Repurposing Low Dose Lisdexamfetamine as Agonist Therapy for Stimulant Use Disorder: A Case Series

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Abstract

Introduction and Aims: Lisdexamfetamine is a long acting dopamine and noradrenaline agonist approved for the indication of Attention-Deficit Hyperactivity Disorder in Australia. There is evidence it may minimize symptoms of Binge Eating Disorder and Narcolepsy. As a prodrug, it has less abuse liability due to the rate limiting hydrolysing reaction in red cells to produce Dexamphetamine. Lisdexamfetamine is currently being examined as a potential agonist therapy for Methamphetamine Dependence/Stimulant Use Disorder.

Design and Methods: Patients were retrospectively selected from a cohort of inpatients and outpatients from a single hospital site. Selection criteria were neuroadaptation with Methamphetamine, and the use of pharmacotherapy with Lisdexamfetamine.

Results: 10 patients with Stimulant Use Disorder were treated with low dose Lisdexamfetamine, with varying degrees of clinical success. Any positive treatment effect was lost immediately after cessation of therapy. Illicit drug monitoring and treatment compliance were problematic. One male patient had an exacerbation of a co-existing psychotic disorder. All of the patients selected for inclusion in this case series had Attention-Deficit Hyperactivity Disorder according to DSM-5 criteria.

Discussion and Conclusions: In Stimulant Use Disorder, Lisdexamfetamine may mitigate harm by virtue of blocking cravings and urges for further Methamphetamine consumption. Preferential responder profiles may include female gender, a history of regular (as opposed to erratic or episodic) Methamphetamine use, and patients with antedating eating disorders and/or attentional disorders. Further research is required to determine any potential role of Lisdexamfetamine as agonist therapy for Stimulant Use Disorder, although there is a possibility that appropriately selected patients may benefit.

Keywords: Methamphetamine; Lisdexamfetamine; Stimulant; Dopamine agonists; Craving

Introduction

Methamphetamine Dependence (DSM-IV-TR) or Stimulant Use Disorder (DSM-5) has been declared a high management priority according to the Draft National Drug Strategy 2016-2025 [1-3]. The societal and forensic costs of are often topical, highly politicised issues in the modern world. There is a dearth of evidence-based pharmacological treatments available [4].

Lisdexamfetamine is a long acting dopamine and noradrenaline agonist approved for the indication of Attention-Deficit Hyperactivity Disorder in Australia. There is evidence it may mitigate symptoms of Binge Eating Disorder and Narcolepsy [5-10]. It is a prodrug, converted by a rate limiting hydrolysing reaction in red cells to produce Dexamphetamine and hence has a long duration of action and delayed onset of action reducing the risk of toxidrome [11,12]. According to a systematic review, Lisdexamfetamine has less abuse liability and is thought to have reduced abuse liability in adult stimulant users even if injected at low doses [13-16].

Lisdexamfetamine is currently attracting interest as a potential agonist therapy for Stimulant Use Disorder, based on the premise that long acting agonist therapies have been successful in treating Opioid and Tobacco Use Disorders. Dexamphetamine, the active metabolite of Lisdexamfetamine, has been intermittently studied with some positive results as an agonist therapy for Stimulant Use.
Methods

The study design is an open-label uncontrolled naturalistic case series. Patients were retrospectively selected from inpatients and outpatients of a Psychiatrist at a Queensland private hospital between December 2015 and June 2017. Selection criteria were neuroadaptation with Methamphetamine, and the subsequent use of pharmacotherapy with Lisdexamfetamine. There were no exclusion criteria.

The patients described in this article have been de-identified, and all provided written informed consent for the authors to include their clinical information in this article. Griffith University Human Research Ethics Committee has approved the use of de-identified patient information for research purposes. All patients had previously given informed consent to Lisdexamfetamine treatment after full discussion of risks, benefits and alternatives. Often carers or family were involved in the decision to induct on agonist therapy.

Outcomes assessed were:
1. Subsequent cravings for Methamphetamine, as evidenced by qualitative reports and/or modified Brief Substance Craving Scale (BSCS).
2. Subsequent abstinence or use of Methamphetamine, based on any available data including self-reports, financial statements or urinary screening or confirmatory testing, at arbitrary time points 1 month, 6 months, 12 months and 24 months based on intention-to-treat.
4. Subjective and objective qualitative descriptions of commencing and ceasing treatment.
5. Adherence to urine drug screening.

