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Lisdexamfetamine for the treatment of acute methamphetamine withdrawal: A pilot feasibility and safety trial

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ABSTRACT

Background: There is no effective treatment for methamphetamine withdrawal. This study aimed to determine the feasibility and safety of a tapering dose of lisdexamfetamine for the treatment of acute methamphetamine (MA) withdrawal.

Methods: Open-label, single-arm pilot study, in an inpatient drug and alcohol withdrawal unit assessing a tapering dose of oral lisdexamfetamine dimesylate commencing at 250 mg once daily, reducing by 50 mg per day to 50 mg on Day 5. Measures were assessed daily (days 0–7) with 21-day telephone follow-up. Feasibility was measured by the time taken to enrol the sample. Safety was the number of adverse events (AEs) by system organ class. Retention was the proportion to complete treatment. Other measures included the Treatment Satisfaction Questionnaire for Medication (TSQM), the Amphetamine Withdrawal Questionnaire and craving (Visual Analogue Scale).

Results: Ten adults seeking inpatient treatment for MA withdrawal (9 male, median age 37.1 years [IQR 31.7–41.9]), diagnosed with MA use disorder were recruited. The trial was open for 126 days; enroling one participant every 12.6 days. Eight of ten participants completed treatment (Day 5). Two participants left treatment early. There were no treatment-related serious adverse events (SAEs). Forty-seven AEs were recorded, 17 (36%) of which were potentially causally related, all graded as mild severity. Acceptability of the study drug by TSQM was rated at 100% at treatment completion. Withdrawal severity and craving reduced through the admission.

Conclusion: A tapering dose regimen of lisdexamfetamine was safe and feasible for the treatment of acute methamphetamine withdrawal in an inpatient setting.

1. Introduction

Methamphetamine (MA) use disorder is associated with increased mortality, cardiovascular disease, poor mental health (suicidality, psychosis, depression), and risk of blood-borne viral infection (Farrell et al., 2019). Harms associated with MA have increased in recent years (Jones

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et al., 2022; McKetin et al., 2018), with demand for treatment in Australia and the US increasing (Australian Institute of Health and Welfare, 2021; Han et al., 2021; Man et al., 2022; McKetin et al., 2021; United Nations, 2021). A significant challenge in treating MA use is managing the methamphetamine withdrawal syndrome, for which there are no effective pharmacotherapies and which is usually managed symptomatically.

Once tolerance has developed, abrupt cessation of MA use will result in a withdrawal syndrome characterised by dysphoric mood, sleep disturbance, appetite changes and vivid or unpleasant dreams (American Psychiatric Assosciation, 2013). MA withdrawal is characterised by an early "crash" phase of exhaustion and fatigue over hours or days, followed by an acute withdrawal phase lasting up to 2–4 weeks (McGregor et al., 2005; Newton et al., 2004; Shoptaw et al., 2009), with symptoms peaking within the first 7 days (McGregor et al., 2005). A protracted extinction phase of up to 12 months or longer, with cognitive deficits and affective symptoms, has been described (Iudicello et al., 2010; Wang et al., 2004). Unmanaged withdrawal symptoms and cravings can cause significant discomfort, which can be relieved by return to methamphetamine use (Brecht et al., 2000). Withdrawal treatment aims to reduce severity of symptoms (Allsop et al., 2014; Werneck et al., 2018), driving retention and post withdrawal treatment engagement (Timko et al., 2015). Pharmacotherapies for MA withdrawal have been identified as a priority by clinicians and people with lived experience of MA use (Siefried et al., 2022). Although up to 97% of people recently abstinent from amphetamines experience withdrawal symptoms (Cantwell and McBride, 1998; McGregor et al., 2005; Schuckit et al., 1999; Shoptaw et al., 2009), very few studies have investigated pharmacological treatments for MA withdrawal.

There are currently no effective treatments, pharmacological or otherwise, for MA withdrawal (Shoptaw et al., 2009; Siefried et al., 2020). A systematic review yielded nine randomised controlled trials of pharmacological treatments for MA withdrawal, investigating mirtazapine, modafinil, ibudilast, amineptine, varenicline and amantadine, all of which failed to demonstrate effectiveness in managing withdrawal symptoms or MA cravings (Acheson et al., 2022a). Agonist therapies such as dexamphetamine have shown promise for managing MA withdrawal symptoms in studies assessing MA dependency (Galloway et al., 2011; Longo et al., 2010; Shearer et al., 2001; Siefried et al., 2020). Recently, the utility of a stimulant assisted withdrawal has been described in a pilot study, with 60 mg/day of dexamphetamine reducing MA withdrawal symptom severity during the first week of withdrawal (Thompson et al., 2021). This line of investigation employs the idea of agonist therapy, used commonly to treat withdrawal for other substances, such as nicotine for tobacco, buprenorphine for opioid and nabiximols for cannabis withdrawal (Allsop et al., 2014; Bisaga et al., 2022; Gowing et al., 2009; Shiffman et al., 2006; Werneck et al., 2018).

