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SUMMARY WITH CRITICAL APPRAISAL

Treatment for Methamphetamine Addiction: A Review of Guidelines

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Authors: Ke Xin Li, Hannah Loshak

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Abbreviations

SR	Systematic review
RCT	Randomized controlled trial
OCEBM	Oxford Centre for Evidence-Based Medicine

Context and Policy Issues

Methamphetamine is a recreational drug of abuse synthesized illegally in laboratories using a variety of ingredients of over-the-counter medications, including ephedrine or pseudoephedrine.[1] The Canadian government introduced regulations in 2006 to move the ephedrine-containing products behind the pharmacy counter in order to limit access to the precursor chemicals.[1] Methamphetamine is often sold in powder, crystal or tablet formulations and can be inhaled, ingested, smoked, or injected after mixing with water.[1] In Canada, the prevalence of methamphetamine use is about 0.2% of the population.[1] However, there was a 590% increase in the number of methamphetamine-possession incidents between 2010 and 2017.[1] Methamphetamine has a long half-life of 12 hours and the altered mental state can last up to 12 hours depending on the route of administration.[1] Short-term effects associated with its use include alertness, decreased appetite, headache, dizziness, increased body temperature, heart rate, blood pressure, and respiratory rate.[1] Longer-term effects may include psychotic symptoms such as violent behaviour, paranoia, and hallucinations. [1] Extreme itching, mood swings, memory loss, and insomnia are also the potential long-term effects.[1] Across Canada, the prevalence of lifetime methamphetamine use is higher for males than for females.[1] The withdrawal effect of amphetamine can include intense craving, tiredness, anxiety, depression.[1] The objective of this report is to summarize evidence-based guidelines regarding treatment immediately after acute detoxification and post-treatment care for patients with methamphetamine addiction.

Research Questions

1. What are the evidence-based guidelines regarding the treatment for patients with methamphetamine addiction immediately after acute detoxification?
2. What are the evidence-based guidelines regarding post-treatment care for patients with methamphetamine addiction?

Key Findings

Three evidence-based guidelines were identified that addressed the research questions. Although published separately, all three publications represented one unique guideline; therefore, one evidence-based guideline is reported. A variety of recommendations were made regarding treatment immediately after acute detoxification and post-treatment care for patients with methamphetamine addiction. Needs-centred or motivation-centred psychotherapeutic counseling, sports therapy such as exercise therapy and physical conditioning were recommended by the guideline. The guideline recommended that sertraline, combined intravenous pharmacotherapy with flumazenil, gabapentin and hydroxyzine should not be given to patients with methamphetamine-related disorder. The guideline also recommended that needs-specific self-help groups and family support should be an integral part of all services offered.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline and PsycINFO via OVID the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was methamphetamine. Search filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and June 3, 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**: Selection Criteria**.

Table 1: Selection Criteria

Population	Patients with an addiction to methamphetamine, including crystal methamphetamine
Intervention	Q1: Treatment immediately after acute detoxification Q2: Post-treatment care (e.g., transitional, residential supports)
Comparator	No comparator necessary
Outcomes	Evidence-based guidelines and recommendations
Study Designs	Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2009. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included evidence-based guidelines were critically appraised by one reviewer using the AGREE II instrument.[2] 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 531 citations were identified in the literature search. Following screening of titles and abstracts, 528 citations were excluded and three potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the hand search for full text review. Of these potentially relevant articles, one

publication was excluded as its intervention did not meet the inclusion criteria, and three publications met the inclusion criteria and were included in this report. These are comprised of three evidence-based guidelines. Although published separately, all three publications represented one unique guideline; therefore, one evidence-based guideline is reported. Appendix 1: Selection of Included Studies presents the PRISMA[3] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5: Additional References of Potential Interest.

