

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

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Background and rationale

- Cessation of MA elicits a characteristic withdrawal syndrome¹
- Ineffective treatment of withdrawal symptoms → high rates of relapse to use²
- Reduction in withdrawal / craving severity → better treatment outcomes³
- There is **no evidence-based pharmacotherapy** for the management of MA withdrawal⁴
- Last Cochrane review conducted in 2009⁴
 - 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 - Information out of date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

- We searched MEDLINE (1966-2020), CINAHL (1982-2020), PsychINFO (1806-2020) and EMBASE (1947-2020)
 - 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

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Jittiwutikan 1997	—	?	+	+	?	—
Srisuaroanont 1999	?	+	+	+	?	!
Kongsakon 2005	?	?	+	—	—	—
Cruickshank 2008	+	+	+	+	+	+
Mahoney 2012	+	+	+	+	—	—
Lee 2013	?	+	+	+	+	!
Kalechstein 2014	+	+	?	+	—	—
Birath 2017	—	+	+	+	—	—
Modarresi 2018	+	—	—	+	+	—

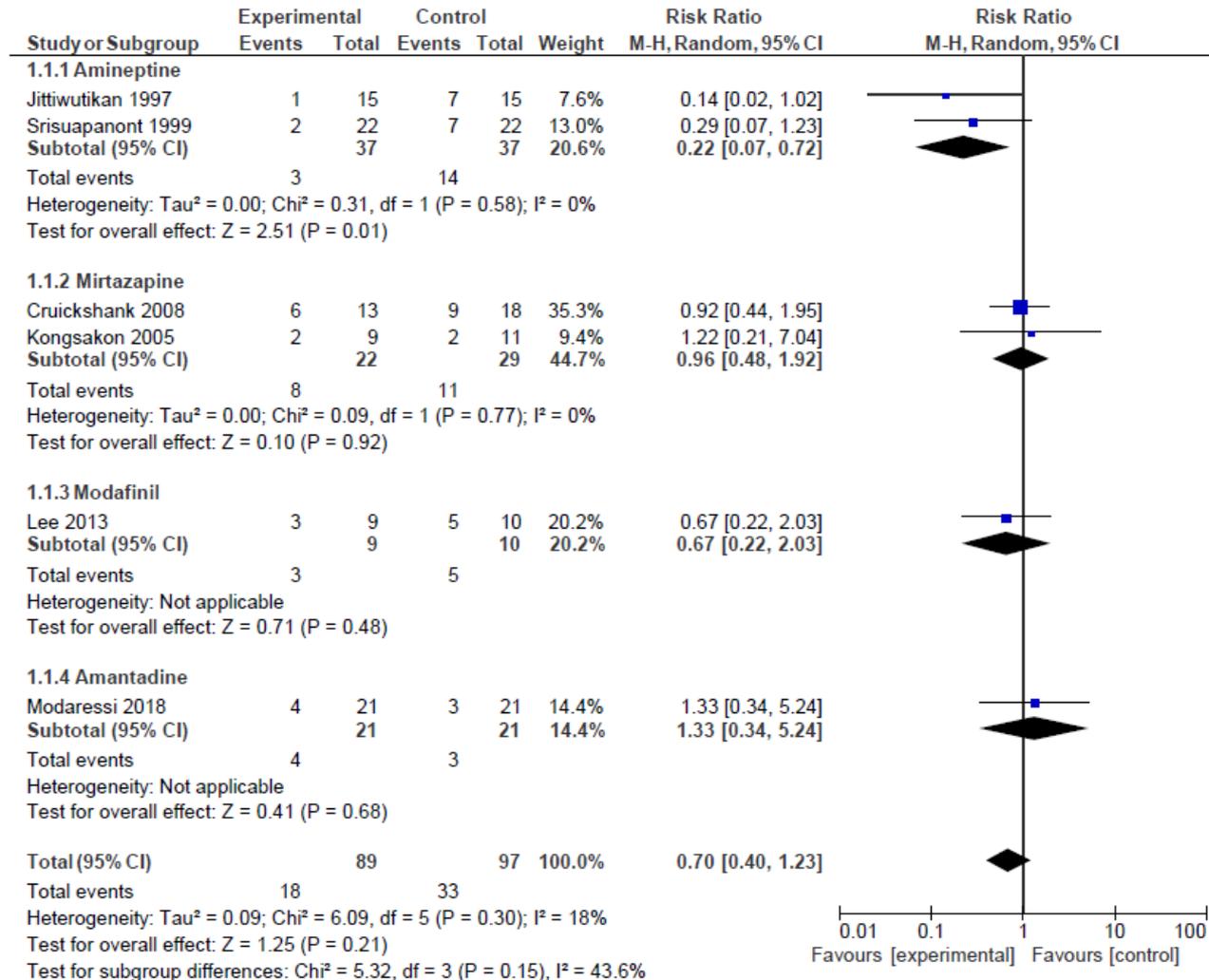
Low risk

Some concerns

High risk

Discontinuation Rates

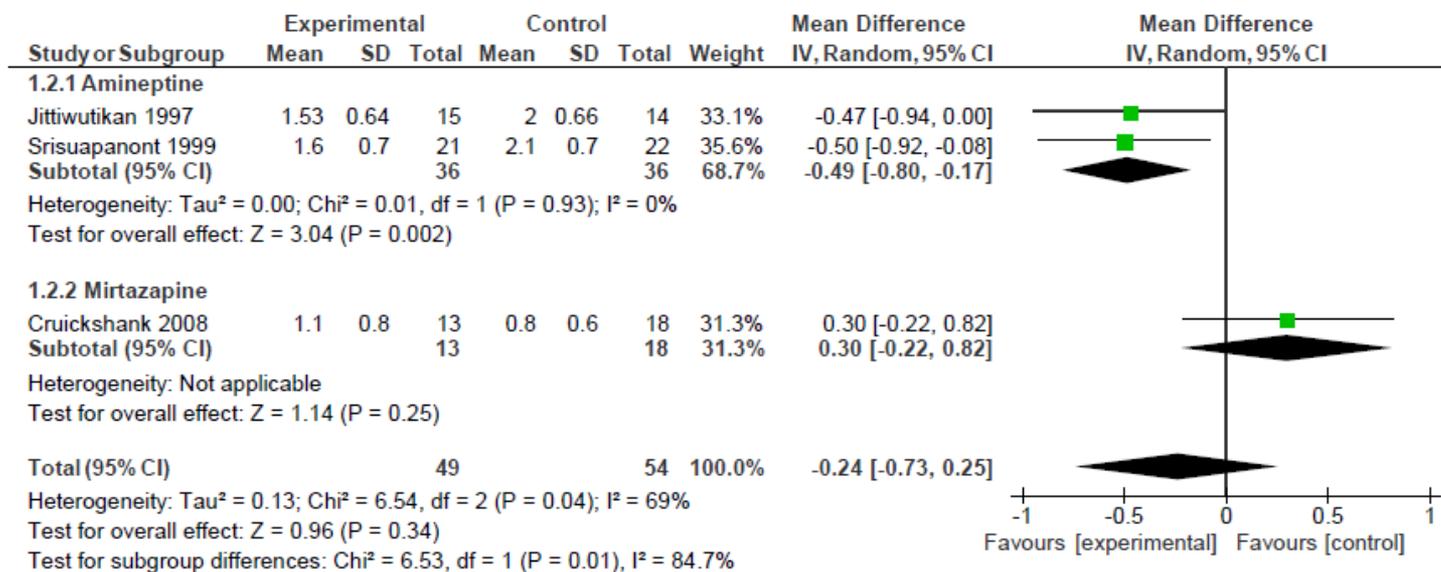
- Measured by number of participants not retained to end of treatment
- No overall significant difference
- Small effect for amineptine over placebo (very low evidence)



0.01 0.1 1 10 100
Favours [experimental] Favours [control]

