Lisdexamfetamine for the management of acute methamphetamine withdrawal: Protocol for an open-label safety and feasibility study

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Australasia has the highest rate of amphetamine dependence worldwide.

In people who use methamphetamine (MA), daily and weekly use has increased from 9.3% in 2010 to 17% in 2019.

MA is the second most common drug of concern in Australian treatment settings, accounting for 26% of treatment episodes.

Abrupt cessation of MA → characteristic withdrawal symptoms.
Rationale

- Ineffective treatment of withdrawal symptoms $\rightarrow$ high rates of relapse to use
- Reduction in withdrawal / craving severity $\rightarrow$ better treatment outcomes
- There is no evidence-based pharmacotherapy for the management of MA withdrawal
- Agonist-like therapies have shown promise
  - i.e. dexamphetamine
- Lacked efficacy
Why lisdexamfetamine?

- Traded under Vyvanse® for ADHD / binge eating disorder
- Lisdexamfetamine (LDX) is an inactive prodrug of dexamphetamine, hydrolysed into dexamphetamine in whole blood
- LDX has slower onset and lower peak dopamine concentrations
- Lower abuse liability, less positive reinforcing effects compared to dexamphetamine
- Cannot be diverted

Hydrolysis of lisdexamfetamine dimesylate to (d-)amphetamine and (l-)lysine
Study Design and Aims

Open label, single arm clinical trial of a tapering dose regimen of LDX for management of acute MA withdrawal

Primary Aim:
To determine the safety and feasibility of delivering a five-day tapering dose regimen of LDX for the inpatient treatment of acute MA withdrawal

Secondary Aims:
- Acceptability
- Retention in care
- Changes in withdrawal / craving
- Sleep quality

Study design and procedures developed with consumer consultation
Participants

n=15 adults presenting for admission for management of acute methamphetamine withdrawal at SVHS

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tr>
<td>Adults over the age of 18 years</td>
<td>Women lactating, pregnant or of childbearing potential who are not willing to avoid becoming pregnant during the study</td>
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<tr>
<td>Presenting to inpatient drug treatment services seeking treatment for acute MA withdrawal</td>
<td>Expected concurrent withdrawal from alcohol, opioids, benzodiazepines, gamma-hydroxybutyrate or other gabapentinoids</td>
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<td>Methamphetamine use disorder as determined by an addiction medicine specialist according to DSM-5 criteria</td>
<td>Known contradictions to lisdexamfetamine</td>
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<td>Last MA use within 72 hours of planned first study drug dose</td>
<td>Medically significant condition which in the opinion of a study medical officer renders a patient unsuitable for the study</td>
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<td>Have a positive urine drug screen for methamphetamines</td>
<td>Involuntary patients</td>
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<td>Willing and able to provide written informed consent</td>
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Recruitment: Opportunistic - through Centralised Intake, treatment services or on admission
Intervention

Lisdexamfetamine dimesylate

- Tapering dose starting at 250mg
  - Equivalent to approximately 74mg of dexamphetamine
- Once daily dosing

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<thead>
<tr>
<th>Study day (inpatient)</th>
<th>Lisdexamfetamine dose</th>
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<tr>
<td>Day 1</td>
<td>250mg OD</td>
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<tr>
<td>Day 2</td>
<td>200mg OD</td>
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<tr>
<td>Day 3</td>
<td>150mg OD</td>
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<tr>
<td>Day 4</td>
<td>100mg OD</td>
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<tr>
<td>Day 5</td>
<td>50mg OD</td>
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Procedure

Day 0: Screening and baseline assessment

Day 1 to Day 5: Inpatient period, participants receive medication and undergo daily assessment of adverse events, treatment satisfaction, withdrawal and craving severity and sleep

Day 6 to Day 7: Inpatient period, participants receive no medication and undergo assessment of adverse events, treatment satisfaction, withdrawal and craving severity and sleep

Rescue medication: diaz/olanzapine available days 1-7

Days 14, 21 and 28: Outpatient telephone follow up to assess adverse events, access to wrap around health services, substance use
Novel Sleep Measures

- Sleep is poorly investigated in substance use related research
  - Point surveys
- Gold standard sleep measurement requires objective and subjective measurement over time
- No study to date has investigated sleep in this was in people who use or are withdrawing from stimulants
- In this study:
  - Continuous actigraphy
  - Daily sleep diary
- Proof of concept only
Conclusions

- First study to investigate LDX for the management of acute MA withdrawal
- If safe and feasible will inform development of a fully powered RCT
  - Consumer input
  - Novel sleep measures
- If effective, LDX has the potential to be the first pharmacotherapy for MA withdrawal
Thank You

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