

National Centre for Clinical  
Research on Emerging Drugs



## **New directions in the treatment of methamphetamine use disorder**

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## **Methamphetamine use disorder – growing interest in treatments**



- Stimulants second to cannabis as most commonly used illicit drug worldwide, with 68 million past-year consumers
- Expansion of use in many regions of the world, with 29 million people world-wide age 15-65 consumed methamphetamine (MA) or amphetamine (AMPH) in past 12 months
- MA second only to alcohol as most common drug of concern in clients attending alcohol and other drug services in Australia
- Clear demand for evidence based treatments

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## **Changes in the International Classification of Diseases (ICD), 10<sup>th</sup> and 11<sup>th</sup> revision**

International standard for the reporting and classification of diseases

### ICD-10

- Endorsed May 1990
- Classifies stimulants as:
  - Cocaine
  - Other stimulants, including caffeine



### ICD-11

- Released June 2018, for implementation January 2022
- Addition of “addictive behaviours” i.e. gambling
- Classifies stimulants as:
  - Cocaine
  - Stimulants including amphetamines, methamphetamine or methcathinone
  - Synthetic cathinones (bath salts)
  - Caffeine
  - MDMA or related drugs, including MDA

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## **ICD-11 Disorders due to use of methamphetamine**

- Episode of harmful use
- Harmful pattern of use
  - Episodic
  - Continuous
- Dependence
  - Current
  - Early full remission
  - Sustained partial remission
  - Sustained full remission
- Intoxication
- Withdrawal
- Stimulant induced delirium, psychosis, mood or anxiety disorder
- Hazardous use

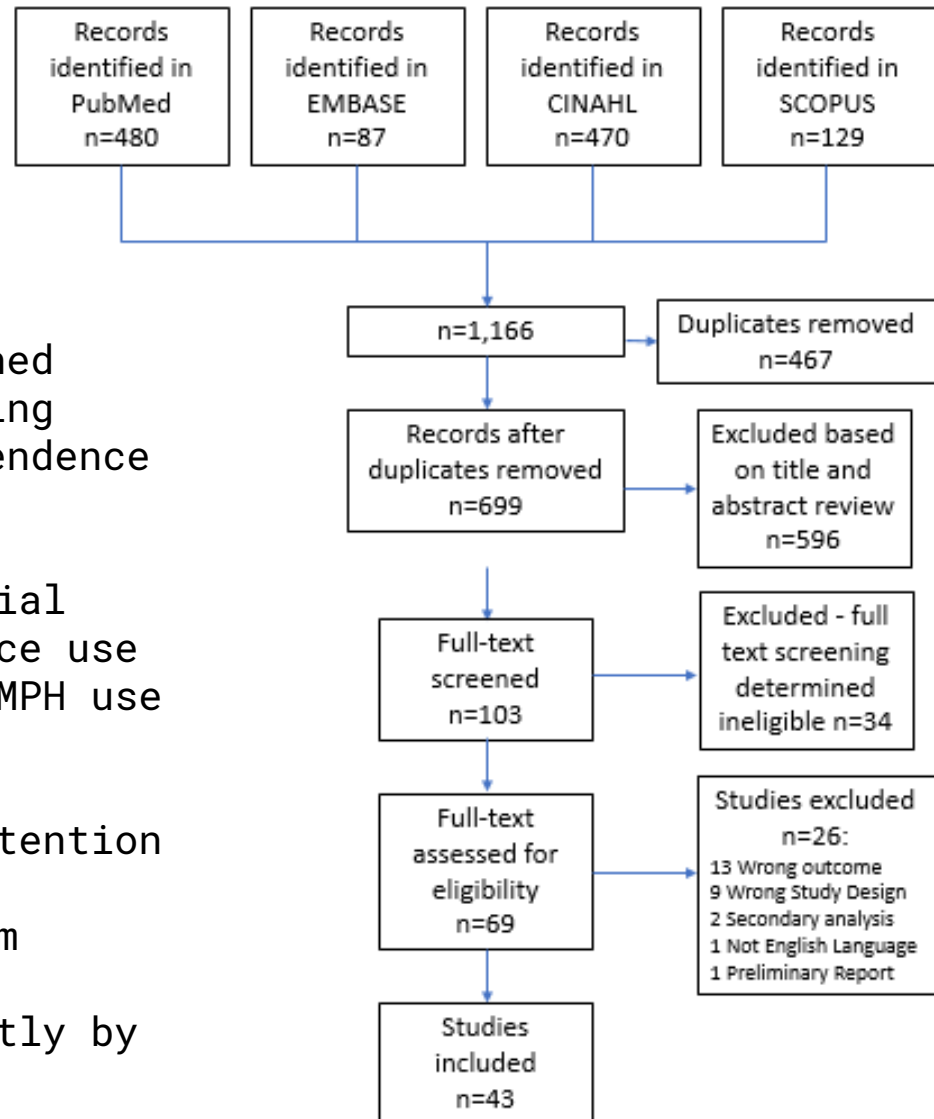
[www.who.int](http://www.who.int)

