Safety and tolerability of oral lisdexamfetamine in adults with methamphetamine dependence: a phase-2 dose-escalation study

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Abstract

Background: Methamphetamine (MA) dependence is a growing global health issue with no effective pharmacotherapy. Lisdexamfetamine (LDX) is approved for use in the treatment of attention-deficit/hyperactivity disorder (ADHD) and binge eating disorder (BED) in doses ranging from 30 to 70mg/day. LDX has a longer duration of action and lower abuse potential than other amphetamines, and presents a promising candidate for agonist-type treatment of MA dependence. People seeking treatment for MA dependence may require doses of LDX higher than used in ADHD and BED. We examined the safety of LDX at 250mg/day among adults with MA dependence, approximately equivalent to previously trialled doses of dexamphetamine.

Methods: We conducted a dose-escalating, phase-2, open label, single-group study of oral LDX at two Australian drug treatment services. Eligible participants were MA dependent adults who reported use of MA on at least 14 of the preceding 28 days. Once daily, supervised LDX doses of 100 to 250mg/day were provided as a single-blinded, ascending-descending dose regimen over 8 weeks. The primary outcomes were safety, drug tolerability, and regimen completion at the end of Week 4 (maximum dose). Participants were followed through to Week 12. Secondary outcomes included: change in MA use; craving; withdrawal; severity of dependence; risk behaviour; change in other substance use; medication acceptability; potential for non-prescription use; adherence; and neurocognitive functioning.

Results: Fourteen of 16 participants (87.5%) successfully completed the four week escalation regimen to 250mg/day. Two participants withdrew from the trial in the first week. No participant was withdrawn due to adverse events. MA use decreased significantly (p=0.013) from a median of 21 days (IQR: 16-23) to 13 days (IQR: 11-17) over the four week escalation period.

Conclusions: LDX at a dose of up to 250 mg/day was safe and well tolerated in this population, with high retention. Larger trials of LDX as a pharmacotherapy for MA dependence are warranted.

Trial Registration : Australian and New Zealand Clinical Trials Registry ACTRN12615000391572.

Background

Amphetamine-type stimulants, including methamphetamine (MA), present a global public health concern. Globally, they make up the second most commonly used illicit drug class. An estimated 29 million people used amphetamines in 2019 (1), with 7 million estimated to be dependent (2). For people who use MA, poor health outcomes are seen particularly among those who use the drug several times a week (3) including psychosis, depression, anxiety, blood-borne virus transmission, sexually transmitted infections, and cardio/cerebral vascular events (4, 5).

Currently, treatment for MA dependence is based on psychological therapies such as cognitive behaviour therapy (CBT) (6, 7). Psychological therapies are labour-intensive and predicated on high levels of attendance and participation by patients. No pharmacotherapy has yet achieved comparable efficacy, and

there are as yet none licensed for the treatment of MA dependence, though agonists show some promise (8). The efficacy of agonist therapies for treatment of MA dependence is uncertain, with one systematic review showing no benefit over placebo, although limitations in retention and power of published studies were noted (9). Dexamphetamine, an MA agonist, has similar neurochemical and behavioural effects to MA (10), and has been used off-label for both amphetamine and MA dependence in the United Kingdom (11, 12) and Australia (13).

Lisdexamfetamine (LDX) is a pharmacologically inactive pro-drug of dexamphetamine approved for the treatment of attention deficit/hyperactivity disorder (ADHD) in Australia, Brazil, Canada, Europe, the United Kingdom, and the United States of America (USA), and more recently for binge eating disorder (BED) in Australia and the USA. Potential advantages of LDX over immediate release dexamphetamine include once-daily dosing, a slower onset, lower peak concentration, longer duration of action and lower abuse potential (14). LDX presents a candidate pharmacotherapy for MA dependence.

There are no clinical trial data on the effectiveness of LDX for the treatment of MA dependence. Chronic use of high doses of MA may lead to physiological adaptation so that a dose higher than the licenced therapeutic range of medication is required (9). For the treatment of ADHD and BED in stimulant-naïve populations, LDX is licensed for doses ranging from 30 to 70mg/day. A previous study of dexamphetamine has trialled doses up to 110mg (approximately equivalent to 250mg/day of LDX) for this population without serious adverse events (15). Doses of 250mg/day of LDX were tolerated in one pharmacokinetic study of non-MA dependent volunteers (16) and in a study of participants with schizophrenia receiving antipsychotic pharmacotherapy (17).

This study aimed to determine the safety of LDX in people with MA dependence, at doses higher than those currently approved for the treatment of ADHD and BED. The primary objectives of the study were to describe the safety, tolerability, and regimen completion of ascending doses of LDX in adults with MA dependence. Secondary objectives included measures of efficacy, drug-liking and neurocognition.

Methods

Trial design

A phase-2, open label, single-group trial was undertaken at two stimulant treatment outpatient clinics in New South Wales, Australia (18). Ethical approval was granted by the St Vincent's Hospital Human Research Ethics Committee for both study sites (HREC/14/SVH/202). All participants provided written, informed consent prior to undergoing study assessments. An independent data safety and monitoring board reviewed safety data during and at completion of the study.

Recruitment and enrolment

Notices were displayed at clinics at both sites, as well as at other drug and alcohol services, associated community organisations, and local general practice clinics. Interested participants either approached or

were referred to a research nurse who undertook a standardised pre-screening. If basic inclusion criteria and no exclusion criteria were met, potential participants attended a screening visit with a site principal investigator. Recruitment continued at all sites until the available number of potential participants was exhausted within the study frame.

Participants

Eligible participants were at least 18 years of age who had been dependent on methamphetamine for at least the preceding two years, determined by an Addiction Medicine physician (AD, NE) using ICD-10 criteria (19). Inclusion additionally required reported use of MA on 14 days or more of the previous 28 days at the time of screening, confirmed by two urine samples positive for MA one week apart. Patients who had used dexamphetamine in the previous four weeks were excluded, as were those with known sensitivity or previous adverse reaction to LDX or prescribed drugs which may interact with LDX (venlafaxine, desvenlafaxine, monoamine oxidase inhibitors), known contraindications to LDX (severe and symptomatic peripheral vascular disease or Raynaud's phenomenon, significant prior or symptomatic cardiovascular disease, moderate to severe hypertension, glaucoma, phaeochromocytoma, hyperthyroidism, motor and phonic tics, Tourette's syndrome, high suicide risk, voicing suicidal ideation, active psychosis, severe agitation or unstable use of alcohol or drugs other than MA as assessed by a specialist in addiction medicine (20)). Patients with well-controlled mild to moderate hypertension on a single antihypertensive agent were permitted, and those with a past history of psychosis were permitted on review by a psychiatrist. Pregnant or breastfeeding women, and women not willing to avoid becoming pregnant during the study were also excluded.