Lisdexamfetamine (LDX) is a pharmacologically inactive prodrug of dexamphetamine (known as dextroamphetamine in some jurisdictions), hydrolysed in red blood cells to dexamphetamine (Pennick, 2010). Compared with dexamphetamine, LDX results in longer time to peak and lower peak dexamphetamine concentrations (maximum dexamphetamine concentrations achieved 3.5 h after dosing, duration of clinical action 10–12 h), facilitating once-daily administration (Krishnan et al., 2008). Further, LDX offers advantages over dexamphetamine in the treatment of MA withdrawal in the community, which is constrained by concerns regarding diversion for non-medical use. Intravenous injection of LDX does not result in more rapid onset of action, and the blunted dopaminergic response would be expected to reduce mesolimbic positive reinforcement (Jasinski and Krishnan, 2009). LDX has the potential to ameliorate withdrawal symptoms and craving for MA during the acute withdrawal phase, whilst the advantages discussed above may make it easier to upscale in clinical and outpatient settings as compared to dexamphetamine.

This study reports on the first trial of LDX for the treatment of acute MA withdrawal. We aim to determine the safety and feasibility of a tapering-dose regimen of LDX in addition to treatment as usual during acute MA withdrawal in an inpatient setting.

2. Materials and methods

2.1. Trial design and setting

An open-label, single-arm clinical trial was conducted in an inpatient withdrawal management unit at St. Vincent's Hospital Sydney, Australia. The hospital is a smoke-free environment (including vaporised nicotine products). Nicotine replacement therapies are offered to patients who require them.

2.2. Participants

Eligible participants were at least 18 years of age, voluntarily presenting to the inpatient drug treatment service, seeking treatment for MA withdrawal, and met DSM-5 criteria for MA use disorder (American Psychiatric Assosciation, 2013). Participants last used MA within 72 h of the planned first dose of study drug, confirmed by a positive urine drug screen on admission. Participants had to provide written informed consent, and indicate willingness to participate and adhere to the study protocol. Participants were ineligible for the trial if they: were breast/chest feeding, pregnant or unwilling to avoid becoming pregnant during the trial; had an expected concurrent withdrawal from alcohol, opioids, benzodiazepines, gamma-hydroxybutyrate or other gabapentinoids; had known contraindications to LDX other than drug dependence (Australian Product Information: Vyvanse®, 2013 (Updated 2020)) (see Supplementary File 1 for detail); had a medical condition which in the opinion of a study medical officer rendered them unsuitable for the study; or, were involuntarily admitted to the unit.

2.3. Intervention

Tapering dose of LDX, beginning at 250 mg oral once daily (OD), reducing by 50 mg per day to 50 mg OD on Day 5. LDX at a dose of 250 mg (about three times higher than approved for other indications) is equivalent to approximately 74 mg of dexamphetamine (Dolder et al., 2017), and similar doses of sustained release dexamphetamine (60–110 mg) have previously been demonstrated to decrease MA withdrawal severity and cravings, and increase retention in care (Galloway et al., 2011; Longo et al., 2010). This dose of LDX has previously been shown to be safe in methamphetamine dependent people in a community setting (Ezard et al., 2021a), and is closer to recreational amphetamine doses. LDX was formulated in 50 mg capsules and dispensed each morning under supervision of nursing staff. All participants received inpatient treatment as usual, consisting of symptom management and supportive care.

2.4. Study procedures

On admission to the withdrawal unit, informed consent was obtained by a study medical officer and participants were screened for participation. If eligible, detailed medical, sociodemographic and substance use history were obtained, an electrocardiogram to assess cardiovascular risk and to establish a baseline in case of any cardiovascular Adverse Events, and a human chorionic gonadotrophin (hCG) blood test for pregnancy (for people of childbearing potential) were conducted.

Participants were given the first dose of study medication on the first morning of their admission (Day 1). Participants were admitted for a minimum of 5 days to complete the treatment regimen, with an optional further two days extension to complete a 7-day abstinent period under supervision. Each morning during admission a study coordinator conducted study assessments. Participants were followed up once a week for three weeks after discharge (Days 14, 21, 28) by a researcher via telephone to assess medium term safety and efficacy outcomes.

Concomitant medications for coexisting conditions were permitted, other than monoamine oxidase inhibitors which are contraindicated (Australian Product Information: Vyvanse®, 2013 (Updated 2020)). Standard care permitted providing medication for symptomatic relief of severe anxiety or symptoms of psychosis including oral diazepam (maximum 10 mg up to four times a day) and oral olanzapine (maximum 5 mg up to three times a day) (St. Vincent's Health Network Sydney, 2019).

All participants were offered concurrent psychosocial support, and long term psychosocial treatment referrals following discharge from the inpatient unit. Participants received supermarket vouchers for attending research assessments (AU$20–30 per assessment; up to $170 in total).

