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Hello Again, Colleagues,

Patients with methamphetamine (MA) use disorder present a treatment challenge. Contingency management has a good evidence base, though not always available or preferred by patients. **The question is often raised about whether providing a prescription for stimulants will indeed suppress or substantially reduce illicit MA use.** ASAM guidelines give tentative support to this practice based on meta-analyses that show marginal effects driven by findings in a few studies on higher-dose stimulants as well as observational data.^{1,2} The experimental trials are short-term, though treatment for this disorder will likely require long-term therapy. The article reviewed here and published in *Addiction* sought to deepen the evidence base for high-dose stimulant therapy with a multicenter randomized placebo control trial at several sites in Australia.

Participants in the trial received a placebo or a whopping **250 mg daily dose of lisdexamfetamine** (lisdex). The trial lasted 12 weeks, and the primary outcome was self-reported past 28 days of MA use at the end of the trial. Importantly, even though the trial required modifications to protocol due to interruption by C19 pandemic, participants visited a minimum of every 14 days and most commonly had **visits one to two times per week** (depending on when they enrolled). Patients were observed taking medication at those visits and were prescribed only enough to reach the next one. At baseline, study participants reported an average of 24 out of 28 days of use, and **at the end of the trial, there was a non-statistically significant difference of 2.2 days of use in the treatment group compared with the placebo.** 61% of the sample remained at the end of the study.

The authors did not appraise this as a negative trial and focused instead on one of 12 secondary outcomes: self-reported use over the entire 12-week trial. This is an outcome that is likely less reliable than the primary outcome, given the challenges of recalling daily substance use over a three-month period. In addition, there was no difference in urine drug tests between the two groups.

Contingency management remains the only treatment with substantial efficacy for MA use disorder and has a favorable safety profile. Prescribed stimulant therapy, even at this 'robust' dose, does not appear beneficial and has potential risks to patients and the community.

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Title: There is no benefit of high dose lisdexamfetamine x12weeks for reduction in methamphetamine (MA) use in MA use disorder.

Citation:

Ezard, N., Clifford, B., Siefried, K. J., Ali, R., Dunlop, A., McKetin, R., Bruno, R., Carr, A., Ward, J., Farrell, M., Graham, R., Haber, P., Lubman, D., Donoghoe, M. W., Olsen, N., Baker, A., Hall, M., Arunogiri, S., Lintzeris, N., & LiMA Investigator Group (2024). Lisdexamfetamine in the treatment of methamphetamine dependence: A randomised, placebo-controlled trial. *Addiction (Abingdon, England)*, 10.1111/add.16730. Advance online publication. <https://doi.org/10.1111/add.16730>

Link: <https://pubmed.ncbi.nlm.nih.gov/39701142/>

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METHODS

This is a randomized double-blind placebo-controlled trial that took place in six outpatient clinics in Australia from 2018 to 2021. Patients were recruited through local clinics and advertisements. They were included if they used MA at least 14 of the last 28 days and had one urine test positive for methamphetamine. Excluded were patients on opioid agonist therapy, severe psychiatric or other medical disorder, dependent use of alcohol or other substances that were considered potentially interfering with the study participation. Patients could not be taking another prescribed stimulant, and could not be under other monitoring (i.e., for child protection, court or work ordered testing).

Participants received placebo or lisdexamfetamine (lisdex) for 15 weeks. Those assigned to lisdex had a one-week induction at 150mg and 12 weeks of maintenance at 250mg and then tapered over two weeks. Patients were followed until four weeks after the end of treatment, but primary outcome took place at the end of the 12-week maintenance phase. Those who studied before the C19 pandemic had visits daily for 5days then twice per week and those who studied later had visits daily for 2days then weekly. There was no new enrollment during the height of pandemic lockdown (Apr – Oct 2020) but those who had study visits then were seen once every two weeks. At study visits, patients had supervised medication administration, urine sample collection, vital signs, and recording of adverse events. Any unused medication was counted and returned. Self-reported use was assessed weekly and one urine per week was selected at random for immunoassay analysis. There were long research visits every four weeks where additional safety measures were assessed. Patients received supermarket vouchers for these longer visits.

MAIN RESULTS

Average age of patients was 39yrs with 61% male, and 89% neither Aboriginal nor Torres Strait Islander. 73% were heterosexual, 46% had a year 10 education or less, 19% working full-time and 55% on a pension or benefit. 17% were homeowners, 39% had a +screen for childhood ADHD. Average use of MA in the last 28days was 24. 49% had any injection drug use.

