Pharmacological treatment for methamphetamine withdrawal: A systematic review and meta-analysis of randomised controlled trials

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Disclosures

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Background and rationale

- Cessation of MA elicits a characteristic withdrawal syndrome\(^1\)
- Ineffective treatment of withdrawal symptoms \(\rightarrow\) high rates of relapse to use\(^2\)
- Reduction in withdrawal / craving severity \(\rightarrow\) better treatment outcomes\(^3\)
- There is **no evidence-based pharmacotherapy** for the management of MA withdrawal\(^4\)
- Last Cochrane review conducted in 2009\(^4\)
  - Found no pharmacotherapy efficacious
  - Information out of date
Research Question:

What is the level of evidence for **efficacy** of **pharmacological interventions** for **methamphetamine withdrawal**?

In terms of:
- Discontinuation from treatment
- Overall mental health functioning
- Withdrawal symptoms
- Craving for methamphetamine
- Safety
Methods

  - Two reviewers independently screened and evaluated studies for inclusion
- Risk of bias was assessed with the Cochrane Risk of Bias II tool
- Evidence quality was evaluated using GRADE
- Data was extracted into purpose built and piloted Excel spreadsheets
- Analysed in RevMan 5.4
  - Relative risk and weighted mean differences were used to analyse data, with 95% confidence intervals reported
Overview of Studies

- **Nine studies** involving **242 participants** met criteria for this review
- Only **six studies** of **186 participants** were meta-analysed
  - Three were excluded as they did not report on our primary outcomes
- Medications investigated include
  - Mirtazapine (2 studies)
  - Modafinil (2 studies)
  - Ibudilast (1 study)
  - Amineptine (2 studies)
  - Varenicline (1 study)
  - Amantadine (1 study)
- Studies were conducted in USA, Thailand, Australia and Iran
- Mean **sample size was 27**, and approx. **88% of the sample was male**
Risk of Bias Assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization Process</th>
<th>Deviations from Intended Interventions</th>
<th>Missing Outcome Data</th>
<th>Measurement of Outcome</th>
<th>Selection of the Reported Result</th>
<th>Overall</th>
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- Low risk
- Some concerns
- High risk
Discontinuation Rates

-Measured by number of participants not retained to end of treatment
-No overall significant difference
-Small effect for amineptine over placebo (very low evidence)
Global State

- Measured by Brief Symptom Inventory Global Severity Index and Clinical Global Impression scales
- No overall significant difference
- Moderate effect for amineptine over placebo (low evidence)
Withdrawal Symptoms

- Measured by Amphetamine Withdrawal Questionnaire and Amphetamine Cessation Symptoms Assessment
- No overall significant difference
Craving for Methamphetamine

- Measured by a 100mm Visual Analogue Scale and Questionnaire for Evaluating Cocaine Craving and Related Responses
- No overall significant difference
Safety

- Measured by number and type of adverse events
- No significant difference (only one study reported number of AEs)
Discussion

• **No medication efficacious** for the treatment of MA withdrawal, **in any domain**
  • Amineptine the exception, however low to very low evidence for effect and medication removed from market in 1999; of little clinical utility

• Lack of amelioration of withdrawal symptoms and craving particularly important

• **Cannot conclusively rule out any** medication due to:
  • High risk of bias across studies
  • Low quality of evidence
  • Very low numbers of participants
  • Serious gender imbalance
Discussion cont.

• **Safety very poorly addressed** in the literature, making assessment of risks impossible
  • Four trials did not mention any safety outcomes
• Implications for policy and practice limited
  • Risk of bias
    • Predominantly due to selective reporting and randomisation issues
  • Number of studies and participants
  • Lack of harmonization across outcome measures, measures not validated for MA
• **In the last 12 years** since Shoptaw et al.’s review, **only 5 RCTs have been published** for MA withdrawal, and only 2 of those were able to be meta-analysed
  • This is despite withdrawal being the first step in someone seeking to cease or cut down on use, and is an important barrier to people meeting their treatment goals
Conclusion

- **No medication** is efficacious in the treatment of MA withdrawal

- *But* there is insufficient evidence to rule any out

- There is a clear **need** and **opportunity** for high impact research which is
  - Well designed
  - Adequate sample sizes
  - Accurate and detailed safety reporting
Thank You

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