Study Procedures

At the screening visit, informed consent was obtained as well as a detailed medical and substance use history, physical and mental state examinations, an electrocardiogram (ECG), and a urine human chorionic gonadotrophin (HCG) test (for women of childbearing potential) to verify eligibility.

All participants were commenced on a dose escalation regimen of supervised daily dispensing of ascending doses of LDX from 100mg to 250mg over four weeks, followed by a four week dose reduction regimen from 250mg to 100mg, and attended a follow-up visit four weeks after ceasing the study drug (see **Figure 1**). All participants were supervised at the point of administration by a dispensing nurse. Both participants and dispensing nurses were aware that the dose would first be escalated and then reduced, and of the dose range (100mg to 250mg); but they were blinded to the time points at which the doses changed. To achieve this, the dose comprised 5 identical size 0 capsules, each containing either 50 mg LDX or placebo according to the dose escalation phase. Participants received each dose for 7 days, based on the data that steady state for LDX is achieved after five days (21), and were reviewed by a medical officer weekly.

Participants not already engaged with psychological therapy were offered concurrent weekly counselling, although attendance was not mandatory. Participants were offered supermarket vouchers with a value of

AUD $80 at the end of each of six visits: Baseline; Weeks 1 to 4 (escalation phase); and follow-up (Week 12) (total possible value of $480).

Criteria for withdrawing participants were: resting heart rate greater than 120 beats per minute (BPM) for more than 60 minutes; hypertension (two consecutive readings within one hour of each other where the systolic blood pressure [SBP] was greater than 160mmHg, or the diastolic blood pressure [DBP] greater than 100mmHg); clinically significant psychosis; or significant or serious adverse event related to the study drug. Other withdrawal criteria were diversion of study medication, missing more than one planned medical review, and missing three or more doses of study drug over a 7-day period. Full details of the study protocol were published prior to study completion (18), and the study was listed on the Australian and New Zealand Clinical Trials Registry (ACTRN12615000391572).

Outcome Measures

The primary outcomes of the study were the safety, tolerability, and regimen completion of ascending doses of LDX in adults with MA dependence.

Safety was assessed with a number of measures. Blood pressure, pulse, and temperature were recorded daily. Participants were assessed weekly by a physician and had treatment emergent adverse events (TEAEs) recorded. TEAEs were volunteered by the participants during or between visits, as well through physical examination, laboratory test, or other assessments. Severity of TEAEs was determined by a site principal investigator (both addiction medicine specialists). Severity of symptoms was graded as mild if they caused no or minimal interference with usual social and function activities and required no intervention. Moderate TEAEs were those which caused greater than minimal interference with usual social and functional activities, requiring only minimal intervention. Severe TEAEs were classified as those which resulted in an inability to perform usual social and functional activities and medically significant events which required intervention. Serious adverse events (SAEs) were medically significant events that were; fatal or life-threatening; resulted in persistent or significant disability or incapacity; or required unplanned inpatient hospitalisation. The Psychosis and Hostility items of the Brief Psychiatric Rating Scale (BPRS) (22) were administered weekly. The Insomnia Severity Index (ISI) (23), Patient Health Questionnaire 9 (PHQ9) (24) and the Generalised Anxiety Disorder 7 (GAD7) scale (25) were administered every two weeks and at Follow-up, measuring insomnia, depression, and anxiety respectively. The Patient Health Questionnaire 15 (26) was administered to assess for changes to somatic symptoms and weight in kilograms measured every four weeks. ECGs were recorded at Baseline and at Weeks 2 and 4.

Tolerability of LDX was assessed by the side-effects item of the Treatment Satisfaction Questionnaire for Medication (TSQM) (27), administered weekly from Week 1, and at Follow-up.

Regimen completion was defined as the proportion of participants enrolled who completed the escalation phase to the end of Week 4, at which point they would have received at least five days of 250mg of LDX.

Secondary outcomes were: efficacy measures; change in other substance use; medication acceptability; potential for non-prescription use; adherence; and neurocognitive functioning. Efficacy measures comprised changes in MA use (self-reported and urine screen), withdrawal, craving, severity of dependence, HIV transmission risk and criminal behaviours as well as participant-reported effectiveness measures. MA and other substance use was recorded weekly with a validated self-report tool, the Time Line Follow Back Questionnaire (TLFB) (28, 29). Urine samples were obtained weekly, and tested for the presence of MA. Craving and withdrawal were measured weekly from Baseline and at Follow-up. Craving was measured with a single item 0-100 Visual Analogue Scale (VAS) (30) and withdrawal with the Amphetamine Withdrawal Scale (AWS) (31). Severity of dependence was measured with the Severity of Dependence Scale (SDS) (32) at Baseline, Week 8 and Follow-up. The HIV risk behaviour and crime sections of the Opiate Treatment Index (OTI) (33) were completed at Baseline, Weeks 4 and 8, and at Follow-up. The TSQM Questionnaire (27) was administered weekly from Week 1 and at Follow-up to measure self-rated medication effectiveness, convenience and global satisfaction. Potential for non-prescription drug use was measured weekly from Baseline until Week 4 using the Drug Effects Questionnaire 5 (DEQ5) (34), the Acute Subjective Response to Substances questionnaire (ASRS) for amphetamines (35), a VAS to measure similarity to methamphetamine, and asking participants what price they would pay for the drug (PWP) (36).

General cognition was assessed using the Wechsler test of adult reading (37) and the Montreal Cognitive Assessment (38) at Baseline. Paper-based neurocognitive tests were administered at Baseline, Week 2, Week 4, and at Follow-up 4 weeks after drug discontinuation assessing switching (Trail making test (39, 40)), working memory (Digit-sequencing (41)) and verbal learning and memory (Rey Auditory Verbal Learning Task (42)). Electronic neurocognitive testing was conducted using the Penscreen Six software (43) on an Android 7” tablet assessing: processing speed (Digit-symbol test (41)), sustained attention (Rapid Visual Information Processing), attention/focus (Arrow flankers (44)) and inhibition (go/no-go (44)) weekly from Baseline until Week 4 and at Follow-up (45).

Statistical Analysis

Adverse events were described by the proportion of participants who experienced TEAE by type, severity and dose. Non-parametric tests of paired data (Wilcoxon rank-sum test) were performed for measures taken at the beginning of Week 1 (Baseline), and compared to those taken at the primary endpoint, the end of Week 4 (at presumed steady state of 250 mg/day of LDX). Mixed Models for Repeated Measures (MMRM) were performed for primary cardiovascular (SBP, DBP, and heart rate) and neurocognitive outcomes. MMRM analyses makes use of all available data and is reliable for effect estimates under missing at random (MAR) assumption. The secondary outcomes of does adequacy, medication acceptability, and potential for non-prescription use are described using median scores and interquartile ranges at each dose. Missing urine drug results are assumed positive for methamphetamine. As per protocol, change in days of MA use were analysed separately for participants who partook in at least four sessions of counselling over the eight week trial period. Other secondary outcomes were tested for statistical significance with Wilcoxon rank-sum test for non-parametric data.

