An update on pharmacotherapy trials for substance use disorder – methamphetamine type and withdrawal in Australia

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Aim: This symposium aims to provide an update on the current research on pharmacotherapies for stimulant use disorder - methamphetamine type (SUD-MA), and the recently completed, currently recruiting, and future pharmacotherapy studies in Australia.

PRESENTATION 1: Testing new medications for stimulant use disorder methamphetamine type in young people

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Introduction and Aims: Methamphetamine use commonly starts in adolescence or early adulthood. New treatment approaches for young people are required. We are conducting two studies assessing candidate pharmacotherapies for safety and tolerability in young people (15-25 year olds) with stimulant use disorder-methamphetamine type (SUD-MA) who wish to reduce their use.

Design and Methods: Study 1 (MethAmphetamine use in young people: Sub-anaesthetic ketamine open-label trial; MASKOT) is an open-label investigation of two sub-cutaneous doses of ketamine (initial dose 0.6 mg/kg). Participants (N=20) will receive 2 ketamine doses separated by 1 week, with follow-up at weeks 2, 3, 4, and 6. Primary endpoints are safety (assessed by change in past month use of ketamine from baseline to week 6 and liver function tests at week 2) and tolerability (number of participants withdrawing from the study due to adverse medication effects). Study 2 (Cannabidiol – A novel pharmacotherapy for

Lowering Methamphetamine use; CALM) is an open-label trial of the non-intoxicating cannabinoid cannabidiol (CBD; 800-1000 mg/day). Participants (N=12) will complete 8 weeks of oral CBD, with follow-up at weeks 4, 8, and 12. Primary endpoints are safety (liver function tests at weeks 4 and 8) and tolerability (number of participants withdrawing from the study due to adverse medication effects).

Results: MASKOT commenced recruitment in June 2021; two individuals have volunteered, but neither met inclusion criteria. CALM is currently being implemented.

Discussion and Conclusions: MASKOT and CALM will provide feasibility and tolerability data on two candidate pharmacotherapies in young people with SUD-MA.

Presentation 2: Predicting reductions in methamphetamine use in the n-ice trial: a randomised controlled trial of n-acetyl cysteine for methamphetamine dependence

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Introduction and Aims: We evaluated the safety and efficacy of N-acetylcysteine (NAC) for methamphetamine dependence and found no benefit over placebo. However, large post-treatment reductions in methamphetamine use were observed in both groups, suggesting a therapeutic benefit of participating in the trial. We explored what factors predicted this post-treatment reduction in methamphetamine use.

Design and Methods: A double-blind randomised placebo-controlled trial (ACTRN12618000366257). Participants dependent on methamphetamine were allocated to

receive either 12 weeks of oral NAC (2400 mg/day) or matched placebo. Reductions in self-reported methamphetamine use at follow-up were assessed using the Timeline Followback. We explored whether the following factors were associated with reductions in methamphetamine use: readiness to change; concomitant treatments and medications; belief about group allocation; and under-reporting of methamphetamine use (any false reporting of no use against weekly oral fluid tests).

Results: Participants (N = 153; 59% male, mean [SD] age 38 [8] years) who received placebo (n=77) or NAC (n=76) significantly reduced their methamphetamine use (mean [SE] reduction of 7.3 [1.2]) days for placebo, 6.8 [1.2] for NAC) with no significant group difference (0.5 days, 97.5% confidence interval [CI] -3.4–4.3). Factors associated with greater reductions in methamphetamine use at follow-up included greater readiness to change (Action stage: mean difference -2.3 days, 95% CI -6.3–1.7, *P*=0.032), belief of being on NAC (-3.5 days, 95% CI -7.2–0.1) and under-reporting methamphetamine use (-5.4 days, 95% CI -10.0–-0.8), which was more pronounced for participants who believed they were on NAC (-7.6 days vs. -2.6 days, *P*=0.024).

Discussion and Conclusions: Significant reductions in methamphetamine use observed during the trial appear to be related to readiness to change and under-reporting of methamphetamine use, particularly amongst people who believed they were receiving NAC.