2.5. Outcomes

2.5.1. Primary outcomes

The primary outcomes were feasibility and safety.

Feasibility was defined as the proportion of people who failed to complete the screening and pre-screening procedures, and the time taken to enrol the sample.

Safety measures were adverse events (AEs) across the sample at all time points, by system organ class (SOC), including the number of participants with AEs of vital signs recorded outside expected limits (see below). The primary safety measure was the number of adverse events (AEs) by SOC, described by seriousness, severity, causality and expectedness (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Annotated with TGA Comments, 2016; National Health and Medical Research Council, 2016). AEs were documented during daily medical assessments or volunteered by the participant during study visits transcribed verbatim and reported in line with the Medical Dictionary for Regulatory Activities (MedDRA). Severity was graded from Grade 1 – mild to Grade 5 – death by the site principal investigator (National Institute of Allergy and Infectious Diseases Division of AIDS DAIDS, 2018). Causality was determined by the site principal investigator, and expectedness in accordance with international guidelines and the product label for LDX (Australian Product Information: Vyvanse®, 2013 (Updated 2020); Council for International Organizations of Medical Sciences, 2005). Any known reaction listed on the product label was considered potentially causally related.

Vital signs were recorded four-times daily during admission (heart rate [HR], systolic blood pressure [SBP], diastolic blood pressure [DBP], oxygen saturation [SpO_2], respiratory rate [RR] and temperature). AEs related to vital signs were a-priori defined as values which exceeded the 'Between the Flags' criteria used in New South Wales Health (Australia) hospitals (Green et al., 2018): HR less than 50 or greater than 120 beats per minute (bpm); SBP less than 100 millimetres of mercury (mmHg) or greater than 180 mmHg; $SpO_2 < 95\%$; RR less than 10 or great than 25 respirations per minute; temperature of less than 35.5 °C or greater than 38.5 °C. All vital sign results across all time points (to Day 7) are reported.

2.5.2. Secondary outcomes

Secondary outcomes were retention in treatment, treatment acceptability, withdrawal severity, cravings for MA, psychoses and hostility, suicidality, and substance use.

Retention in treatment was defined as the proportion of participants retained at Day 5.

Treatment acceptability was assessed by medication adherence (i.e. refused or missed doses), proportion and type of symptomatic medication required, and the Treatment Satisfaction Questionnaire for Medications-II (TSQM) conducted daily during treatment, rated out of 100 on the subscales of Global Satisfaction, Effectiveness, Side Effects and Convenience (Atkinson et al., 2004).

Withdrawal severity was measured using the amphetamine withdrawal questionnaire (AWQ) daily during admission (Srisurapanont et al., 1999a), and once weekly during follow up. The AWQ yields scores from 0 to 40; higher scores indicate more severe withdrawal.

MA craving was assessed with a 100 mm Visual Analogue Scale (VAS) daily during the inpatient period only, in which participants were asked to indicate "How much are you craving methamphetamine right now?" with 0 being no cravings and 100 being unbearable cravings (Lee et al., 2002).

Measures of psychosis and hostility were assessed using the hostility, suspiciousness, hallucinatory behaviour and unusual thought content items of the Brief Psychiatric Rating Scale (BPRS), with each item being rated on a scale of 1–7, and higher values indicating more apparent symptoms (McKetin et al., 2013; Overall and Gorham, 1962). Suicidality was assessed using the Columbia Suicide Severity Rating Scale (C-SSRS) at Baseline (Day 1) and follow-up at Day 5 (Posner et al., 2011).

Post discharge substance use was assessed by weekly timeline follow-back (TLFB) where participants were asked to retrospectively estimate their daily MA use for 7 days prior to the follow-up interview date.

2.6. Statistical analysis

A sample size of 15 was initially nominated (Hertzog, 2008; Julious, 2005). Recruitment was curtailed at 10 participants due to COVID-related restrictions on clinical trials being conducted in the inpatient unit. Adverse events were described by type, severity, causality and expectedness, and each AE was reported regardless of severity or repetition. Descriptive statistics (median, interquartile range (IQR)) were used to describe continuous measures. Proportions were used to describe categorical variables. Changes over time for HR, SBP, AWQ and VAS scores were analysed using repeated-instrument ANOVA with Bonferroni corrections and violations in sphericity corrected (Greenhouse and Geisser, 1959).

2.7. Ethics and reporting

This study was approved by the SVHS Human Research Ethics Committee (2020/ETH02039) and prospectively registered with the Australian and New Zealand Clinical Trials Registry (ANZCTN:12621000045819). A trial protocol was prospectively published (Acheson et al., 2022b). This trial was reported in line with the CONSORT and CONSERVE guidelines, and the CONSORT Checklist is available in Supplementary File 2.

3. Results

3.1. Baseline characteristics

Of 38 people who were pre-screened, 10 participants consented to the study, met eligibility screening, and enroled in the trial (Fig. 1). Recruitment commenced on 13 April 2021 and the final participant was recruited on 12 November 2021. Recruitment was disrupted by the response to the COVID-19 pandemic, resulting in an 87 day pause in recruitment and a total of 126 days recruitment time.