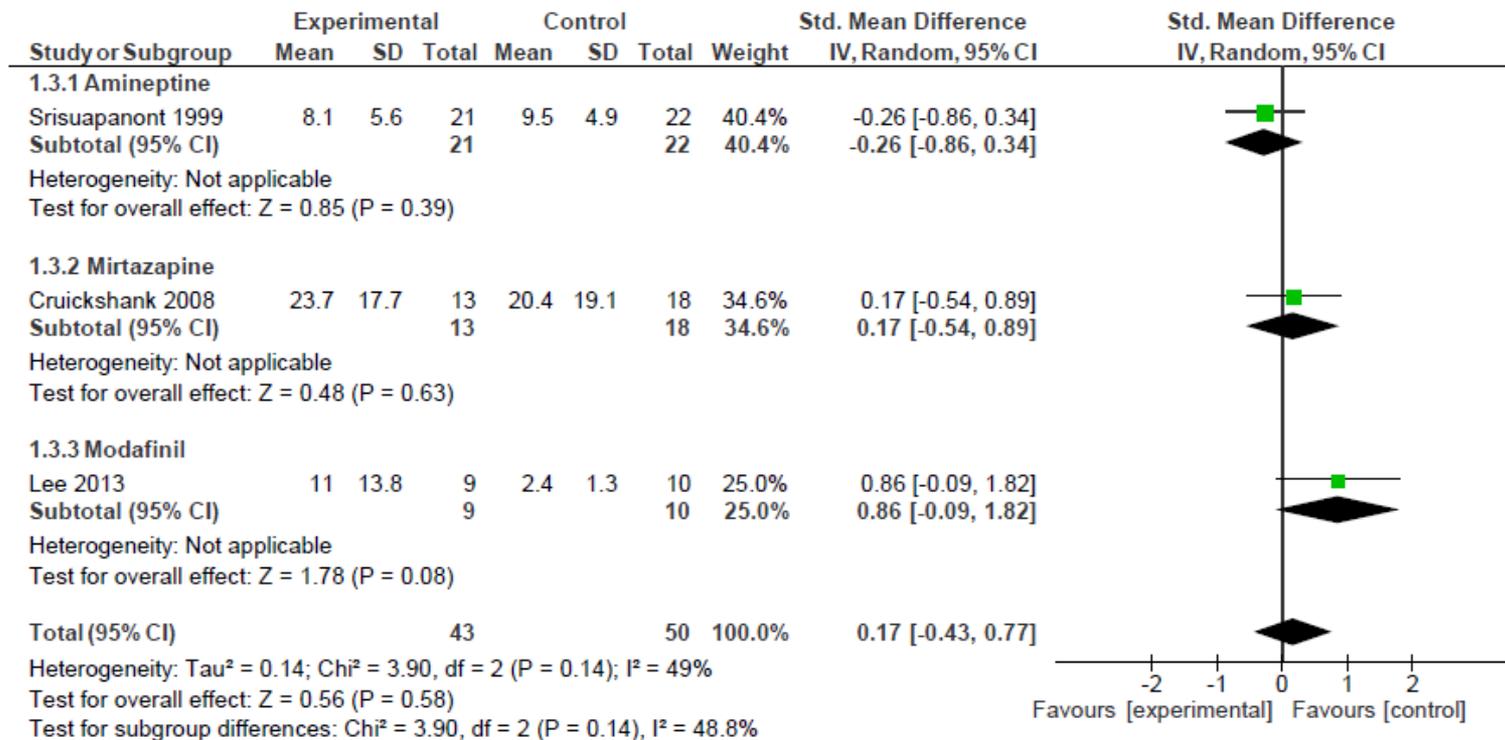
Global State

- 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)