Results

Study sample

Of the 68 potential participants pre-screened for the study, sixteen were enrolled and commenced on the LDX regimen (**Figure 1**) between June 2015 and December 2016. Mean age of the 16 participants was 41 years (SD 6.7), and 75.0% (n=12) were male. Other sample demographics at study enrolment are provided in **Table 1**. Participants had a mean of 12 years (SD 8.4) problematic MA use and had used MA a mean of 21 days (SD 5.4) of the previous 28.

Primary Outcomes

Regimen completion

Fourteen (87.5%) participants achieved each of the doses of 100mg, 150mg, 200mg, and the primary endpoint of 250mg at the end of four weeks. Ten participants (62.5%) completed eight weeks of study drug and 12 (75.0%) were followed up four weeks after the last dose.

Two participants (12.5%) withdrew prior to the primary endpoint at the end of Week 4. One participant stopped presenting to the clinic after five days of 100mg LDX in Week 1. At follow up the participant reported: “I’m OK pills made me angry and not nice feeling don’t won’t [sic] to continue”. The other participant withdrew in Week 1 due to relocation away from study site.

Four participants (25.0%) were withdrawn due to non-adherence (missing three doses in a five day period after the escalation regimen was completed) after reaching the primary endpoint but prior to study completion: one (6.3%) in Week 6 (at the 200mg dose); two (12.5%) in Week 7 (150mg dose); and one (6.3%) in Week 8 (100mg dose) (see **Figure 1**).

Adverse Events

No participant was withdrawn due to TEAEs. The proportion of participants experiencing TEAEs by dose, week and severity are shown in **Figure 2.** There was one (6.3%) SAE of suicidal ideation requiring hospitalisation, deemed possibly study-drug-related and classified as severe. This SAE occurred on the final day of the de-escalation regimen. The participant had a prior history of self-harm, which had not been disclosed during screening. The SAE resolved following a seven-day admission in a short stay psychiatric emergency care centre during which time atomoxetine was commenced. There were three moderate TEAEs (18.8% of participants who received at least one dose of study drug): irritability (Week 1, 100mg); viral respiratory illness (Week 7, 150mg de-escalation phase); and an episode of hypomania during the follow-up period (four weeks after LDX cessation). All were determined to be possibly study-related. An additional eight (50.0%) participants experienced at least one mild TEAE. TEAEs occurring in at least two participants throughout the 12 week study are shown in **Table 2**.

No clinically significant hostility or psychosis was detected using the relevant BPRS items (22). No participant met the study protocol discontinuation parameters for elevated SBP or experienced a treatment-limiting adverse cardiovascular event. One participant had a single DBP reading of 101mmHg and heart rate of 134bpm after 5 days of 100mg LDX. Another participant had a single pulse reading of 124bpm during Week 3 (after 5 days of 200mg LDX), which was assessed to be not clinically significant. Participants' mean change in SBP over the escalation regimen (Baseline to end of Week 4) was +3.4mmHg (range -21.0 to +27.0, standard deviation [SD] 14.6), mean change in DBP was -0.4mmHg (range -22.0 to +24.0, SD 14.5), and mean change in heart rate was 7.3bpm (range -17.0 to +37.0, SD 13.4). Individual level change for cardiovascular outcomes are shown in **Figures 3-5**. Post hoc analysis did not detect significant correlation between frequency of MA use on enrolment and change in blood pressure (SBP: rho=0.04, p=0.88; DBP: rho=0.16, p=0.57). Mixed-effect Model Repeated Measure (MMRM) demonstrated no significant overall difference across the five time-points in either SBP [F(4, 39)=1.43, p=0.241], DBP [F(4,35)=0.07, p=0.990], or HR [F(4,35)=1.30, p=0.288], all measured at peak LDX concentrations (four hours post-dose) over the course of the escalation regimen, the multiple comparison of each post-baseline measure versus baseline are summarised in **Table 3**. Daily measurements of tympanic temperature were within normal range.

Study Drug Tolerability

Participant-rated treatment tolerability of LDX using the TSQM side effects item (27) was high, with no significant difference detected (z=-0.639, p=0.524) between the lowest dose at Week 1 and the highest escalated dose at the end of Week 4 (**Table 4**).

Secondary Outcomes

Secondary outcomes are provided in **Table 4**. Days of MA use decreased significantly over the four week escalation regimen from a median of 21 (IQR: 16-23) to 13 days (IQR: 11-17) of the previous 28 days (z=-2.485, p=0.013). Individual level data of MA use are given in **Figure 6**. Participants who had attended four or more sessions of counselling (n=9) during the eight week period had a significant decrease (z=-2.075, p=0.038), which differed from those who did not (n=7, z=-1.461, p=0.144). All urine drug screens provided during the escalation phase (Weeks 1 to 4) were positive for MA. A post hoc analysis showed three participants achieved two consecutive weeks of self-reported abstinence during the eight weeks of LDX administration. There was a significant decrease in craving from a median of 64mm (IQR: 20-85) to 31mm (z=-2.105, p=0.035) on a VAS. Five (36%) of the participants reported slight increase in the frequency of other substance use over the four weeks (alcohol, tobacco, gamma-hydroxybutyrate, heroin), with four (29%) of these having a concurrent reduction in MA use. Self-reported medication efficacy using the TSQM was rated significantly higher at the end of Week 4 than at Week 1 (z=-2.301, p=0.021). Adherence to study medication was maintained from Week 2 to Week 5, with no participants missing more than two days of study medication in a seven-day period. There was an indication of improvement amongst participants in sleep quality, physical and mental health measures, and weight over the four week period**.** The "high" item of the DEQ-5 questionnaire increased from a median score of 9

(IQR: 2-35) to 28 (IQR: 5 – 48) (z=-2.622, p=0.009). Other non-significant changes are reported in **Table 5**. Large magnitude improvements in focused attention (Hedges' g=1.59 at peak dose) and inhibitory control (Hedges' g=1.12 at peak dose) were seen over the course of the trial and were maximal at 200mg and above. Moderate magnitude but non-significant improvements were apparent on measures of processing speed and sustained attention (Hedges' g >0.6 at peak dose for Digit Symbol, Trails A, RVIP). No meaningful changes were observed in working memory, learning, retention and switching (Hedges' g <0.4 at peak for all) (**Table 5**).

Discussion

We found that dose escalation of LDX over 4 weeks to a maximum of 250mg/day appeared to be safe in people who use methamphetamine frequently (at least 14 out of the previous 28 days).