Nine out of ten participants were male; other demographic data are described in Table 1. Participants self-reported using MA for a median 23 days of the last 28 (interquartile range (IQR) 20–28), and consuming 0.6 g (IQR 0.2–0.7 g) of MA each day, with smoking and injecting reported as routes of administration. Median age of first use was 22 years (IQR 18.5–26.5). Half of the participants reported using cannabis or gamma-hydroxybutyrate (GHB), and no participant reported cocaine, non-prescribed opioid or hallucinogen use within the previous 28 days (Table 2). By UDS, 5 (50%) participants recorded positive results for benzodiazepines, and 3 (30%) participants recorded positive results for cannabis. No other substances were recorded.

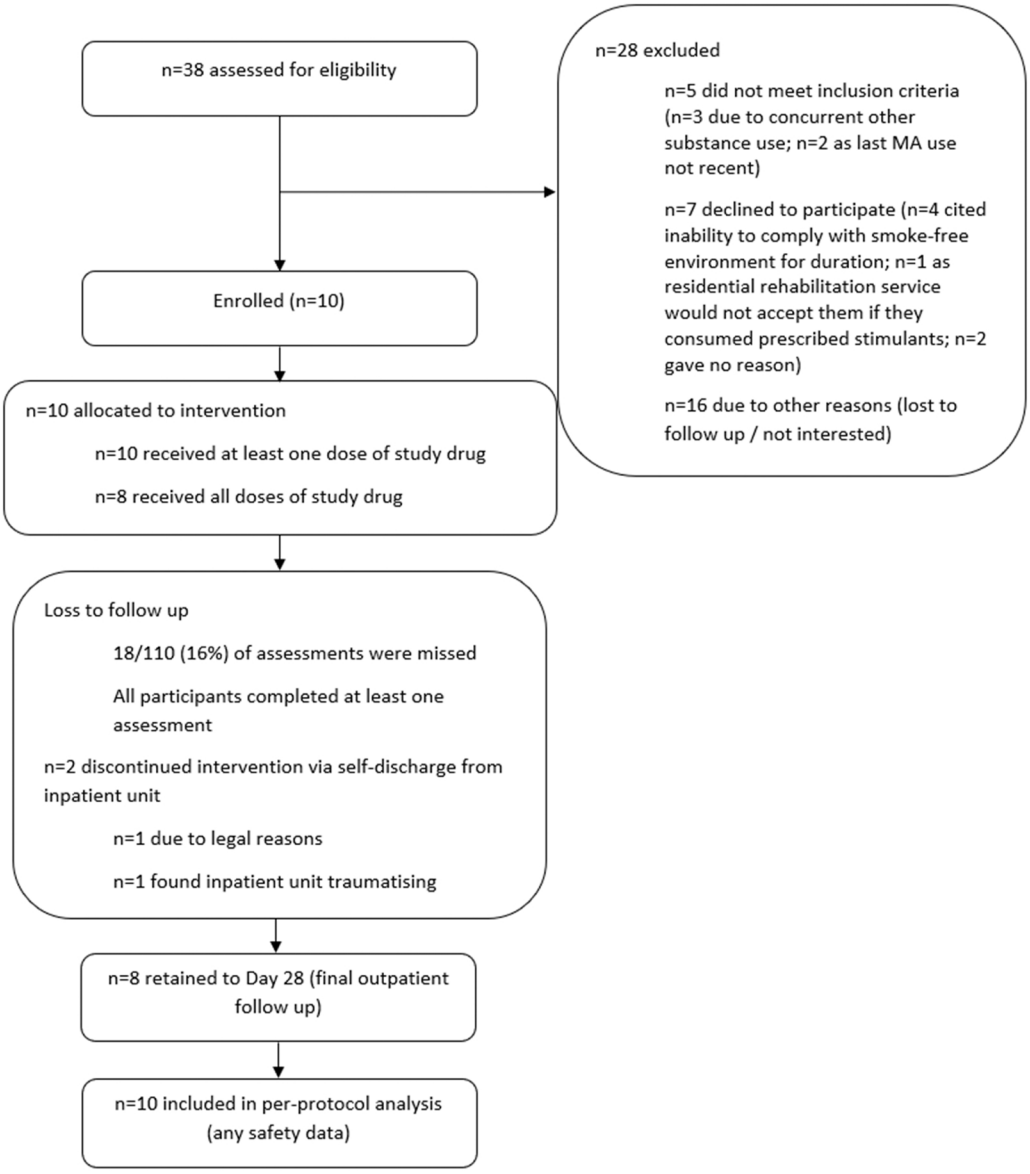

Fig. 1. CONSORT flow diagram.

Table 1
Demographics.