Implications for Practice or Policy: Reductions in self-reported methamphetamine use seen in clinical trials may be partly related to motivation to change and social desirability bias, rather than engagement with other treatments or therapeutic processes.

PRESENTATION 3: Covid and the LiMA study, a randomised, double-blind, placebo controlled trial of Lisdexamfetamine for the treatment of MethAmphetamine dependence

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Introduction / Issues: The LiMA study is a randomised, double-blind, placebo-controlled trial of lisdexamfetamine for the treatment of methamphetamine dependence. The first participant was randomised in May 2018. The COVID-19 pandemic required adaptation to trial procedures from March 2020.

Method / Approach: A COVID-19 plan was established for all 5 sites and the study protocol was amended to allow for up to 14 unsupervised takeaway doses, a decrease in face-to-face visits from twice weekly to weekly, and increase in use of telephone assessments.

Key Findings: No participant was recruited between 12 March 2020 and 15 November 2020. Participants enrolled in the study prior to 12 March 2020 were able to remain in the study, although 5 of the 22 participants (23%) in the active study medication phase withdrew during this period. Recruitment recommenced at 4 out of 5 sites from 16 November 2020. Prior to 12 March 2020; 117 participants were randomised to the trial and received at least one dose of study medication (5 participants per month), and 28 participants between 16 November 2020 and 21 June 2021 (4 per month).

Discussion and Conclusions: The COVID-19 pandemic period in Australia resulted in relaxation of the strictly supervised procedures by necessity. Adapted methods facilitated retention and enabled ongoing recruitment post-the initial shut down period. Findings have relevance for intensity of supervision in study procedures going forward. Results are anticipated early 2022.

Implications for Practice or Policy (optional)**:** Findings from this “natural experiment” into altered study procedures in response to the COVID-19 pandemic may have implications for supervisory requirements of medication for the treatment and research of methamphetamine dependence.

PRESENTATION 4: The future of pharmacotherapy clinical trials in Australia: the OLAM Trial; the mOXY trial; the PSiMA Trial; the TINA Trial

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Introduction and Aims: This presentation overviews current pharmacotherapy trials for adults seeking to reduce their methamphetamine use.

Design and Methods:
The OLAM trial: An open-label, single-arm trial (n=15) of a tapering dose of lisdexamfetamine for acute methamphetamine withdrawal: 250mg Day 1 reducing by 50mg daily, until 50mg on Day 5, alongside treatment as usual in an inpatient withdrawal unit. Primary outcomes are safety and feasibility.

The mOXY trial: An open-label, single-arm trial (n=15) of 24IU intranasal oxytocin twice daily for 7 days for methamphetamine withdrawal, in an inpatient withdrawal unit. Primary outcomes are length of stay, withdrawal symptoms, relapse rates, and treatment engagement.

The PsiMA trial: An open-label, single-arm trial (n=15) of 25mg psilocybin (single dose) facilitated psychotherapy for MUD consisting of: 3 preparatory psychotherapy sessions, a psilocybin dosing day and up to 3 post-psilocybin integration psychotherapy sessions. Primary outcomes are safety, tolerability and feasibility.

The TINA trial: A Phase III double-blind placebo-controlled randomised trial (N = 340) of mirtazapine (30mg/day for 12 weeks) for MUD in routine clinical practice. The primary outcome is days of methamphetamine use. Other outcomes include depression, safety, and tolerability.

Results: OLAM has commenced recruitment, enrolment is brisk. TINA has been funded by an MRFF grant. PSiMA is supported by an NCCRED Clinical Research Scholarship. mOXY is supported by an NCCRED seed grant. Studies will commence recruitment mid-late 2021.

Discussion and Conclusions: Studies evaluating pharmacotherapies for MUD address an ongoing public health priority in Australia.

Implications for Practice or Policy (optional)**:** There are no approved pharmacotherapies for MUD. Studies to evaluate new, novel, or repurposed pharmacotherapy candidates could provide future options to enhance clinical practice.