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>Mean Age (range)</th>
<th>Median Age (Interquartile range)</th>
<th>Gender</th>
<th>Mean LDX dose</th>
<th>Mean Duration of Treatment</th>
<th>Pattern of METH use</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>32.1 years (19-41)</td>
<td>34.5 years (IQR 31 – 36)</td>
<td>6 (60%) Female, 4 (40%) Male</td>
<td>51mg daily</td>
<td>8.25 months</td>
<td>Intravenous 60% (6/10), Regular frequent use 50% (5/10)</td>
</tr>
</tbody>
</table>

Legend: METH = Methamphetamine, LDX = Lisdexamfetamine

Table 1: Collective Patient Demographics.

Table 2: Individual Patient Demographics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Dose (mg)</th>
<th>Comorbid Addictions</th>
<th>Comorbid Mental Disorders</th>
<th>Route of METH use</th>
<th>Washout prior to LDX induction (days)</th>
<th>Location of induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>34</td>
<td>M</td>
<td>50mg increased to 70mg</td>
<td>Nicotine, Cannabis</td>
<td>ADHD, ABI, METH use associated with severe hyper-sexuality</td>
<td>IV regular heavy use every 2-3 days</td>
<td>0</td>
<td>O/P</td>
</tr>
<tr>
<td>B</td>
<td>19</td>
<td>F</td>
<td>50mg decreased to 30mg</td>
<td>Benzodiazepines, Cannabis, Nicotine</td>
<td>ADHD, BPD</td>
<td>Smoked, regular heavy use</td>
<td>3</td>
<td>I/P</td>
</tr>
<tr>
<td>C</td>
<td>41</td>
<td>M</td>
<td>30mg</td>
<td>Nicotine (remission)</td>
<td>ADHD, METH induced Psychotic Disorder, MDD (remission)</td>
<td>IV and smoked, regular heavy use</td>
<td>520</td>
<td>O/P</td>
</tr>
<tr>
<td>D</td>
<td>35</td>
<td>F</td>
<td>70mg reduced to 50mg</td>
<td>Nil</td>
<td>ADHD, MDD (remission), EDNOS, BPD</td>
<td>IV on weekends, assisted by her dealer.</td>
<td>0</td>
<td>O/P</td>
</tr>
<tr>
<td>E</td>
<td>36</td>
<td>F</td>
<td>50mg</td>
<td>Tobacco, Opioids (remission), Cannabis (remission)</td>
<td>ADHD, BPD, BN</td>
<td>IV heavy daily use.</td>
<td>14</td>
<td>I/P</td>
</tr>
<tr>
<td>F</td>
<td>36</td>
<td>F</td>
<td>50mg increased to 70mg</td>
<td>Tobacco, Opioids, ID, Cannabis (remission)</td>
<td>ADHD, Dysthymia, Dependent Personality Disorder/Traits</td>
<td>IV mostly, Binge pattern of use on a weekly basis.</td>
<td>14</td>
<td>I/P</td>
</tr>
<tr>
<td>G</td>
<td>37</td>
<td>M</td>
<td>50mg increased to 70mg</td>
<td>Tobacco</td>
<td>Antisocial, Borderline and Dependent Personality traits</td>
<td>Smoked only, erratic pattern</td>
<td>7 (1st induction), 5 (2nd induction)</td>
<td>I/P twice and O/P once</td>
</tr>
<tr>
<td>H</td>
<td>31</td>
<td>F</td>
<td>30mg increased to 70mg</td>
<td>Tobacco, Opioids, Cannabis, Benzodiazepines (remission)</td>
<td>ADHD, METH Induced Psychotic Disorder, PTSD, AN/BN</td>
<td>IV and heavy regular use.</td>
<td>14</td>
<td>I/P</td>
</tr>
<tr>
<td>I</td>
<td>20</td>
<td>M</td>
<td>30mg increasing to 70mg</td>
<td>Opioid, Alcohol, Tobacco, Cannabis, Benzodiazepines, Hallucinogens,</td>
<td>METH Induced Psychotic Disorder, Antisocial Personality</td>
<td>Smoked</td>
<td>14 (1st induction), 60 (2nd induction)</td>
<td>O/P twice</td>
</tr>
<tr>
<td>J</td>
<td>32</td>
<td>F</td>
<td>30mg</td>
<td>Cannabis (remission), Hallucinogens (remission)</td>
<td>ADHD, BPD, AN (remission)</td>
<td>Intraluminal powder, reduced use in recent years</td>
<td>89</td>
<td>O/P</td>
</tr>
</tbody>
</table>

Legend: F = Female; M = Male; METH = Methamphetamine; LDX = Lisdexamfetamine; IV = Intravenous; BPD = Borderline Personality Disorder; ABI = Acquired Brain Injury; ADHD = Attention-Deficit Hyperactivity Disorder; ID = Intellectual Disability; BN = Bulimia Nervosa; AN = Anorexia Nervosa; MDD = Major Depressive Disorder; PTSD = Post-Traumatic Stress Disorder; I/P = Inpatient; O/P = Outpatient

Disorder [17].
6. Treatment effect on neuropsychiatric comorbidities.