The physiological effects of LDX were not treatment-limiting in this sample. Changes in participant blood pressure and heart rate at the completion of the escalation to 250mg were mild and non-significant. This contrasts with a study among stimulant-naive populations where single sequential doses up to 250mg per day observed dose-dependent adverse changes in blood pressure, with more than half of their participants (11 of 20) withdrawn due to meeting blood pressure endpoints (17). These findings were not observed in a study of up to 250mg LDX daily among people with stable schizophrenia treated with antipsychotic medication, which may attenuate the pressor effects of LDX (17). In our study, tolerance to the pressor effects may result from chronic stimulant exposure among methamphetamine dependent participants (46), though the small study sample prevents any conclusions on inverse correlation between frequency of MA use prior to enrolment and change in blood pressure.

One SAE was reported during the study. A participant reported suicidal ideation on the last day of the eight week LDX administration period, and required hospitalisation. Additionally, one participant withdrew from the study due to feelings of anger and hostility. This occurred at the lowest dose (100mg) during Week 1, and was likely related to the drug rather than to the dose. While no clinically significant results were obtained with the BPRS, these events suggest it would be prudent to ensure close monitoring of the mental state of patients receiving higher doses of LDX, as well as comprehensive treatment planning for when the drug is ceased. The slight increase in other substance use over the escalation period suggests that this should also be monitored during periods of LDX administration.

Other TEAEs reported during the study likely to be drug related were known side effects of LDX (agitation, headache, loose stool, decreased appetite, and jaw clenching). Other measures of general health (weight, PHQ-15, PHQ-9, GAD-7) either improved or showed no deterioration, and participant subjective rating of side effects (TSQM-side effects) show high participant tolerability of LDX at all doses. These findings support the feasibility and acceptability of LDX as a possible pharmacotherapy for MA dependence.

A reduction in self-reported MA use was significantly associated with LDX administration, indicating possible efficacy as a treatment for MA dependence. In addition, three participants achieved two consecutive weeks of self-reported MA cessation by the end of the eight weeks of LDX administration.

Higher rates of MA cessation could be obtained by a period of longer than two weeks at the highest dose of 250mg LDX; and higher doses could be explored. There was also a significant decrease in MA craving, as well as subjective rating of drug efficacy, supporting the utility of larger trials of LDX for this population. The high proportion of participants (n=14 [87.5%]) to complete the protocol to the highest dose is also promising, given studies in this population are typically challenged by low recruitment and low retention (8).

LDX is theorised to have lower propensity for non-prescription use, having a slower onset of action than similar agonist formulations such as dexamphetamine and methylphenidate (47, 48). Studies show lower drug-liking for LDX compared to other stimulant medications for doses up to 100mg (49). In this study, the DEQ-5 item “Do you feel high?”, increased from 9mm at baseline but remained low at 29mm at 250mg/day LDX on a 100mm VAS, a clinically insignificant finding. PWP remained consistent at AUD $5 across dose ranges, and other changes in the drug liking effects were not significant. This indicates that LDX may have less potential for non-prescription use than other candidate agonists.

Neurocognitive data showed no safety concerns and promising efficacy signals, with moderate to large magnitude improvements in processing speed, focussed attention, sustained attention and inhibitory control. No meaningful changes in measures of working memory, learning, retention and switching were seen. Performance improvement may reflect task learning due to the repeated administration of neurocognitive assessments. General improvements on speeded tasks may be due to the stimulant effects of LDX, as improvements were dose-dependent, though the improvement of both speed and accuracy in some tasks may indicate a more general effect rather than enhanced speed. It is also possible that improvement reflects stabilisation of cognitive performance with chronic/tonic stimulant use compared with phasic/intermittent illicit stimulant use, with most participants continuing illicit stimulant use during the study. Should LDX enhance cognition even among people with unstable use, this may have additional benefits in treatment adherence and functional outcomes. These findings require clarification in randomised controlled trial settings where task learning effects can be established, and associations between cognition and functional outcomes assessed.

This study has a number of limitations. The small sample size and short duration of treatment is typical of pilot safety studies; but the study is not powered to explore efficacy and this precludes more sophisticated statistical analysis. The maximum dose tested with the protocol was chosen on the basis of equivalence of doses of dexamphetamine used in agonist maintenance therapy in this population (15). Although we tested 250mg, this was not dose-limiting; it remains possible that a higher dose might yield greater benefits. Further studies of longer duration with larger sample sizes are required. Our group is currently conducting a multi-centre, randomised, controlled trial to assess efficacy (ACTRN12617000657325) (50).

Conclusions

For people with MA dependence, this study is the first to demonstrate the safety, tolerability and acceptability of higher doses of LDX than used for ADHD. Findings suggest the feasibility of larger scale studies to determine the efficacy of LDX for this indication.

Declarations

Ethics approval and consent to participate

Ethics approval was granted by the St Vincent's Hospital Sydney Human Research Ethics Committee for both study sites (HREC/14/SVH/202). All participants provided written, informed consent.

Consent for publication

N/A

Availability of dataset

The datasets generated and/or analysed during the current study are not publicly available due to the small sample size but are available from the corresponding author on reasonable request.

Competing interests

NE and AC are employed by St Vincent's Hospital Sydney, a public health service funded by the NSW Ministry of Health. BC is employed by St Vincent's Health Australia and has no conflicts to declare. AD is employed by Hunter New England Local Health District, a public health service funded by NSW Health and reports research and travel support from Braeburn/Camurus, research support from Indivior, and has served on an advisory board for Mundipharma, all for unrelated work. RB has received investigator-initiated untied educational grants from Reckitt Benckiser/Indivior for the development of an opioid-related behaviour scale and a study of opioid substitution therapy uptake among chronic non-cancer pain patients. RB has received an untied educational grant from Mundipharma for a postmarketing study of reformulated oxycodone. 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, all of which are unrelated to this present study. ZL is employed by UNSW and has no competing interests to declare. KJS is employed by UNSW and has received unrelated travel sponsorship from Gilead Sciences. NL is employed by South East Sydney Local Health District, a public health service funded by the NSW Ministry of Health; he has received research funding from Camurus, and has served on Advisory Boards for Mundipharma, Camurus and Indivior for work unrelated to this study.

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design or the reporting of the study.

Authors' contribution

NE, BC, AJD, RB, AC, KJS & NL designed the study. NE, BC, and KJS drafted the manuscript. BC & ZL undertook statistical analyses. NE & AJD were site leads. All authors critically revised and approved the final manuscript.

