Zielinski L, Baker-Beal L, et al. Efficacy and safety of psychostimulants for amphetamine and methamphetamine use disorders: a systematic review and meta-analysis. *Systematic reviews*. 2016 Nov 14;5(1):189.

PubMed: PM27842569

Hellem TL. A Review of Methamphetamine Dependence and Withdrawal Treatment: A Focus on Anxiety Outcomes. *J Subst Abuse Treat*. 2016 Dec;71:16-22.

PubMed: PM27776672

Randomized Controlled Trials – Alternative Intervention

Briones M, Shoptaw S, Cook R, et al. Varenicline treatment for methamphetamine dependence: A randomized, double-blind phase II clinical trial. *Drug Alcohol Depend*. 2018 Aug 1;189:30-36.

PubMed: PM29860057

Coffin PO, Santos GM, Hern J, et al. Extended-release naltrexone for methamphetamine dependence among men who have sex with men: a randomized placebo-controlled trial. *Addiction*. 2018 Feb;113(2):268-278.

PubMed: PM28734107

Dean AC, Nurmi EL, Moeller SJ, et al. No effect of attentional bias modification training in methamphetamine users receiving residential treatment. *Psychopharmacology (Berl)*. 2018 Nov 10.

PubMed: PM30415277

Farahzadi MH, Moazen-Zadeh E, Razaghi E, Zarrindast MR, Bidaki R, Akhondzadeh S. Riluzole for treatment of men with methamphetamine dependence: A randomized, double-blind, placebo-controlled clinical trial. *Journal of psychopharmacology (Oxford, England)*. 2018 Dec 11:269881118817166.

PubMed: PM30526230

Schottenfeld RS, Chawarski MC, Sofuoglu M, et al. Atomoxetine for amphetamine-type stimulant dependence during buprenorphine treatment: A randomized controlled trial. *Drug Alcohol Depend*. 2018 May 1;186:130-137.

PubMed: PM29573648

Zhu Y, Jiang H, Su H, et al. A Newly Designed Mobile-Based Computerized Cognitive Addiction Therapy App for the Improvement of Cognition Impairments and Risk Decision Making in Methamphetamine Use Disorder: Randomized Controlled Trial. *JMIR mHealth and uHealth*. 2018 Jun 20;6(6):e10292.

PubMed: PM29925497

Runarsdottir V, Hansdottir I, Tyrfingsson T, et al. Extended-Release Injectable Naltrexone (XR-NTX) With Intensive Psychosocial Therapy for Amphetamine-Dependent Persons Seeking Treatment: A Placebo-Controlled Trial. *J Addict Med*. 2017 May/Jun;11(3):197-204.

PubMed: PM28379861

Watkins KE, Ober AJ, Lamp K, et al. Collaborative Care for Opioid and Alcohol Use Disorders in Primary Care: The SUMMIT Randomized Clinical Trial. *JAMA internal medicine*. 2017 Oct 1;177(10):1480-1488.

PubMed: PM28846769

Rezaei F, Ghaderi E, Mardani R, Hamidi S, Hassanzadeh K. Topiramate for the management of methamphetamine dependence: a pilot randomized, double-blind, placebo-controlled trial. *Fundam Clin Pharmacol*. 2016 Jun;30(3):282-289.

PubMed: PM26751259

Mousavi SG, Sharbafchi MR, Salehi M, Peykanpour M, Karimian Sichani N, Maracy M. The efficacy of N-acetylcysteine in the treatment of methamphetamine dependence: a double-blind controlled, crossover study. *Arch Iran Med*. 2015 Jan;18(1):28-33.

PubMed: PM25556383

Rezaei F, Emami M, Zahed S, Morabbi MJ, Farahzadi M, Akhondzadeh S. Sustained-release methylphenidate in methamphetamine dependence treatment: a double-blind and placebo-controlled trial. *Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences*. 2015 Jan 15;23:2.

PubMed: PM25588930

Polcin DL, Bond J, Korcha R, Nayak MB, Galloway GP, Evans K. Randomized trial of intensive motivational interviewing for methamphetamine dependence. *J Addict Dis*. 2014;33(3):253-265.

PubMed: PM25115166

Solhi H, Jamilian HR, Kazemifar AM, Javaheri J, Rasti Barzaki A. Methylphenidate vs. resperidone in treatment of methamphetamine dependence: A clinical trial. *Saudi pharmaceutical journal : SPJ : the official publication of the Saudi Pharmaceutical Society*. 2014 Jul;22(3):191-194.

PubMed: PM25061402

Non-Randomized Studies

No Comparator

McKenna B, McEvedy S, Kelly K, et al. Association of methamphetamine use and restrictive interventions in an acute adult inpatient mental health unit: A retrospective cohort study. *Int J Ment Health Nurs*. 2017 Feb;26(1):49-55.

PubMed: PM27860236

Alternative Intervention

Mooney LJ, Hillhouse MP, Thomas C, et al. Utilizing a Two-stage Design to Investigate the Safety and Potential Efficacy of Monthly Naltrexone Plus Once-daily Bupropion as a Treatment for Methamphetamine Use Disorder. *J Addict Med*. 2016 Jul-Aug;10(4):236-243.

PubMed: PM27379819

Evidence-based Guidelines – Alternative Intervention

Hartel-Petri R, Krampe-Scheidler A, Braunwarth WD, et al. Evidence-Based Guidelines for the Pharmacologic Management of Methamphetamine Dependence, Relapse Prevention, Chronic Methamphetamine-Related, and Comorbid Psychiatric Disorders in Post-Acute Settings. *Pharmacopsychiatry*. 2017 May;50(3):96-104.

PubMed: PM28445899