Age (median (IQR))	37.1 (31.7–41.9)
Gender and sexuality	
Heterosexual man (n(%))	4 (40)
Gay man (n(%))	5 (50)
Heterosexual woman (n(%))	1 (10)
Highest education completed	
Year 10 or below (n(%))	3 (30)
Year 12 (n(%))	3 (30)
Trade or vocational school (n(%))	2 (20)
University degree (n(%))	2 (20)
Income source	
Full time work (n(%))	4 (40)
Temporary benefit (n(%))	5 (50)
No income (n(%))	1 (10)
Living arrangements	
Renting - private (n(%))	6 (60)
Renting - state housing (n(%))	1 (10)
No usual residence / homeless (n(%))	3 (30)

Table 2
Substance use history.

Duration of MA use (median (IQR)) (years)	13.6 (10.1–19.3)
Age first used MA (median (IQR)) (years)	21.5 (18.5–26.5)
Days used in last 28 days (median (IQR)) (days)	23 (20–28)
Quantity used per day[a] (median (IQR)) (grams)	0.6 (0.2–0.7)
Primary route of administration[b]	
Smoke (n(%))	4 (40)
Inject (n(%))	5 (50)
Both (n(%))	1 (10)
Other recent substance use (any use last 28 days)	
Tobacco (n(%))	3 (30)
Alcohol (n(%))	3 (30)
GHB (n(%))	5 (50)
Cannabis (n(%))	5 (50)
Benzodiazepines (n(%))	1 (10)
Ecstasy (n(%))	1 (10)
Amyl Nitrate (n(%))	1 (10)

a; Points were converted to grams at a rate of 1 point = 0.1 g.
b; Participants could self-report multiple primary routes of administration.

3.2. Primary outcomes

3.2.1. Feasibility

Of the total number of potential participants pre-screened, a quarter (n = 10 (26%)) met eligibility criteria and were enroled in the trial (Fig. 1). One participant was enroled every 12.6 days.

3.2.2. Safety

Of the 47 adverse events (AEs) reported, 17 (36%) were potentially causally related to LDX, all of which were mild (Grade 1). All AEs were treatment emergent except one case of nausea and one case of anxiety. One serious adverse event (SAE) was reported, a shigellosis infection, which was unrelated to the trial medication. AEs are described in detail in Table 3.

There were no AEs related to vital statistics. Systolic blood pressure and HR are presented in Fig. 2a and b throughout the intervention period. Vital statistics are summarised in Table 4. There was no significant change in daily median HR ($p = 0.051$) or SBP ($p = 0.447$). Measures of SBP above 140 mmHg occurred in 5 (50%) participants (12% of measures, over half of which were from one participant). The maximum recorded SBP was 159 mmHg, occurring in one participant on one occasion. No HR measure was greater than 120bpm, HRs between 100bpm and 120bpm were recorded in 7 (70%) participants (11% of measures). Each participant's baseline (admission [pre-intervention]) BP and subsequent daily morning measurement are presented in Supplementary File 3.

3.3. Secondary outcomes

3.3.1. Retention

Eight (80%) participants were retained to Day 5 and completed the treatment protocol. Two participants self-discharged and stopped treatment early, one due to legal reasons, and one who found the inpatient unit traumatising due to a history of incarceration. Both consented to continue data collection as outpatients, but were later lost to follow up. Eight (80%) participants were retained to Day 7, and were followed up until Day 28.

3.3.2. Acceptability

Medication adherence was 100% in those who were retained in the study, up to the date of discharge (conformed by supervised dosing).

During inpatient admission the most common concomitant medication prescribed was diazepam, with 8 (80%) participants receiving at least one dose, predominantly for sleep disturbance and anxiety. Three (30%) participants received olanzapine prescribed off-label for sleep disturbance, and 2 participants received paracetamol for headache. No other concomitant medications were recorded to ameliorate withdrawal symptoms. Other concomitant medications are listed in Supplementary File 4.

Median Global Satisfaction on the TSQM was 82% (IQR 71–93) on Day 1% and 100% (IQR 100–100) on Day 5 of treatment, as measured by the TSQM Global Satisfaction subscale. Perceived medication effectiveness was 72% (IQR 61–89) on Day 1% and 97% (IQR 92–100) on

Table 3
Adverse events by system organ class, severity, and relatedness.