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Abbreviations

ADHD: Attention-Deficit/Hyperactivity Disorder

AE: Adverse Event

ASRS: Acute Subjective Response to Substances

AUD: Australian dollars

AWS: Amphetamine Withdrawal Scale

BED: Binge eating disorder

BL: Baseline

BPM: Beats per minute

BPRS: Brief Psychiatric Rating Scale

CBT: Cognitive Behaviour Therapy

DEQ5: Drug Effects Questionnaire 5

DBP: Diastolic Blood Pressure

ECG: Electrocardiogram

GAD7: Generalised Anxiety Disorder 7

GHB: Gamma-Hydroxybutyrate

hCG: Human Chorionic Gonadotropin

HCV: Hepatitis C Virus

HIV: Human Immunodeficiency Virus

HR: Heart rate

ICD-10: International Classification of Diseases 10th Revision

IQR: Interquartile Range

ISI: Insomnia Severity Index

LDX: Lisdexamfetamine

MA: Methamphetamine

MAR: Missing at Random

mg: Milligram

mmHg: Millimetres of Mercury

mm: Millimetre

MMRM: Mixed effect Model Repeated Measurement

OTI: Opioid Treatment Index

PHQ9: Patient Health Questionnaire 9

PWP: Price Would Pay

SAE: Serious Adverse Event

SBP: Systolic Blood Pressure

SD: Standard Deviation

SE: Standard Error

SDS: Severity of Dependence Scale

TEAE: Treatment Emergent Adverse Event

TLFB: Timeline Follow Back

TSQM: Treatment Satisfaction Questionnaire for Medications

USA: United States of America

VAS: Visual Analogue Scale

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Tables

Table 1: Sample characteristics at enrolment

Demographics	All (n=16) n (% [unless otherwise indicated])
Mean age (SD)	41 (6.7)
Gender	
Cis-male	12 (75.0)
Cis-female	4 (25.0)
Aboriginal/Torres Strait Islander	2 (12.5)
Sexual Identity	
Heterosexual	9 (56.3)
Gay or lesbian	3(18.8)
Bisexual	3 (18.8)
Something else	1 (6.3)
Medical History	
HIV infection	3 (18.8)
HCV infection	5 (31.3)
Self-reported history of childhood ADHD diagnosis	2 (12.5)
Wender Utah Rating Scale[a] >46	7 (43.8)
Current Opioid Agonist Therapy	2 (12.8)
Other Substance Use (prior 28 days)	
Tobacco	10 (62.5)
Cannabis	5 (31.3)
GHB	4 (25.0)
Alcohol	3 (18.8)
Opioids (oxycodone/heroin)	2 (12.5)
Methamphetamine use	**Mean (SD)**
Age at first use (years)	22 (9.0)
Years of self-reported problematic use	12 (8.4)
Days use of previous 28	21 (5.4)
Reported injecting MA in past 28 days n (%)	12 (69.0)
Neurocognition	**Mean (SD)**
Montreal Cognitive Assessment (MoCA)	26 (2.6)
MoCA <26, n (%)	8 (50.0)
Wechser Test of Adult Reading (Estimated WAIS-III IQ)	105 (11.4)

[a] Score >46 considered positive for the retrospective assessment of the presence of symptoms of ADHD in childhood

Table 2. Adverse Events reported by at least 2 participants at any time (Baseline to Week 12)

Adverse event category	n (%)
Agitation/irritability	4[a] (25.0)
Cardiovascular	2 (12.5)
Gastrointestinal	4 (25.0)
Headache	3 (18.8)
Loss of appetite	2 (12.5)
Muscular tension/jaw clenching	3 (18.8)
Pain	3 (18.8)
Psychiatric	2[b] (12.5)
Respiratory complaints	3 (18.8)
Skin/soft tissue/mucosal infections	5 (31.3)
Sleep disturbances	2 (12.5)

n = number of people reporting AE, %= of total sample (n=16)

[a] including one participant in Week 1 who was subsequently withdrawn due to lack of adherence to protocol (missed 3 doses)

[b] including one participant meeting definition of a serious adverse event (admission to hospital)

Table 3: Cardiovascular Safety Parameters (n=16)

	BL to Week 1: estimate (SE) p-value*	BL to Week 2: estimate (SE) p-value*	BL to Week 3: estimate (SE) p-value*	BL to Week 4: estimate (SE) p-value*
Unadjusted				
SBP (4-hours post dose)	5.5 (3.4) p=0.436	-1.6 (3.5) p=1	2.7 (3.6) p=1	3.3 (3.8) p=1
DBP (4-hours post dose)	-0.8 (2.9) p=1	0.9 (3.1) p=1	0.1 (3.1) p=1	-0.7 (3.4) p=0.1
HR (4-hours post dose)	4.2 (2.9) p=0.633	3.0 (3.1) p=1	6.6 (3.1) p=0.172	6.2 (3.4) p=0.303
Adjusted (for: age; sex at birth; baseline methamphetamine use [days])				
SBP (4-hours post dose)	5.8 (3.4) p=0.368	-1.7 (3.5) p=1	2.5 (3.5) p=1	3.2 (3.7) p=1
DBP (4-hours post dose)	-0.3 (2.9) p=1	0.3 (3.1) p=1	-0.5 (3.1) p=1	-1.4 (3.4) p=1
HR (4-hours post dose)	4.1 (2.9) p=0.662	2.9 (3.1) p=1	6.6 (3.1) p=0.174	6.2 (3.4) p=0.305

All analyses use Mixed Models for Repeated Measures

BL=baseline

[a] at two consecutive readings at least 60 minutes apart

[b] for greater than 60 minutes

* Bonferroni correction for multiple comparisons (4 pairs) applied

Table 4: Outcomes

	All Enrolled (n=16) Baseline	*Completed Week 4 (n=14) Baseline*	*Completed Week 4 (n=14) Week 4*	*z-score*	*p-value*	*Completed Week 8 (n=10)*	*Followed up Week 12 (n=12)*
Primary outcomes							
SBP mmHg (Median [IQR])	119 (101-136)	119 (103-130)	123 (112-130)	-0.980	0.327	124 (118-130)	129 (106-131)
DBP mmHg (Median [IQR])	77 (65-90)	77 (65-89)	74 (67-85)	-0.031	0.975	78 (76-82)	80 (72-83)
Heart Rate bpm (Median [IQR])	90 (76-96)	89 (73-93)	90 (76-103)	-1.888	0.059	81 (75-91)	82 (77-83)
Weight (kg) (Median [IQR])	73 (68-82)	73 (68-76)	74 (69-83)	-2.264	**0.024**	-	73 (67-80)
Insomnia (ISI) (Median [IQR])	11 (5-15)	10 (5-13)	7 (3-9)	-2.208	**0.027**	9 (1-14)	7 (3-10)
Physical health (PHQ15) (Median [IQR])	8 (5-10)	7 (5-9)	6 (3-8)	-2.847	**0.004**	7 (3-10)	5 (2-9)
Depression (PHQ9) (Median [IQR])	11 (7-14)	11 (7-14)	4 (3-9)	-3.050	**0.002**	8 (6-10)	9 (8-11)
Anxiety (GAD7) (Median [IQR])	9 (5-11)	9 (5-10)	4 (1-9)	-2.600	**0.009**	6 (1-8)	7 (4-10)
TSQM – tolerability (Median [IQR])	100 (86-100)	100 (88-100)	100 (98-100)	-0.638	0.524	100 (84-100)	100 (89-100)
Secondary outcomes							
Methamphetamine use (days out of last 28) (Median [IQR])	21 (16-23)	21 (18-26)	13 (11-17)	-2.485	**0.013**	11 (2-13)	13 (9-19)
Urine Drug Screen for methamphetamine (n [%] negative)	0 (0.0)	0 (0.0)	0 (0.0)	-	-	3 (18.8%)	1 (6.3%)
Cravings (VAS) (Median [IQR])	64 (20-85)	64 (23-82)	31 (12-52)	-2.105	**0.035**	40 (22-67)	42 (22-87)
Withdrawal (AWQ) (Median [IQR])	16 (9-18)	16 (10-18)	12 (7-18)	-1.022	0.307	9 (7-22)	13 (11-20)
Medication efficacy (TSQM) (Median [IQR])	50 (37-68)[a]	50 (39-67)[a]	64 (50-79)	-2.301	**0.021**	69 (58-82)	80 (63-83)
Medication convenience (TSQM) (Median [IQR])	78 (61-83)[a]	78 (67-83)[a]	83 (56-100)	-0.513	0.608	78 (63-83)	61 (56-78)
Medication global satisfaction (TSQM) (Median [IQR])	64 (48-87)[a]	64 (50-86)[a]	71(63-88)	-1.792	0.073	75 (66-79)	79 (71-100)