7. Risk behaviours, inclusive of diversion and any associated morbidity and mortality.

8. Functional outcomes including employment, housing and relationship indices.


There were no funding or sponsorship sources for this case series.

Results

Lisdexamfetamine was prescribed in addition to standard treatments, with strict controls, according to Schedule 8 legislation and/or under approval from Medicines Regulation and Quality in Queensland. Outpatients were initially inducted on daily supervised dosing and later were increased to allow takeaways for pharmacy closed days if stable and at least recently compliant with urine drug screening. Inpatients had supervised medication dosing on the ward. Urine drug screening was routinely requested with Amphetamine/Methamphetamine differential. Only a small proportion of process tests had additional confirmatory testing in the laboratory, despite the clear request. All patients were examined periodically for evidence of intravenous drug use.

Table 1,2 demonstrate collective and individual patient demographics, respectively. Figures 1,2 demonstrate overlapping comorbidities.

Overall, 10 patients with Stimulant Use Disorder (based on neuroadaptation to Methamphetamine) were inducted on Lisdexamfetamine treatment. All of the patients selected for inclusion in this case series had Attention-Deficit Hyperactivity Disorder (according to DSM-IV-TR) albeit not all were formally diagnosed in childhood; hence the remainder was offered “off-label” treatment. Lisdexamfetamine was selected as a treatment on the basis of Attention-Deficit Hyperactivity Disorder symptoms being apparent, with proposed by-treatment of reducing Methamphetamine cravings and harm minimisation.

The mean dose was 51mg and the mean duration of treatment was 8.25 months.

Figure 3, Table 3,4 summarise the patient outcomes. Low dose Lisdexamfetamine (between 30 mg and 70 mg) was used with varying degrees of clinical success. The rates of abstinence during treatment were 50% (5/10), the time points as follows:
Table 4: Individual Outcomes – Qualitative Descriptions.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Qualitative description of cravings, withdrawals and other clinical effects of LDX induction</th>
<th>Effect of cessation of LDX</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Dramatic but incomplete reduction in cravings. Approximately 10 fold reduction in METH use. METH withdrawal symptoms subjectively reduced.</td>
<td>N/A</td>
<td>Associated hyper-sexuality reduced.</td>
</tr>
<tr>
<td>B</td>
<td>Cravings ceased completely. Verbal and less psychomotor agitation on LDX. Totally abstinent from METH. Coincidentally ceased sex working on the advice of her partner, continued to work in a traditional occupation, Denied pre or post-treatment METH withdrawals.</td>
<td>Unknown</td>
<td>Patient’s mother and co-patients continuously told her how “normal” and “nice” she appeared.</td>
</tr>
<tr>
<td>C</td>
<td>Felt reasonably well, reported abstinence from METH, reduced social anxiety, improved sense of well-being and absent cravings.</td>
<td>N/A</td>
<td>Occupational functioning did not alter.</td>
</tr>
<tr>
<td>D</td>
<td>Cravings ceased completely. Much calmer and less psychomotor agitation on LDX. Totally abstinent from METH. Coincidentally ceased sex working on the advice of her partner, continued to work in a traditional occupation, Denied pre or post-treatment METH withdrawals.</td>
<td>Decided to cease very shortly after reduction from 70mg to 50mg. Initially she had improved sleep, then return of ADHD symptoms and began to develop Benzodiazepine and Codeine addictions.</td>
<td>Corroborative history from her pharmacist, weekday employer and 2 close friends supported a very positive effect from LDX when compliant including improved parenting abilities and improved relationships in general.</td>
</tr>
<tr>
<td>E</td>
<td>Dramatic but incomplete reduction in cravings. Problem-solving ability improved. Less purposeless behaviour and excessive psychomotor activity. Extricated herself from an abusive relationship, organised moving interstate. Totally abstinent from METH. Moving interstate and handed over to another Psychiatrist who continued LDX treatment. No METH withdrawal symptoms immediately prior to starting LDX.</td>
<td>N/A</td>
<td>Patient appraised LDX treatment as a replacement therapy and was afraid to cease out of fear of METH relapse. No return of bulimic symptoms.</td>
</tr>
<tr>
<td>F</td>
<td>Immediate cessation of cravings. Discontinuation of impulsive behaviours including a reduction in irritability towards clinicians when limits were placed. Almost completely abstinent from METH. No METH withdrawal symptoms immediately prior to starting LDX.</td>
<td>Immediate return to regressed and argumentative behaviour during brief period of refusing LDX treatment.</td>
<td>Pharmacist reported respectful and compliant presentation. No weight loss.</td>
</tr>
<tr>
<td>G</td>
<td>Early wearing off (midday) with return of cravings delayed (4pm-5pm) with higher doses. ADHD symptoms reduced almost entirely. Attended programs and was polite. Patient refused treatment for 1 week prior to discharge possibly in an attempt to delay his discharge. As an outpatient, after low dose depression of METH and associated alcohol use, he agreed to restart LDX with previous efficacy. No METH withdrawal symptoms immediately prior to starting LDX.</td>
<td>N/A</td>
<td>Reunited with wife.</td>
</tr>
<tr>
<td>H</td>
<td>Immediate cessation of cravings. Partial treatment of ADHD symptoms. Vulnerability continued, discharged herself in order to use Heroin with her partner. Re-inducted as outpatient with partial success (white compliant with LDX she was well, relapsed with noncompliance). METH withdrawal symptoms subjectively reduced. Re-inducted again an inpatient. Precipitously moved out of area.</td>
<td>Rapid return to disinhibition and METH use.</td>
<td>When compliant with LDX she re-engaged with her father whom she hadn’t contacted in years, and broke up with her abusive partner who was also using METH. Despite low BMI she weight-restored on LDX but without return of bulimic symptoms.</td>
</tr>
<tr>
<td>I</td>
<td>Immediate cessation of cravings. ADHD symptoms treated well, file notes state his Mental State Examination was &quot;pristine&quot;. Eventually started studying again, was also able to organise himself to commence Suboxone. Psychotic symptoms antedated LDX, also emerged intermittently while on LDX when also precipitously withdrawing from Clonazapam or with relapse of METH. No METH withdrawal symptoms immediately prior to starting LDX.</td>
<td>Return to METH and other substance use.</td>
<td>Psychotic symptoms not related to LDX commencement or dose increase, but may have contributed to psychosis diathesis. Reduction in flaccid penis size on LDX reduced compliance.</td>
</tr>
<tr>
<td>J</td>
<td>No cravings pre or post LDX treatment. Financially less vulnerable, much more organised at home, working more hours. Dramatic improvement in circadian rhythm. No further use of METH. No METH withdrawal symptoms immediately prior to starting LDX.</td>
<td>N/A</td>
<td>Self-harming behaviour ceased.</td>
</tr>
</tbody>
</table>