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## Systematic Review

Recently completed, unpublished systematic review investigating pharmacotherapies for MA dependence

- Eligibility criteria:
  - Randomised clinical trial
  - Diagnosed with substance use disorder due to MA / AMPH use
  - Reported on an outcome related to treatment efficacy, MA use or retention in care
- All databases searched from inception to June 2019
- Papers reviewed independently by two reviewers



## Pharmacotherapies

**23 distinct pharmacotherapies were reviewed in 43 RCTs**

- Antidepressants
  - Studies investigated amineptine (n=1), mirtazapine (n=3), bupropion (n=6), sertraline (n=1) and imipramine (n=1)
  - No evidence for reduced use
  - Sertraline was inferior to placebo and studies have been discontinued due to this. Bupropion showed efficacy as a smoking cessation aid in this population.
- Atypical anti-psychotics
  - Aripiprazole (n=2) and aripiprazole and methylphenidate (n=1)
  - Evidence limited, however aripiprazole inferior to placebo and methylphenidate in one study, leading to early termination
- Anticonvulsants
  - Topiramate (n=2)
  - No evidence that topiramate increases rates of abstinence

- Central nervous system agents
  - Dexamphetamine (n=2), methylphenidate (n=3), atomoxetine (n=1) and modafinil (n=4)
  - Stimulants may aid in reducing craving or retaining patients in treatment, however do not show evidence of reducing use.
  - Post-hoc analysis low strength evidence for reduced use with methylphenidate in two RCTs.
- Opioid agonists and antagonists
  - Buprenorphine (n=1), buprenorphine and methadone (n=1) and naltrexone (n=5)
  - Buprenorphine may show promise in reducing craving only during treatment. Naltrexone demonstrates conflicting results
- Glutamatergic agents
  - N-acetyl cysteine (NAC) (n=1), NAC and naltrexone (n=1) and riluzole (n=1)
  - May reduce cravings, however results are conflicted

## **Pharmacotherapies**



- Other pharmacotherapies
  - Baclofen and gabapentin (n=1), ondansetron (n=1), varenicline (n=1), pexacerfont (n=1) and flumazenil, gabapentin and hydroxyzine (the PROMETA protocol) (n=2)
  - Varenicline may improve cravings with no effect on use. PROMETA results conflicting. All other therapies similar to placebo

## Psychotherapies

- Cognitive Behavioural Therapy
  - Identify and challenge unhelpful thoughts and learn practical self-help strategies
  - Shows promise<sup>1,2</sup>, however not enough evidence to establish efficacy due to lack of research
  - May improve abstinence and reduce mental health symptom, even over the short term (2-4 sessions)<sup>3</sup>
- Contingency Management
  - Stimulus control and positive reinforcement to change behaviour (reward)
  - May reduce MA use, however studies are conflicting and unclear if reduction remains after follow-up<sup>4,5</sup>
  - Efficacious in SUD overall with small effect size (0.15)<sup>6</sup>
  - Efficacy in Australian context may be limited due to healthcare / welfare

<sup>1</sup>Baker *BJPsych* 2006

<sup>2</sup>Gonzales *JSAT* 2009

<sup>3</sup>Feeney *Addict Behav* 2006

<sup>4</sup>Shoptaw *Drug Alcohol Depend* 2005

<sup>5</sup>Rajasingham *AIDS Patient Care STDS* 2012

<sup>6</sup>Roll *Addiction* 2007

## Psychotherapies

- Acceptance and Commitment Therapy
  - Combines acceptance and mindfulness strategies with commitment and behaviour change
  - Improved retention rate compared to control (similar to CBT)<sup>1</sup>
  - Promising results<sup>2</sup>, however only a small number of studies with low power have been conducted
- Matrix Model Therapy
  - Social support groups, CBT including CM, family education and individual counselling<sup>3</sup>
  - Commonly used in conjunction with pharmacotherapies in treatment studies
  - May improve retention, abstinence and mental health outcomes, however differences disappear at follow up<sup>4,5</sup>

<sup>1</sup>Smout *Substance Abuse* 2010

<sup>2</sup>Luoma *Addict Res Theory* 2012

<sup>3</sup>Roll 2006

<sup>4</sup>Lee 2008

<sup>5</sup>Rajasingham 2012

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## New directions – digital interventions

Registered trials (22/9/2019)