Crime (OTI) (Median [IQR])	2 (0-5)	3 (0-7)	0 (0-2)	-2.038	**0.042**	-	0 (0-0)
HIV risk behaviour (OTI) (Median [IQR])	11 (7-14)	10 (7-12)	9 (5-14)	-0.979	0.327	-	10 (8-17)
Severity of Dependence Scale (Median [IQR])	11 (8-12)	11 (8-12)	-	-	-	11(10-12)	11 (9-12)
Drug liking							
Price Would Pay (AU$) (Median [IQR])	8 (0-33)	5 (0-20)	5 (0-30)	-0.813	0.416	-	-
ASRS (Median [IQR])	3 (2-7)	3 (3-7)	3 (3-7)	-0.239	0.811		
Similarity to MA (Median [IQR])	22 (8-52)	17 (8-45)	20 (5-57)	-1.224	0.241	-	-
DEQ5 “Feel” item (Median [IQR])	15 (8-46)	15 (7-46)	26 (13-45)	-0.221	0.221	-	-
DEQ5 “More” item (Median [IQR])	48 (17-85)	48 (13-80)	49 (9-86)	-0.804	0.421	-	-
DEQ5 “High” item (Median [IQR])	9 (2-35)	9 (2-24)	28 (5-48)	-2.622	**0.009**	-	-
DEQ5 “Like” item (Median [IQR])	40 (11-58)	40 (11-45)	47 (20-62)	-1.258	0.208	-	-
DEQ5 “Dislike” item (Median [IQR])	4 (0-12)	5 (1-12)	2 (2-28)	-0.105	0.916	-	-

[a] measured at Week 1

Table 5: Cognitive effects of lisdexamfetamine (n=16)

Domain	Measure	Overall Effect	BL to 100mg: Estimate (SE) Sidak-adj p	BL to 150mg: Estimate (SE) Sidak-adj p	BL to 200mg: Estimate (SE) Sidak-adj p	BL to 250mg: Estimate (SE) Sidak-adj p	BL to FU: Estimate (SE) Sidak-adj p
Unadjusted Processing speed	Trail making test (A)	**F(3, 11)=4.80, p=0.022**		1.8 (1.9) p=0.931		**6.4 (1.9) p=0.017**	3.8 (2.4) p=0.577
Processing speed	Digit Symbol RT	**F(5, 16)=3.43, p=0.026**	237.3 (135.8) p=0.795	366.1 (150.4) p=0.300	313.6 (137.5) p=0.425	345.0 (136.7) p=0.289	317.9 (140.0) p=0.423
Attention	Flankers RT	**F(5, 38)=9.07, p<0.001**	27.8 (13.5) p=0.496	**44.4 (14.0) p=0.035**	**50.1 (12.5) p=0.010**	**58.3 (12.5) p<0.001**	16.6 (17.1) p=0.998
Attention	Flankers Percent Correct	F(5, 29)=2.18, p=0.084	0.5 (0.2) p=0.188	0.2 (0.3) p=0.999	0.5 (0.2) p=0.085	0.3 (0.2) p=0.768	0.2 (0.3) p=0.999
Sustained attention	RVIP RT	**F(5, 16)=3.26, p=0.032**	28.3 (25.5) p=0.992	**70.1 (19.5) p=0.031**	58.9 (22.2) p=0.189	60.7 (18.1) p=0.058	73.3 (25.2) p=0.153
Sustained attention	RVIP Percent Correct	**F(5, 14)=5.42, p=0.011**	0.4 (1.2) p=0.999	*3.2 (1.0) p=0.061*	**3.9 (1.1) p=0.019**	2.8 (1.2) p=0.332	2.9 (1.2) p=0.262
Working memory	Digit Sequencing Span	F(3, 12)=1.79, p=0.202		1.2 (0.6) p=0.377		0.3 (0.5) p=0.980	0.9 (0.5) p=0.510
Immediate memory	RAVLT Trial 1	F(3, 11)=0.55, p=0.660		0.3 (0.6) p=0.998		0.6 (0.5) p=0.791	0.5 (0.6) p=0.978
Learning	RAVLT Trials 1-5	F(3,13)=3.01, p=0.068		4.1 (3.2) p=0.783		1.9 (3.1) p=0.990	7.0 (2.4) p=0.125
Retention	RAVLT % Retained	F(3, 18)=0.52, p=0.677		-0.6 (10.3) p=0.999		4.3 (8.5) p=0.997	-4.4 (10.6) p=0.999
Switching	Trail making test (B)	**F(3, 13)=5.18, p=0.015**		5.2 (8.9) p=0.993		7.9 (7.6) p=0.892	**18.0 (6.2) p=0.029**
Inhibition	Go-NoGo False Positives	**F(5, 21)=6.53, p=0.001**	**2.3 (0.6) p=0.015**	**2.4 (0.7) p=0.016**	2.6 (0.9) p=0.097	**2.9 (0.5) p=0.001**	**3.0 (0.6) p=0.001**
Adjusted Processing speed	Trail making test (A)	F(3,10)=2.91 p=0.090		0.1 (2.4) p=0.999		5.6 (2.6) p=0.240	4.2 (3.5) p=0.840
Processing speed	Digit Symbol RT	F(5, 12)=2.08 p=0.141	322.5 (157.3) p=0.599	414.7 (177.6) p=0.362	383.9 (163.1) p=0.382	383.9 (163.1) p=0.263	394.7 (169.0) p=0.399
Attention	Flankers RT	**F(5, 40)=9.13 p<0.001**	34.3 (14.0) p=0.227	**51.3 (14.7) p=0.013**	**60.5 (15.3) p=0.002**	**68.8 (13.9), p<0.001**	24.1 (18.0) p=0.956
Attention	Flankers Percent Correct	F(5, 30)=1.22 p=0.323	0.3 (0.2) p=0.727	0.1 (0.3) p=0.999	0.3 (0.2) p=0.863	0.1 (0.2) p=0.999	0.1 (0.3) p=0.999