	Adverse event		AE	SAE	Related?
Day 1–5 (intervention)	Ear and labyrinth disorders	*Tinnitus*	1		No
		Vertigo	1		No
	Eye disorders	*Ocular photosensitivity*	1		Yes
	Gastrointestinal Disorders	*Nausea**	2		n = 1 Yes n = 1 No
		Abdominal pain	1		Yes
		Diarrhoea	1		Yes
		Gastrointestinal distress	1		Yes
	General disorders and administration site conditions	*Hot flush*	2		No
		Feeling jittery	1		Yes
		Overheating	1		No
		Sweating	1		Yes
	Infections and infestations	*Blastocycstis infection*	1		No
		Rectal gonorrhoea	1		No
	Injury, poisoning and procedural complications	*Acute nausea following unexpected ingestion of nicotine lozenge*	1		No
	Musculoskeletal and connective tissue disorders	*Back pain*	1		No
		Muscle cramps[a]	1		No
		Muscle pain[b]	1		No
		Wrist pain	1		No
	Nervous system disorders	*Headache*	2		Yes
	Psychiatric disorders	*Depressed mood*	2		No
		Trouble sleeping	2		Yes
		*Anxiety**	1		No
		Excessive sleep	1		No
		Mood swings	1		No
		Poor concentration	1		Yes
		Bad dreams	1		No
	Skin and subcutaneous tissue disorders	*Itchiness*	2		No
Days 6–7	General disorders and administration site conditions	*Swelling (foot)*	1		No
	Musculoskeletal and connective tissue disorders	*Muscle pain*[b]	1		No
	Renal and urinary disorders	*Painful urination*	1		No
Days 14, 21 and 28	General disorders and administration site conditions	*Swelling (knee)*	1		No
	Infections and infestations	*Shigellosis infection*		1	No
	Injury, poisoning and procedural complications	*Burn (candle wax)*	1		No
		Knee injury	1		No
	Nervous system disorders	*Headache*	3		Yes
	Psychiatric disorders	*Difficulty sleeping*	2		Yes
	Skin and subcutaneous tissue disorders	*Pimple*	1		No
	Gastrointestinal Disorders	*Root canal infection*	1		No

a; Participant reported cramping in muscles.
b; Participant reported generalised muscle pain.
*; AE designated not related as it emerged prior to treatment with study drug.

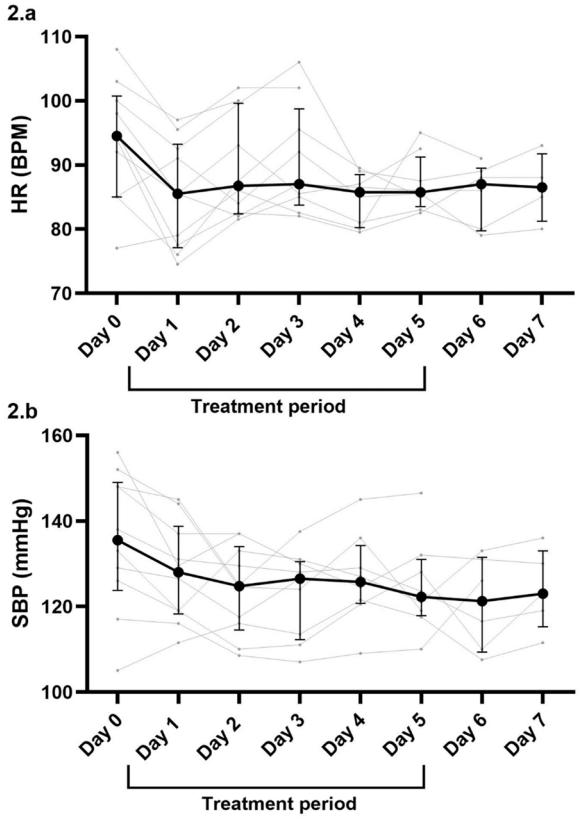

Fig. 2. Heart rate (a) and systolic blood pressure (b) during admission, Black = sample daily median (IQR), Grey = participant daily median (1 line for each participant), HR; Heart rate, BPM; beats per minute, SBP; systolic blood pressure, mmHg; millimetres of mercury.

Table 4
Physiological data summary.

	Median	IQR[a]	Minimum	Maximum
HR[b] (BPM[c])	86	80–93	69	120
SBP[d] (mmHg[e])	123	116–132.5	100	159
DBP[f] (mmHg)	78	71–83	61	99
SpO_2^g (%)	99	98–99	96	100
RR[h] (BPM)	17	16–17.25	12	20
Temp (°C)	36.5	36.4–36.6	35.6	37.3

a; interquartile range, b; heart rate, c; beats per minute, d; systolic blood pressure, e; millimetres of mercury, f; diastolic blood pressure, g; oxygen saturation, h; respiratory rate.

Day 5. Participants indicated side effects did not bother them (median satisfaction 100% on the Side-Effects subscale Days 1 (IQR 91–100) and 5 (IQR 100–100) and that the medication was convenient to use (median satisfaction 97 (IQR 94–100) Day 1% and 100% (IQR 100–100) Day 5) as measured by the TSQM.

3.3.3. *Withdrawal symptoms*

Withdrawal symptoms as measured by the AWQ reduced throughout treatment, from a median score of 23 (IQR 16.8–26.5) at baseline to 6 (IQR 2.75–7.75) at Day 5 ($F(1.084,10.826) = 8.475$, $p = 0.007$, partial $\eta^2 = 0.586$), and 8.5 on Day 7 (post treatment, IQR 5.8–19.5). AWQ scores remained relatively stable to Day 28 (median 10, IQR 4–19) (Fig. 3).