- Apps
  - Scheck app – RCT online sample of Australian adults, early intervention/harm reduction, help seeking (Ezard)
  - “Getting off” – RCT, GBM USA, reduced MA use and condomless anal intercourse (CAI) (Reback)
- Web-based
  - “We can do this” – RCT Aboriginal and Torres Strait Islander adults, reduced MA use (Ward)
- Text messaging
  - CBT based text messaging – pilot randomised crossover %MA negative UDS during 2 week intervention (Galloway)



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## **New directions – computer assisted ABM**

Registered trials (22/9/2019)

- CEASAR (Computerized Exercise to Alter Stimulant Approach Responses) – RCT residential, relapse prevention (Schutz)
- Attention Bias Modification – pilot RCT inpatient withdrawal unit, relapse prevention (Manning)

Dean et al **“No effect of attentional bias modification training in methamphetamine users receiving residential treatment.”** (n=42)

Dean *Psychopharmacology* 2019 236(2):709-721

## **New directions – mindfulness**

Registered trials (22/9/2019)

- **Mindfulness-based relapse prevention combined with virtual reality cue exposure for methamphetamine use disorder (Chen)**
  - 3 group parallel RCT 8weeks of MBRP combined with VRCE, MBRP alone, or treatment as usual, N=180

Positive affect training + CM reduced MA use among HIV positive sexual minority men who use MA cf attention control + CM (n=110, MA use secondary outcome) (Carillo)

Post one month CM, mindfulness based relapse prevention reduced MA use among people with co-existing anxiety and depression cf health ed (pilot RCT n=63 OR= 0.78, p=0.03 & OR=0.68, p=0.04) (Glasner-Edwards)

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## **New directions – rTMS**

Su (2017) RCT, reduced craving in men (n=30)

Liu (2019) RCT, reduced craving in women (n=95)

Liang (2018) RCT, reduced withdrawal symptoms in men (n=50)

Registered trials (as of 22/9/2019 ANZCTR/clinicaltrials.gov)

Conejo (2019) prelim results:

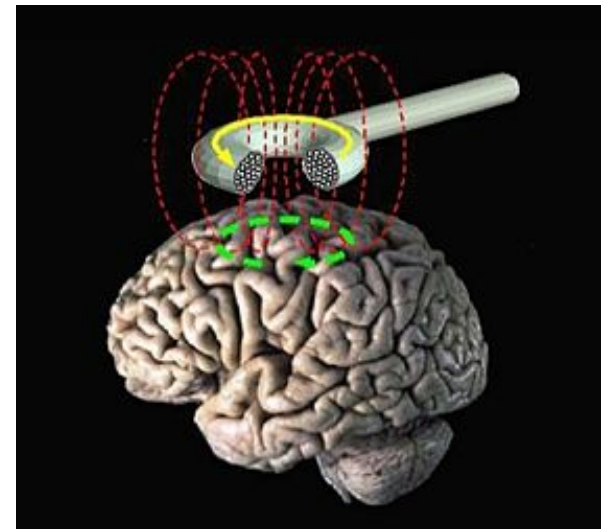
- RCT n=20
- left dorsolateral prefrontal cortex (DLPFC) HF-rTMS
- 50 pulses, 10 Hz, 100% RMT, 20 trains/day, inter-train interval of 15 second
- 10 daily sessions over 2 weeks + maintenance 1 month
- Reduced craving

*Su Drug Alcohol Depend 2017*

*Liu Prog Neuropsychopharmacol Biol Psychiatry 2019*

*Liang JAMA Psychiatry 2018*

*Conejo Brain Stimulation 2019*



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## **New directions – pharmacotherapies**

N-acetyl cysteine (McKetin)

- RCT
- 2400mg/d PO vs PBO
- Change in days MA use/28 week 12
- Adults outpatient setting n=180

Lisdexamfetamine

- RCT
- 250mg/d vs PBO
- 2400mg/d PO vs PBO
- Change in days MA use/28 week 12
- Adults outpatient setting n=180

## **New directions – pharmacotherapies**

Mirtazepine (Coffin CPDD 2019)

- 60mg/d 12 weeks
- Decreased MA use among men and transwomen who have sex with men

Registered trials (22/9/2019)

- Oxytocin enhanced group MI for MSM (Stauffer)
- Ibudolast 50mg/d (NCT01860807 Henzerling – prelim results neg)
- Methamphetamine Antibody (NCT03336866 Webster)
- Pomaglutamed [glutamatergic agonist] Phase I (NCT03106571 Heinzerling)

## Summary / conclusions

- New directions include
  - Pharmacotherapies
  - Technology assisted treatment
  - Magnetic therapies
- Psychosocial interventions are still the mainstay of MA dependence and withdrawal treatment
- Pharmacological research investigator driven and small scale
- Research gaps in
  - Health systems, service delivery, treatment setting
  - Cost-effectiveness
  - Intervention across spectrum of disorder

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**Thank You**

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