Sustained attention	RVIP RT	F(5, 15)=2.07 p=0.125	10.2 (30.7) p=0.999	54.6 (24.2) p=0.431	48.6 (31.0) p=0.876	48.3 (24.5) p=0.631	23.2 (25.6) p=0.999
Sustained attention	RVIP Percent Correct	F(5, 11)=2.37 p=0.105	-0.1 (1.5) p=0.932	*2.6 (1.3) p=0.055*	**3.4 (1.4) p=0.025**	*2.9 (1.6) p=0.081*	2.6 (1.7) p=0.131
Working memory	Digit Sequencing Span	F(3, 11)=0.93 p=0.461		1.3 (0.8) p=0.517		0.5 (0.6) p=0.970	0.4 (0.8) p=0.998
Immediate memory	RAVLT Trial 1	F(3, 9)=0.87 p=0.872		0.2 (0.8) p=0.999		0.2 (0.6) p=0.999	0.7 (0.9) p=0.969
Learning	RAVLT Trials 1-5	**F(3, 13)=4.46 p=0.024**		5.9 (4.3) p=0.722		3.0 (4.2) p=0.982	11.2 (3.1) p=0.088
Retention	RAVLT % Retained	F(3, 13)=0.03 p=0.994		-2.9 (12.3) p=0.999		-0.7 (9.9) p=0.999	0.5 (13.9) p=0.999
Switching	Trail making test (B)	*F(3, 14)=2.97 p=0.067*		8.1 (10.8) p=0.976		16.2 (9.5) p=0.486	*22.2 (7.9) p=0.068*
Inhibition	Go-NoGo False Positives	**F(5, 18)=5.04 p=0.005**	2.1 (0.7) p=0.114	1.6 (0.8) p=0.579	2.9 (1.1) p=0.208	**2.8 (0.7), p=0.010**	**3.1 (0.7) p=0.008**

All analyses use Mixed Models for Repeated Measures; Adjusted for: sex at birth; Wender-Utah ADHD score; WTAR performance and baseline days MA use; RAVLT % retained is RAVLT Trial 6 (delay) as a proportion of words recalled at Trial 5.

Figures

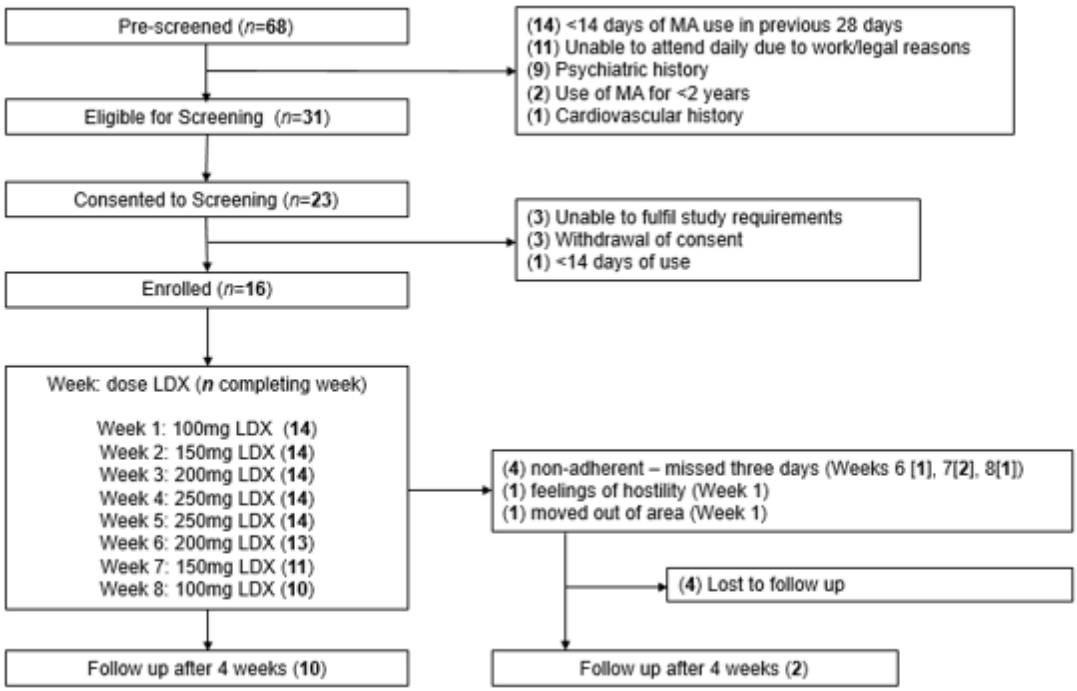

Figure 1

Study participant flow chart

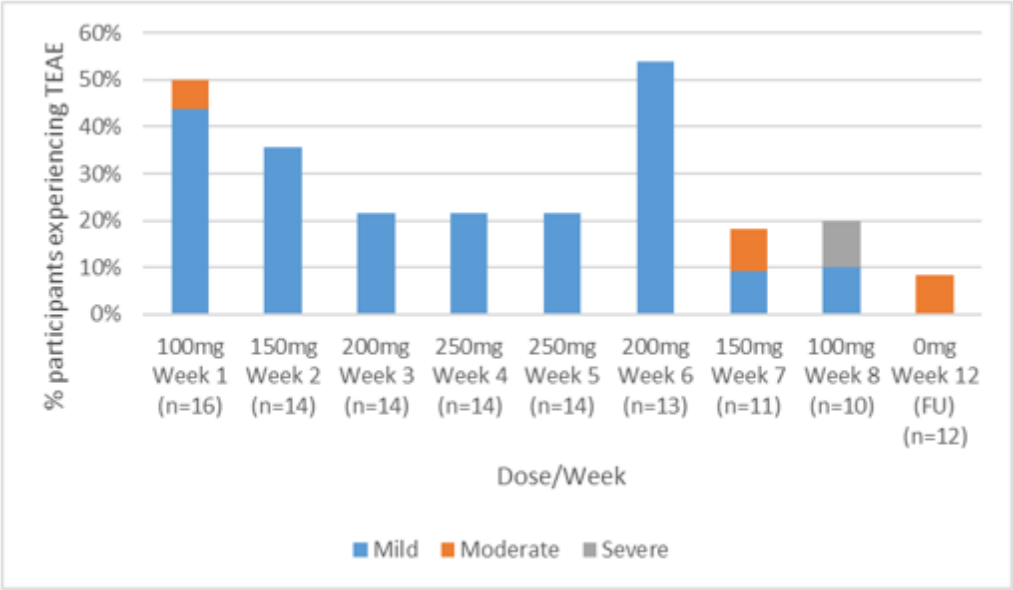

Figure 2

Proportion of participants experiencing adverse events by dose, week, and severity

