Administrative information

Title: Efficacy and Safety of Naltrexone for Amphetamine and Methamphetamine Use Disorder: A Systematic Review of Randomized Controlled Trials

Registration: This protocol is not submitted for registration

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Contributions: LL was responsible for the conception and design of the study. LL and SA were responsible for the process for selecting the study including screening. LL and SA determined the eligibility and inclusion of studies in the systematic review extracted data information independently later cross-checked. LL and JZ performed the quality of assessment independently. LL, XL, MLT, EW contributed to the drafting, revision and final approval of the manuscript.

Amendments: Not applicable

Funding: EWC has received funding from Early Career Scheme (Project No. 789813) and the General Research Fund (Project No. 17111615) from the Hong Kong Research Grants Council (both partially funded this study), Hong Kong Health and Medical Research Fund from Food and Healthy Bureau of Hong Kong; internal funding from The University of Hong Kong; and research funding from Bristol-Myers Squibb, Pfizer and Janssen. All unrelated to the current work.

Conflict of interest: Lam Lam, Shweta Anand, Xue Li, Man Li Tse, Jia Xiao Zhao, and Esther W Chan have no conflicts of interest to declare.

Introduction

Rationale:

Drug abuse remains one of the most prevalent health problems worldwide. There has been an expansion in the global market for amphetamine-type-stimulants (ATS) as it becomes increasingly available (1). Amphetamine is a widely abused potent sympathomimetic psychostimulant with a high potential for abuse that is currently indicated for the treatment of ADHD and narcolepsy (2-8). Another common ATS is methamphetamine, a derivative of amphetamine that is abused for its ability to increase wakefulness and decrease appetite (9). In recent years, methamphetamine intake increased substantially, becoming the second most abused illicit substance after cannabis (10, 11). Due to a large number of disorders caused, there is a surge in treatment-seeking-methamphetamine users, producing an immense burden on global health (1, 12-15). Despite this, there is currently no effective and approved pharmacological treatment by the Food and Drug Administration (FDA) for neither amphetamine nor methamphetamine use disorder (16, 17).

Naltrexone is a μ-opioid receptor antagonist currently indicated to treat alcohol and opioid use disorder (18-20). The mechanism for reducing rewarding effects has been shown to be caused by blocking opiate receptor occupancy (21). However, using dopamine antagonists are not recommended due to side effects at doses deemed effective (22). Due to the similar rewarding pathways of alcohol and drugs of abuse, there has been increasing interest to determine whether naltrexone may also potentially attenuate the subjective effects of amphetamines through blunting positive effects by blocking dopamine release when endogenous opioids are activated (23).

To our knowledge, there has been no previous systematic review done to assess the efficacy and safety of naltrexone on participants with amphetamine or methamphetamine use disorder. As there is great clinical importance in seeking a successful treatment for this global issue, we aim to evaluate the practicality in using naltrexone as a pharmacological treatment.

Objectives: We aim to evaluate the practicality in using naltrexone as a pharmacological treatment for amphetamine and methamphetamine use disorder.

Methods

This systematic review will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (24).

Information sources

Electronic resources such as PubMed, EMBASE Classic + 1980 – via Ovid, and Cochrane Library will be searched using keywords and/or headings such as: (naltrexone AND

amphetamine AND dependence) OR (naltrexone AND amphetamine AND craving) OR (vivitrol AND amphetamine) OR (revia AND amphetamine) OR (naltrexone AND amphetamine) OR (naltrexone AND methamphetamine dependence) OR (naltrexone AND methamphetamine AND craving) OR (vivitrol AND methamphetamine) OR (revia AND methamphetamine) OR (naltrexone AND ice) OR (naltrexone AND crystal meth) OR (naltrexone AND methamphetamine)

Study records

Endnote X8 will be used to store all citations of identified articles. Full texts were retrieved for studies with inclusion potential. All included studies will be cross-checked by both researchers (LL, SA) for applicability.

Quality assessment

Included studies were assessed using the Cochrane tool for risk of bias for all randomized controlled trials. Two researchers (LL, JZ) will conduct the assessment independently. Any discrepancies were reviewed by a third researcher (XL) and discussed to reach a final consensus.