Implications for Translational Research (optional)**:** Collaborative clinical research can enhance the likelihood for larger studies, and translation of research results into clinical practice. This presentation outlines a collaborative approach to working together to generate translational outcomes.

Discussion Section: This symposium provides an update on pharmacotherapy studies for stimulant use disorder – methamphetamine type; including those that are recently completed, currently recruiting, or commencing recruitment. The Discussion following the presentations will focus on collaboration. This includes a discussion regarding study outcomes and measures, to better harmonise clinical research to ensure clinical and consumer relevance, and clinical translation.

Discussant: Not applicable

Discussant's email: Not applicable

Disclosure of Interest Statement:

Presentation 1: The MASKOT and CALM studies are funded by NCCRED Clinical Research Seed Funding Grants (NCR2SF04 and NCR4SF17, respectively). EM was the recipient of an NCCRED Clinical Research Fellowship.

Presentation 2: This research was funded by the Australian NHMRC (Project Grant No. 1128147). OMD has received grant support from Lilly and ASBDD/Servier. She has also received in kind support from BioMedica Nutraceuticals, NutritionCare and Bioceuticals. MB has received Grant/Research Support from the A2 milk company, Meat and Livestock Board, Woolworths, and Avant, has been a speaker for Abbott, Astra Zeneca, Janssen, Lundbeck, Merck, Otsuka, Milken Institute, Sandoz, Allori (for Eisai), Medplan Canada, Servier and Medisquire India, and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Janssen, Lundbeck Merck, Pfizer and Servier, and has licences with Allen and Unwin and Cambridge University Press. MB has received patents for agents that modulate physiological processes and diseases of the central nervous system and related processes, including xanthone-rich plant extracts. DL has provided consultancy advice to Lundbeck and Indivior and has received travel support and speaker honoraria from Astra Zeneca, Camurus, Indivior, Janssen, Lundbeck, Servier and Shire. PD has received investigator-initiated funding from Gilead Sciences, an untied educational grant from Indivior and was an unpaid member of an Advisory Board for Mundipharma for work unrelated to this study. PH has received investigator-driven research funding from Gilead Sciences and Abbvie for work on hepatitis C unrelated to this study. GC has received speaker fees from Otsuka (Australia), Servier, Lundbeck and Janssen, all unrelated to the current study. SA has received speaker honoraria from Gilead, Janssen and Camurus for work unrelated to this study. Other researchers have no interests to declare.

Presentation 3: This research was funded by the Australian NHMRC (Project Grant No. 1109466). NE has grants from the Australian government Department of Health. AD research and travel support from Braeburn/Camurus, research support from Indivior, and has served on an advisory board for Mundipharma. RB has received investigator-initiated untied educational grants from Reckitt Benckiser/Indivior. AC has received research funding from Bristol-Myers Squibb, Gilead Sciences, and ViiV Healthcare; lecture and travel sponsorships from Gilead Sciences and ViiV Healthcare; and has served on advisory boards for Gilead Sciences, MSD and ViiV Healthcare. MF has grants from the Australian Federal Government Department of Health National Centre Core Funding, untied grant from Indivior, and grants from Seqirus United. DL has provided consultancy advice to Lundbeck and Indivior and has received travel support and speaker honoraria from Astra Zeneca, Camurus, Indivior, Janssen, Lundbeck, Servier and Shire. NL has received research funding from Camurus, and has served on Advisory Boards for Mundipharma, Camurus and Indivior. AG, CR, MM, MMcD, JW, KH, PH, RA, RG, RM, & WL have no interests to declare.

Presentation 4: The OLAM study was funded by NCCRED. NCCRED receives its funding from the Department of Health, Australia. The mOXY study was funded by an NCCRED Clinical Research Seed Funding Grant (NCR3SF18). EK was the recipient of an NCCRED Clinical Research Scholarship. The TINA trial is funded by an Australian MRFF Grant.