3.3.4. *Craving for methamphetamine*

The median MA craving score, as measured by the VAS, was 25 (IQR 7–42) across the inpatient period of the study. Cravings were highest on admission: median VAS score 56 (IQR 44–74) at Day 0, reducing to 9.5 (IQR 3–29) on Day 5 ($F(1.421,8.525) = 10.619$, $p = 0.007$, partial $\eta^2 = 0.639$). Post hoc analysis revealed significantly reduced craving scores between Baseline and Days 4 (mean difference 42.3 95%CI 6.0–78.6, $p = 0.023$) and 5 (mean difference 46.1, 95%CI 6.9–85.4, $p = 0.022$) (Fig. 4).

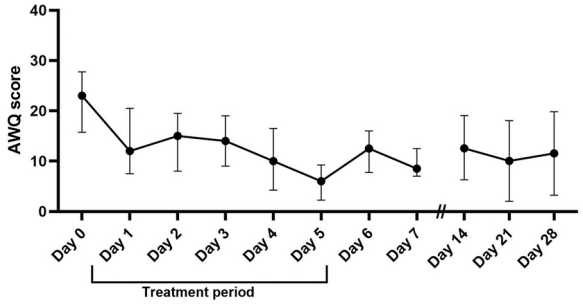

Fig. 3. Withdrawal severity at each time point (n = 10), AWQ; Amphetamine withdrawal questionnaire, sample median (IQR).

3.3.5. *Psychosis, hostility, suicidality*

Median BPRS (hostility, suspiciousness, hallucinatory behaviour and unusual thought content items) scores were 6.5 (IQR 5–8) at baseline and 4 (IQR 4–5) at the end of treatment. Six (60%) participants reported any level of recent (past 12 months) suicidal ideation at baseline, and none reported any suicidal ideation during the inpatient study period.

3.3.6. *Abstinence post-discharge*

Of the 8 participants who completed follow-up measures, 6 (75%) self-reported abstinence by TLFB from MA during the third week of follow up and 4 (50%) reported complete abstinence from MA for the entire follow-up period.

4. Discussion

Findings from this open-label pilot study demonstrated that for participants with MA use disorder seeking treatment for MA withdrawal, a starting dose of 250 mg LDX followed by 50 mg down-titration daily was feasible and safe for the management of acute MA withdrawal. This regimen produced significant ratings of acceptance and retention. Findings also showed significant reductions in ratings of methamphetamine withdrawal and craving that corresponded with the down-titration, reductions that were measured through follow-up to Day 28.

As an unblinded, single-arm study we cannot comment on the efficacy of LDX, nor compare safety with a placebo control, however we did not design this study to do so. In this study participants were able to receive diazepam and olanzapine for management of withdrawal

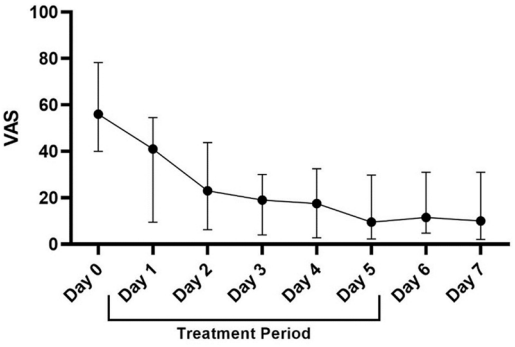

Fig. 4. Craving for methamphetamine at each time point (n = 10), VAS; Visual analogue scale median (IQR), not conducted during follow up due to visual nature of assessment.

symptoms as per treatment as usual during the inpatient period only, and these medications may have reduced symptoms of anxiety and agitation through the study, which therefore has the potential to affect related items within the AWQ. These medications would be unlikely to affect a reduction in craving for MA, a primary predictor of early relapse (Galloway and Singleton, 2008; Hartz et al., 2001; Tuliao and Liwag, 2011). The small sample size and significant gender imbalance of this trial limits generalisability of the results, however given previous investigations into the safety of LDX in stimulant using populations this is unlikely to affect the results of this study (Australian Product Information: Vyvanse®, 2013 (Updated 2020); Ezard et al., 2021a). Future studies of this medication must ensure adequate gender balance and study designs which encourage participation of women. Ward closures due to COVID-19 requirements negatively impacted recruitment.