Summary of Study Characteristics

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

Study Design

One evidence-based guideline, published in 2016 by Bruanwarth et al. was identified that addressed the both of the research questions.[4] Two additional publications by Gouzoulis-Mayfrank et al. and Hartel-Petri et al. published in 2017 represented the same unique guideline by Bruanwarth et al. [4-6] The guideline group conducted a systematic search to identify systematic reviews (SRs) and randomized controlled trials (RCTs) to support their guideline development. Braunwarth et al. used the Oxford Centre for Evidence-based Medicine (OCEBM) tool to assess methodological quality and grade evidence, 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.[4] Recommendations in the guideline were developed using the a structured consensus procedure called nominal group technique, where recommendations were approved the voting results showed greater than or equal to 75% agreement..[4] Detailed explanations of the methods of rating the evidence and recommendations are provided in Table 2: Characteristics of Included Guidelines .

Country of Origin

The included guidelines were produced by a group from Germany.[4-6]

Patient Population

The target population of the guideline by Braunwarth et al.[4] is adults with methamphetamine-related disorders. The intended users include doctors and staff in hospitals, medical practices, and addiction treatment centres.[4]

Interventions and Comparators

The guideline by Braunwarth et al.[4] considered methods of care delivery that might be effective for managing people with methamphetamine-related disorders. This included both psychosocial and pharmaceutical interventions for post-acute period including immediately after acute detoxification and post-treatment.care.[4]

Outcomes

Braunwarth et al.[4] aimed to identify an evidence-based approach for management interventions that would result in a positive change for patients with methamphetamine-related disorders. The level of evidence of each recommendation was assigned using OCEBM with Level 1 being SRs and RCTs, Level 2 being RCTs or observational studies

with dramatic effect, Level 3 being non-randomized, controlled cohort or follow-up study, Level 4 being case series, case-controlled studies, or historically controlled studies and Level 5 being mechanism-based reasoning.[4] The authors of the guideline assigned grades of recommendation using a consensus process, taking into account the evidence, feasibility, clinical relevance, benefit-harm ratio, ethics, applicability to the patient population, and patient preferences.[4]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3: Critical Appraisal of Included Publications.

The guideline clearly described the overall objective, the target population of the guideline, and the intended user group.[4] It is unclear whether the views and preferences of the target population, patients with methamphetamine-related disorders, was sought.[4] The guideline was developed using rigorous systematic methodology and were based on a systematically reviewed and critically appraised body of clinical evidence, which gives more confidence that the recommendations are based on the body of evidence and not only on studies that support the expert opinions of the guideline groups.[4] Recommendations in the guideline were accompanied by a grading of the associated evidence and a measure of strength of the recommendation.[4] Details regarding the exact methods used to form the recommendations and information regarding external peer review and guidelines for updating were lacking.[4] Potential resource implications, implementation guidance, and monitoring or auditing criteria were not described in the guideline.[4] Conflicts of interest were addressed.[4]

Summary of Findings

Braunwarth et al.[4] from Germany, produced a set of recommendations regarding the management of methamphetamine-related disorders in post-acute settings. Appendix 4: Main Study Findings and Authors' Conclusions presents a table of the recommendations.

The authors of the guideline by Braunwarth et al. recommend a number of care delivery structures, psychotherapeutic and pharmacologic treatment options for patients with methamphetamine addiction.[4]

Eight 'strong' recommendations were made.[4] The guideline strongly recommended needs-specific self-help groups and family support, social work-related support, education and referral for rehabilitation, needs-centred or motivation-centred psychotherapeutic counseling, and sports therapy.[4] The guideline strongly recommended against the use of sertraline to achieve abstinence, the use of dopamine analog treatment with narcotic-classified substances beyond acute withdrawal period outside clinical trial settings, and combined intravenous pharmacotherapy with flumazenil, gabapentin and hydroxyzine.[4]

Medium strength recommendations were made for individualized post-acute care settings determination, setting abstinence as primary goal of therapy, fostering re-integration back to workforce, delivering coordinated care for at least a year, participation-oriented support and assistance services, utilization of the stepped-care approach, referral to psychotherapeutic services, offering behavioral therapy or multimodal methamphetamine-specific regimens, and not to use modafinil in post-acute settings.[4] Open recommendations were made for treatment with bupropion in patients with non-daily methamphetamine use, administering

imipramine to increase retention rate, neurofeedback as therapies and auricular acupuncture.[4]

Limitations

The guideline by Braunwarth et al. [4] presented the clinical-effectiveness of psychotherapeutic techniques; but there is research gap of the comparative effectiveness of one method over the other. Many recommendations in the guideline are made with a medium or weak grade of recommendation because of the lack of evidence base and reported therapeutic effects.[4] Additionally, the generalizability of the recommendation of the German guideline[4] to the Canadian context is unknown.