164 patients enrolled and 155 started study med and were included in the analysis. Of those, 100 patients (50placebo, 50 lisdex) completed the week 13 follow up visit, for an attrition of 39%. Sample size was determined to detect a between group difference of 4.5days of use but actual power was lower due to a higher than anticipated attrition rate.

63% of those enrolled were enrolled and completed prior to pandemic (visits twice/week), none were enrolled during the pandemic, and 24% were enrolled post pandemic with a modified protocol (weekly visit). Only 14% were enrolled pre-pandemic and on study at pandemic onset. The post-pandemic cohort had an increased proportion of gay men and with a university education compared with pre-pandemic.

The primary outcome result was a non-significant OR of 0.72 (0.29-1.81, $p = .49$) for reduced days of use in the final 28days of the study. This corresponded to a 2.2 day between group difference. Sensitivity analysis attempting to evaluate impact of missing data assumptions didn't reach a different outcome.

Among 12 secondary outcomes all were nonsignificant except for self-reported days of use over the full 12wks of maintenance (52.7 days placebo vs 43.8 days lisdex) , and a non-significant but high OR (6.2) for those with self-reported 21days abstinence (4.5% in placebo vs 12.8% lisdex). In contrast, trine drug tests which were not different between groups at 4 or 12wks and there were no differences between measures of craving, withdrawal or dependence severity.

80% in the amphetamine group correctly guessed treatment, compared to 62% in the placebo group. There were higher self-reported scores for effectiveness and global satisfaction in the lisdex vs placebo group.

There were eight serious AEs: Five in lisdex and three in placebo (Lisdex: three overdoses, facial cellulitis and bipolar 1. Placebo: schizophrenia , psychosis, Crohn's). Nausea was the only adverse event that reached showed a statistical difference between the two groups (16 % lisdex vs 5% placebo).

CONCLUSION

12 weeks of high dose lisdexamfetamine treatment does not have significant impact on MA use in MA use disorder.

COMMENTARY

Internal validity (how likely are the study results what they appear to be for the study group)

Overall, the internal validity of this trial is good. The major limitation is high loss to follow up (39%) which may have underpowered the study. However, using the assumptions the authors used, this study had a 71% power to detect a 4.5-day difference and 80% power to detect a 5-day difference³ (where 80% power is standard). With this, it seems unlikely that the marked impact of treatment was missed.

Was loss to follow up different between groups? Not in number, though it is possible the losses were for different reasons and biased the results. A sensitivity analysis tried to assess for this impact and found no differences. And with knowledge about the natural history of MA use disorder, it's likely that the outcomes were not different between those lost.

Participants had high ability to guess to which group they were assigned – 80% in lisdex and 62% in placebo. This participant expectancy may influence results especially given this is a self-report outcome. It is unclear exactly what direction that influence would be. For example, some might feel ashamed of getting active compound without effect and therefore underreport more than placebo. Or would it make one assume they had used less. Could knowing you are getting placebo make you want to use more or could knowing you are getting active treatment build confidence to avoid use? Hard to say, but with MA use, it does not seem that subtle pushes lack big impact, so it again does not seem a clear threat to validity. Urine testing, which is more objective, found no difference between groups, as with the primary outcome.

External validity (Can these results be applied beyond the study?)

Patients received significantly more attention than they would in real world care, especially those seen outside of the pandemic (where 63% had twice weekly evaluation and 24% had weekly evaluation). In addition to high visit frequency, these groups would have had observed medication administration and urine testing. This is far more observation, contact and medication control than would likely be afforded in the present US healthcare system and would be expected to overestimate the positive impact of the medication and underestimate the negative, including effects on the community. This visit frequency requirement may have led to more dropout than would less observation.

Conclusion

This is a useful investigation of prior signals for high dose stimulants in treating MA use disorder. Recalling that methadone and buprenorphine's early efficacy was hampered by low dosing, it was an all the more compelling question to ask. However, this is a negative trial. Though the attrition may have reduced the power to find a difference, it is unlikely to have missed a significant impact and one that would merit the risk and resources involved in providing such care in the long term. Contingency management remains the only clearly effective approach to treating this challenging problem.

References

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