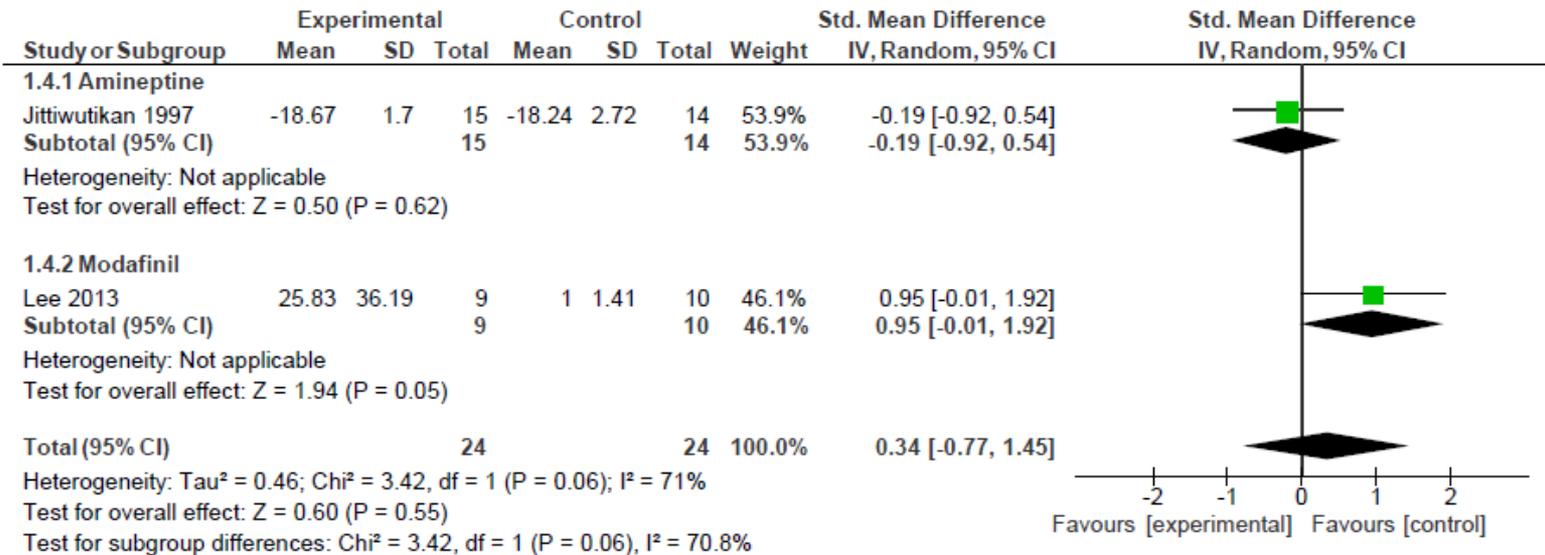
Withdrawal Symptoms

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



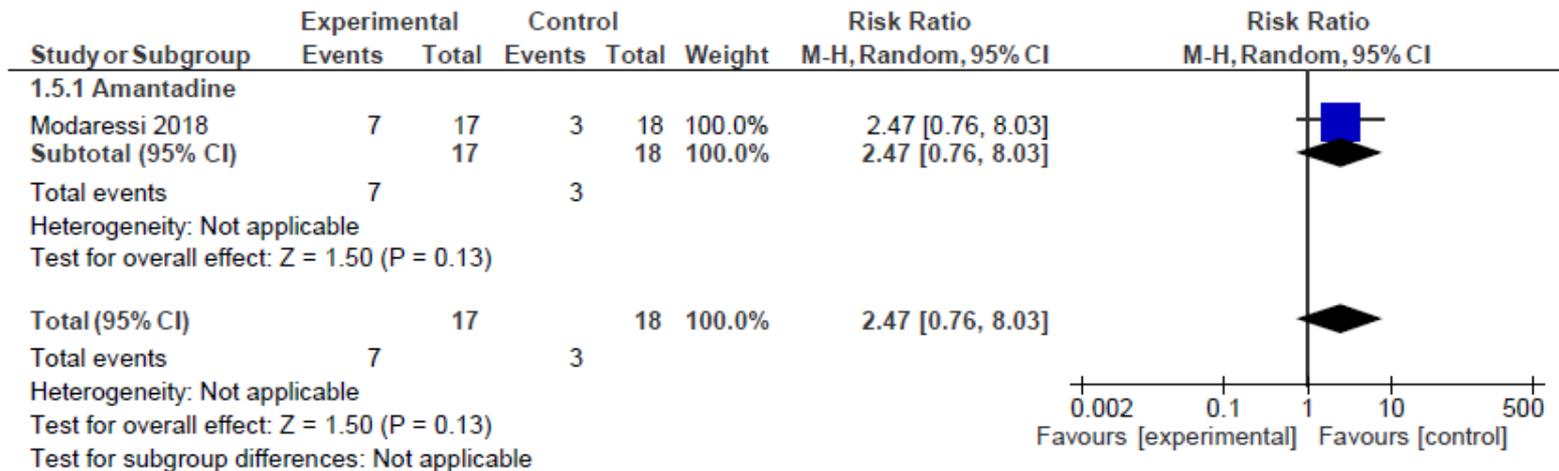
Craving for Methamphetamine

- 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

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Thank You

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