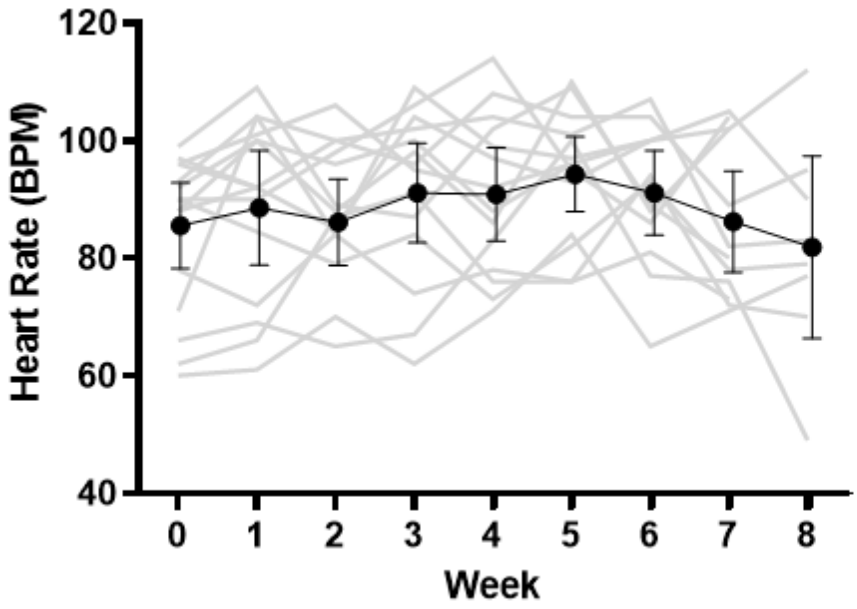

Figure 3

Change in heart rate

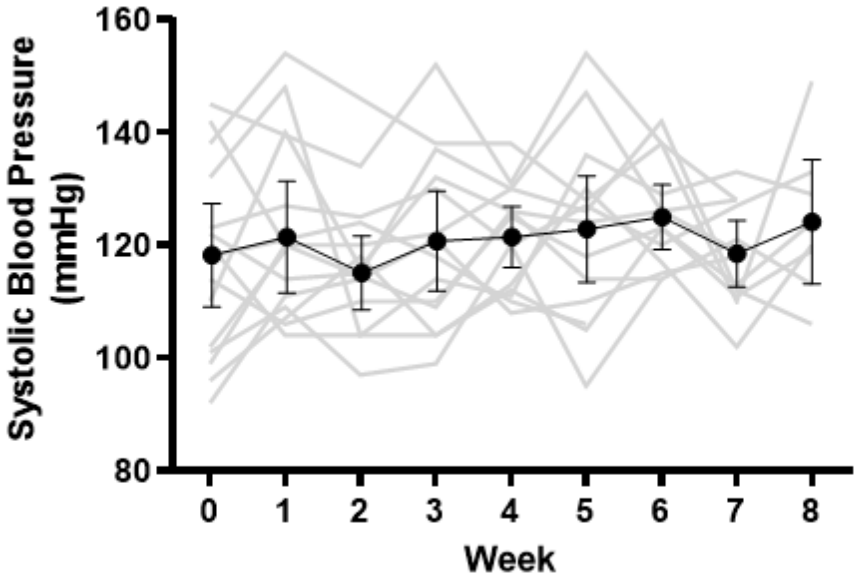

Figure 4

Change in systolic blood pressure

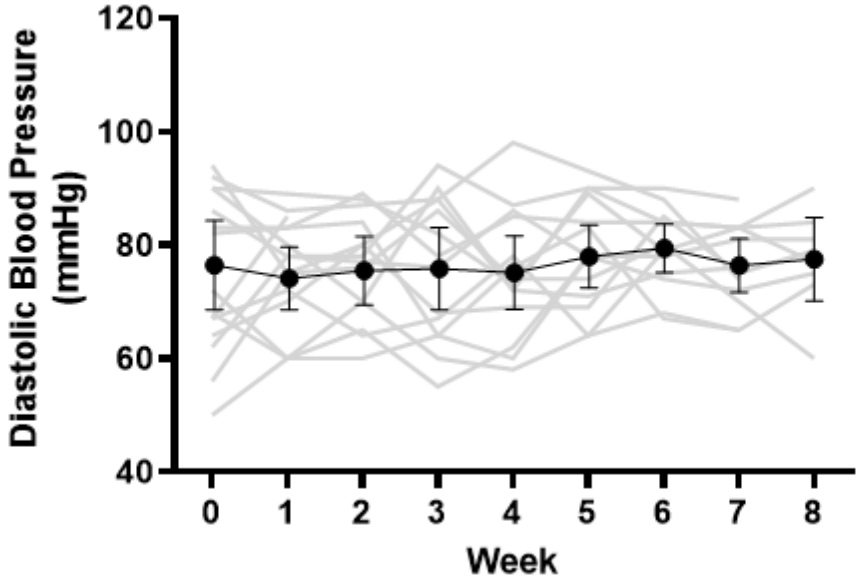

Figure 5

Change in diastolic blood pressure

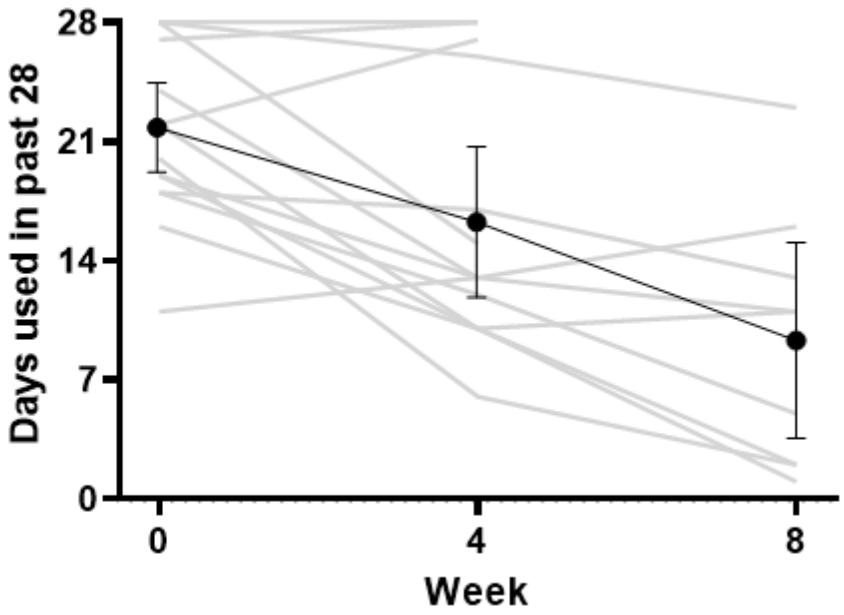

Figure 6

Change in days of methamphetamine use

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- LISDEXCONSORTChecklist.doc