Conclusions and Implications for Decision or Policy Making

Three publications representing one evidence-based guideline[4] was identified that addressed the research questions. A variety of recommendations were made regarding treatment immediately after acute detoxification and post-treatment care for patients with methamphetamine addiction.[4]

The authors of the guideline by Braunwarth et al. recommend a number of care delivery structures, psychotherapeutic and pharmacologic treatment options for patients with methamphetamine addiction.[4] The guideline recommended that patients with a diagnosis of substance abuse should be offered psychotherapy.[4] Structured exercise programs were also recommended.[4] Two weak recommendations were made for pharmacotherapy, including tranquilizers for the short-term treatment of agitation and atypical antipsychotics as needed.[4]. Sertraline should not be administered to achieve abstinence due to adverse events.[4]

Further research comparing the available psychotherapeutic methods with each other may help to reduce uncertainty in this area. The publication considered in this CADTH review was not conducted in Canada.[4] The health care resources requirement, training requirements and budgetary implications may differ between countries. Therefore, the applicability of these findings to the Canadian healthcare setting may be limited.

References

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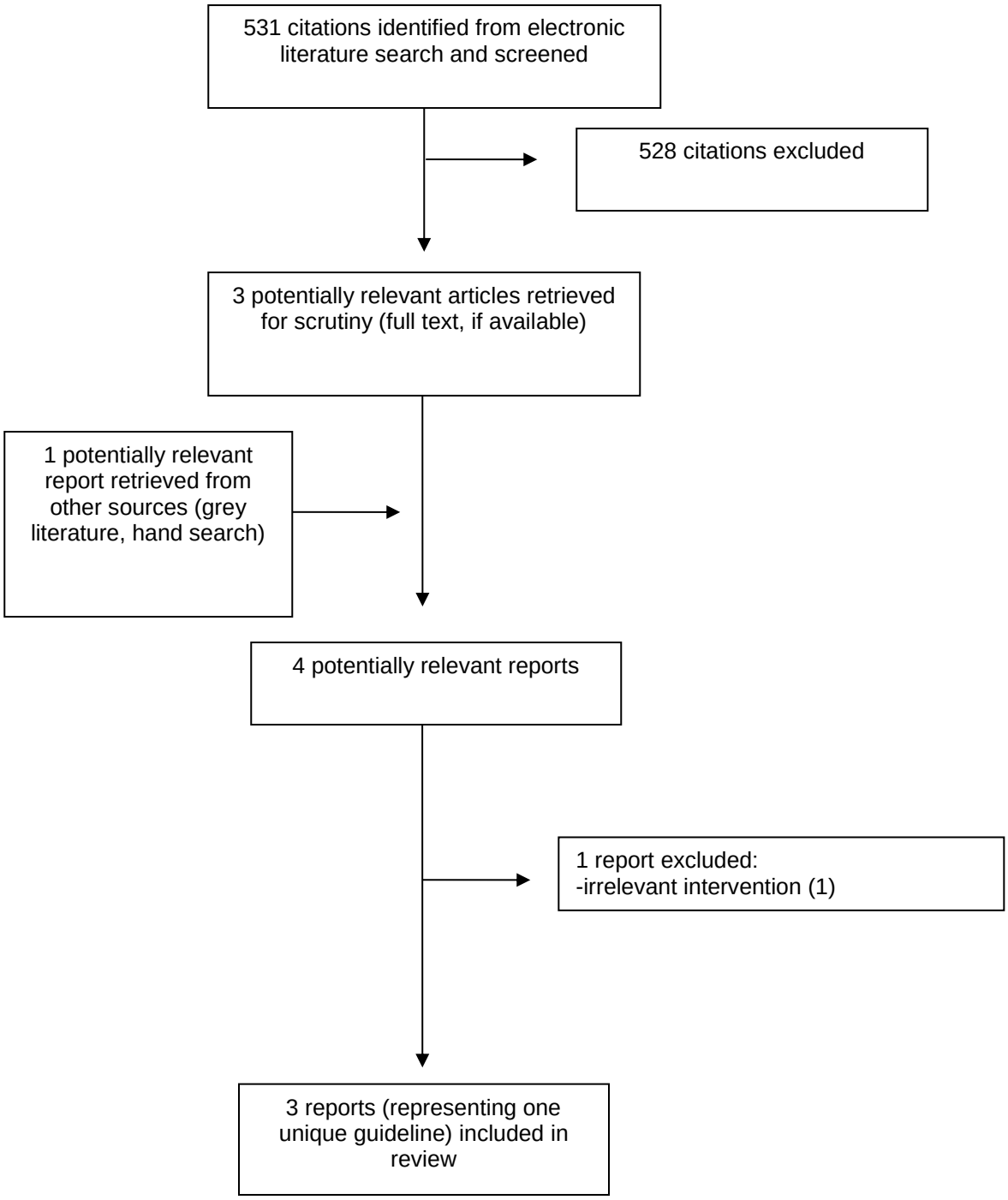
2. Agree Next Steps Consortium. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2019 Jul 2.
3. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
4. Braunwarth WD, Christ M, Dirks H, et al. S3 practice guideline methamphetamine-related disorders. Berlin (DE): Arztliches Zentrum fur Qualitat in der Medizin; 2016: https://www.aezq.de/mdb/edocs/pdf/literatur/s3-gl-methamphetamine-related-disorders-long.pdf. Accessed 2019 Jul 2.
5. Gouzoulis-Mayfrank E, Hartel-Petri R, Hamdorf W, Havemann-Reinecke U, Muhlig S, Wodarz N. Methamphetamine-related disorders. *Dtsch.* 2017;114(26):455-461.
6. 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;50(3):96-104.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: 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
Braunwarth, 2016 [4]						
Intended users: Physicians and staff in hospitals, private medical practices, and addiction treatment centres Target population: Adults with methamphetamine-related disorders	Treatment of methamphetamine-related disorders including: psychotherapeutic techniques and pharmacotherapy	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