The safety profile of LDX in this population aligns with the published product label, despite using doses approximately three times higher than approved for other indications. AEs that were potentially causally related were of mild severity and generally managed without intervention and thus would likely be easily managed by participants at home. However, it is unknown if the prevalence and severity of AEs was reduced by the provision of concomitant medications. This medication is expected to increase HR and BP in some people, however data from a community study where people continued to use MA while receiving LDX suggested changes were minimal in this population (Ezard et al., 2021a). In that study, examining dose-escalation of up to 250 mg LDX for MA dependence, mean change in SBP was + 3.4 mmHg (range −21.0 to +27.0, SD 14.6) and mean change in heart rate was + 7.3 bpm (range −17.0 to +37.0, SD 13.4), suggesting that changes to SBP and HR potentially due to LDX are likely to be tolerable in a similar population (Ezard et al., 2021a). In our study there were no treatment limiting AE's, and no cases of hypertensive urgencies or emergencies (National Heart Foundation of Australia, 2016; Whelton et al., 2018). Despite the well-defined cardiovascular effects of MA there is a lack of data regarding haemodynamic parameters during acute withdrawal, making it difficult to comment on the expected values for our sample. HR and BP were highest at baseline in our sample, and reduced throughout the admission. While a treatment approach utilising LDX has risks of short term excursions in SBP and HR, the benefit toward reducing future high-dose MA use outweighs these relatively minor risks (Kaye et al., 2007).

This protocol was feasible, recruiting one participant every 2 weeks at one site with one study coordinator and no advertising or active recruitment. This is comparable to other studies in the field with active recruitment (Cruickshank et al., 2008; Kongsakon et al., 2005; Modarresi et al., 2018), and perhaps suggests community demand for new treatments for MA withdrawal. The primary reasons people did not progress from pre-screening to enrolment was refusal to participate in a trial or unable to be contacted (i.e. indicated interest, but did not return study coordinator contact). Other reasons included people not consuming MA recently enough to precipitate acute withdrawal, or people likely to experience concurrent withdrawal from other drugs, notably GHB. Four people who expressed interest in participating declined admission into a smoke-free hospital.

Eighty per cent of our sample was retained to treatment completion and Day 28. Treatment completion rates are comparable with similar studies. In a systematic review of 6 studies examining a medication for MA withdrawal, a mean of 73% (range 52–83%) of the sample were retained to the primary endpoint (Acheson et al., 2022a). Furthermore, the TSQM result indicated a highly acceptable treatment regimen. Previous studies have suggested TSQM scores > 80% are associated with high levels of retention (Bharmal et al., 2009; Radawski et al., 2019), and in our study median satisfaction at all timepoints was > 80% for four out of five items. Only one participant rated Global Satisfaction < 80% at treatment completion.

While ratings of withdrawal and craving reported in our study decreased through the intervention period, similar patterns are observed during the natural time course of withdrawal. When compared to other cohorts of un-medicated MA withdrawal (Lee et al., 2013; McGregor et al., 2005; Srisurapanont et al., 1999b), our sample tended to report higher baseline withdrawal severity. McGregor et al. observed a linear decrease in withdrawal severity from baseline to day 8 post-cessation (McGregor et al., 2005), similar to both the treatment and control arms in Lee et al. (2013). Srisurapanont et al. only reported data at baseline and Day 7 post-cessation, with our study reporting higher baseline withdrawal scores but similar scores at Day 7 (Srisurapanont et al., 1999b). The severity of MA withdrawal as measured by the AWQ decreased rapidly in our cohort.

Both withdrawal severity and craving for MA reduced through the admission period, and in the case of withdrawal remained stable through to Day 28. Withdrawal scores reduced in a linear manner over the first 5 days of medication, however a small, non-significant increase in withdrawal severity was documented on Day 6. This may reflect an element of 'rebound' withdrawal symptoms following the cessation of LDX – a phenomenon seen following cessation of methadone or buprenorphine when used in short-term regimens for treating heroin withdrawal (Gossop et al., 1989; Strang and Gossop, 1990). Nevertheless, the increase in withdrawal scores on Day 6 were minor and subsided by Day 7.

Future directions should focus on assessing efficacy of LDX for the treatment of acute MA withdrawal through multi-site randomised, placebo-controlled trials. Further research should also focus on ambulatory withdrawal management applications of LDX due to its favourable safety and diversion profile, and suitability for once daily dosing. Such trials could provide an alternative that may not require daily supervised dosing, with potential for collecting medications on one or two occasions per week, similar to trials of LDX for MA use disorder relapse prevention (Ezard et al., 2021b).

5. Conclusions

This study examined a novel treatment for acute MA withdrawal, which has no effective treatment in any jurisdiction. We found that a tapering dose regimen of LDX was feasible and safe for the treatment of acute MA withdrawal in an inpatient environment. Further, larger, randomised controlled trials in inpatient and outpatient settings are warranted.

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CRediT authorship contribution statement

LSA, KJS, NE, NL and AD conceptualised the study. LSA lead data acquisition under supervision of NE and KJS. All authors contributed to the study protocol and final methodology. LSA analysed the data and prepared the first draft of the manuscript under the supervision of NE, KJS, RM and MF. All authors contributed to the writing of the manuscript and its review.

Conflict of interest

LSA is supported by an NDARC PhD Scholarship. MF has received unrestricted funding for research purposes from Indivior and Sequiiris. SS has received clinical research supplies from Alkermes. NE and KJS are employed by NCCRED. No other investigators have any conflicts of interest to declare.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2022.109692.

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