Legend: METH = Methamphetamine; LDX = Lisdexamfetamine; ADHD = Attention-Deficit Hyperactivity Disorder; I/P = Inpatient; O/P = Outpatient

- 18 months (ongoing treatment)
- 17 months (ongoing treatment)
- 10 months (ongoing treatment)
- 8 months (ongoing treatment)
- 2 months (ceased treatment)

All patients benefited from the treatment in relation to craving, reduction in Methamphetamine use, and treatment of Attention-Deficit Hyperactivity Disorder. All patients reported the ability to plan their recovery more effectively, and objectively their behaviour was more organised. There was a complete absence of non-substance risk behaviours, and a marked reduction in intravenous use of Methamphetamine in all injecting patients while treated on Lisdexamfetamine. There was no known non-prescription use of Lisdexamfetamine, or diversion. The treatment effect was lost immediately after cessation of therapy. One patient had a self-limiting exacerbation of psychotic symptoms requiring cessation of Lisdexamfetamine treatment.

**Discussion**

In Stimulant Use Disorder, Lisdexamfetamine may mitigate harm by virtue of blocking cravings and urges for further
Lisdexamfetamine is significantly cheaper for patients than illicitly purchased Methamphetamine, and conceivably could result in less legal complications and indirect harm to the community. Some possible implications for policy makers include balancing challenges associated with frequent and costly urine drug screening, and ways to standardise agonist treatment approaches should they become evidence-based. Drug monitoring and compliance checking may be important variables in any formalised treatment program, although inevitable breaches of these conditions should not necessarily exclude patients from treatment. There are direct and indirect costs and inconveniences to consider with agonist therapies, similar to opioid replacement programs.

**Conclusion**

Despite methodological limitations, this small case series may indicate grounds for further research in Lisdexamfetamine as agonist therapy in Stimulant Use Disorder. A hedged opinion of this treatment and only hypothesised responder profiles are discussed, with associated cautionary statements.

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**Conflict of Interests**

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**References**