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 3: Strengths and Limitations of Guidelines using AGREE II[2]

Item	Guideline
	Braunwarth, 2016 [4]
1. The overall objective(s) of the guideline is (are) specifically described.	X
2. The health question(s) covered by the guideline is (are) specifically described.	-
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	X
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
7. Systematic methods were used to search for evidence.	X
8. The criteria for selecting the evidence are clearly described.	X
9. The strengths and limitations of the body of evidence are clearly described.	X
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
12. There is an explicit link between the recommendations and the supporting evidence.	X
13. The guideline has been externally reviewed by experts prior to its publication.	-
14. A procedure for updating the guideline is provided.	-
15. The recommendations are specific and unambiguous.	X
16. The different options for management of the condition or health issue are clearly presented.	X
17. Key recommendations are easily identifiable.	X
18. The guideline describes facilitators and barriers to its application.	-
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.	-
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 4: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Braunwarth, 2016 [4]	
"Indications for the different settings of post-acute management (including weaning) ought to be made individually for each patient." (p56)	Level of evidence NR, expert consensus Positive recommendation
"Patients with methamphetamine-related disorder ought to be advised to set methamphetamine abstinence as the primary goal of their therapy." (p56)	Level of evidence NR, expert consensus Positive recommendation
"In patients who are currently unemployed, it is preferable to offer settings that foster re-integration back into the workforce." (p56)	Level of evidence NR, expert consensus Positive recommendation
"Soon after post-acute treatment (including weaning), coordinated addiction-related care ought to be delivered for at least a year to achieve sustainable abstinence stabilization and prevent relapse." (p56)	Level of evidence NR, expert consensus Positive recommendation
"The involvement of needs-specific self-help groups and family support should be an integral part of all services offered." (p57)	Level of evidence NR, expert consensus Strong positive recommendation
"Participation-oriented support and assistance services like outpatient supervision, accommodation services and outpatient sociotherapy ought to be considered whenever patients are observed to have problems with structure and daily routine and appear incapable of solving these problems on their own." (p57)	Level of evidence NR, expert consensus Positive recommendation
"Social work-related support and supervision should always be considered when other individuals in need of protection (i.e. children, relatives, partners) could be affected by a potential relapse." (p57)	Level of evidence NR, expert consensus Strong positive recommendation
"Patients with methamphetamine-related disorder should be educated about the options for vocational and medical rehabilitation and receive the appropriate referrals." (p59)	Level of evidence 5 Strong positive recommendation
"Regardless of whether they are diagnosed with dependence or not, every methamphetamine user should be offered needs- or motivation-centered psychotherapeutic counseling and treatment services." (p64)	Level of evidence 5 Strong positive recommendation
"According to the stepped-care approach, this ought to range from low-threshold education, psychoeducation and (motivational) counseling services extending through behavioral therapeutic treatments (e.g. contingency management) up to multimodal use reduction and withdrawal treatment programs in an outpatient or inpatient setting." (p64)	Level of evidence 3 Positive recommendation

Table 4: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
“If willing, methamphetamine users meeting the diagnostic criteria for a substance-related disorder ought to be offered and referred to psychotherapeutic services.” (p64)	Level of evidence 2 Positive recommendation
“Depending on their willingness to undergo such treatment and its availability, methamphetamine users meeting the diagnostic criteria for a substance-related disorder ought to be offered behavioral therapy or multimodal methamphetamine-specific regimens aimed at use reduction or weaning.” (p65)	Level of evidence 2 Positive recommendation
“In patients with moderate, non-daily methamphetamine use, treatment with bupropion may be attempted in order to support them in achieving abstinence.” (p74)	Level of evidence 2 Open recommendation
“Sertraline should not be given to patients with methamphetaminerelated disorder to achieve abstinence.” (p74)	Level of evidence 2 Strong negative recommendation
“Imipramine may be administered to increase retention rates.” (p75)	Level of evidence 2 Open recommendation
“Dopamine analog treatment attempts with narcotic-classified substances (e.g. amphetamine replacement with sustained-release D-amphetamine, sustained-release methylphenidate aimed at methamphetamine reduction/abstinence) that extend beyond acute withdrawal treatment should only be undertaken within the scope of registered clinical trials.” (p76)	Level of evidence 2 Strong negative recommendation
“Modafinil ought not to be used in the post-acute phase.” (p76)	Level of evidence 2 Negative recommendation
“Combined intravenous pharmacotherapy with flumazenil, gabapentin and hydroxyzine (PROMETA®) should not be given.” (p78)	Level of evidence 2 Strong negative recommendation
“As supportive treatment for alleviating withdrawal symptoms and to stabilize abstinence, methods of sports therapy (exercise therapy, physical conditioning) should be offered and provided.” (p80)	Level of evidence 2 Strong positive recommendation
“Neurofeedback may be offered supplementing other therapies.” (p80)	Level of evidence 2 Open recommendation
“Auricular acupuncture (according to the National Acupuncture Detoxification Association (NADA) protocol) may be offered.” (p80)	Level of evidence 5 Open recommendation

NR = not reported

Appendix 5: Additional References of Potential Interest

Previous CADTH Reports

Management of acute withdrawal and detoxification for adults who misuse methamphetamine: a review of the clinical evidence and guidelines. *(CADTH Rapid response report: summary with critical appraisal).* Ottawa (ON): CADTH; 2019: https://www.cadth.ca/management-acute-withdrawal-and-detoxification-adults-who-misuse-methamphetamine-review-clinical. Accessed 2019 Jul 2.

Evidence-based Guidelines

Alternative Interventions

Wodarz N, Krampe-Scheidler A, Christ M, et al. Evidence-based guidelines for the pharmacological management of acute methamphetamine-related disorders and toxicity. *Pharmacopsychiatry*. 2017 2017;50(3):87-95.