Inclusion criteria

- Randomized controlled trials reporting effects of naltrexone on amphetamine or methamphetamine users
- Any route of administration of amphetamine or methamphetamine
- Any route of administration of naltrexone
- Amphetamine or methamphetamine dependent individuals according to the Diagnostic and Statistical Manual fourth edition
- Participants aged ≥18 years old

Exclusion criteria

- Participants aged <18 years old
- Randomized controlled trials for which naltrexone was given in combination therapy (however, if separate naltrexone stand-alone data is available, then the article would be included but only the naltrexone stand-alone data will be included in the results)
- Concurrent opioid and or alcohol use disorder (to minimize confounding factors as naltrexone is already indicated for opioid and alcohol use disorder)
- Conference abstracts
- Secondary analyses
- Reviews
- Observational studies
- Animal studies

Data extraction

PICO items including, but not limited to, the data source of study, type of study design, demographics of the participants, intervention (naltrexone route of administration, dose, and duration of treatment), outcomes of interest, will be recorded on data extraction form. Outcomes

The primary outcome was attenuated subjective measures of amphetamine or methamphetamine. The secondary outcome was defined as the rate of abstinence, compliance, adverse events and physiological changes (i.e. blood pressure, heart rate).

References

1. United Nations. United Nations Office on Drugs and Crime, World Drug Report 2017: United Nations Publication; 2017 [cited 2017 3 October]. Available from: https://www.unodc.org/wdr2017/field/Booklet_4_ATSNPS.pdf.
2. Covey DP, Bunner KD, Schuweiler DR, Cheer JF, Garris PA. Amphetamine elevates nucleus accumbens dopamine via an action potential-dependent mechanism that is modulated by endocannabinoids. Eur J Neurosci. 2016;43(12):1661-73.
3. Berman SM, Kuczenski R, McCracken JT, London ED. Potential adverse effects of amphetamine treatment on brain and behavior: a review. Mol Psychiatry. 2009;14(2):123-42.
4. Barateau L, Lopez R, Dauvilliers Y. Treatment Options for Narcolepsy. CNS Drugs. 2016;30(5):369-79.
5. Black SW, Yamanaka A, Kilduff TS. Challenges in the development of therapeutics for narcolepsy. Prog Neurobiol. 2017;152:89-113.
6. Hennissen L, Bakker MJ, Banaschewski T, Carucci S, Coghill D, Danckaerts M, et al. Cardiovascular Effects of Stimulant and Non-Stimulant Medication for Children and Adolescents with ADHD: A Systematic Review and Meta-Analysis of Trials of Methylphenidate, Amphetamines and Atomoxetine. CNS Drugs. 2017;31(3):199-215.
7. Advokat C. What are the cognitive effects of stimulant medications? Emphasis on adults with attention-deficit/hyperactivity disorder (ADHD). Neurosci Biobehav Rev. 2010;34(8):1256-66.
8. Adler LA, Newcorn JH. The impact, identification, and management of attention-deficit/hyperactivity disorder in adults. Introduction. CNS Spectr. 2007;12(12 Suppl 23):1-2.
9. Fleckenstein AE, Volz TJ, Riddle EL, Gibb JW, Hanson GR. New insights into the mechanism of action of amphetamines. Annu Rev Pharmacol Toxicol. 2007;47:681-98.
10. Kraemer T, Maurer HH. Toxicokinetics of amphetamines: metabolism and toxicokinetic data of designer drugs, amphetamine, methamphetamine, and their N-alkyl derivatives. Ther Drug Monit. 2002;24(2):277-89.
11. United Nations. United Nations Office on Drugs and Crime: Amphetamines and Ecstasy Vienna, Austria: United Nations Publication; 2011 [cited 2017 3 October]. Available from: https://www.unodc.org/documents/ATS/ATS_Global_Assessment_2011.pdf.
12. Sheridan J, Bennett S, Coggan C, Wheeler A, McMillan K. Injury associated with methamphetamine use: a review of the literature. Harm Reduct J. 2006;3:14.
13. Danks RR, Wibbenmeyer LA, Faucher LD, Sihler KC, Kealey GP, Chang P, et al. Methamphetamine-associated burn injuries: a retrospective analysis. J Burn Care Rehabil. 2004;25(5):425-9.
14. Sevak RJ, Stoops WW, Hays LR, Rush CR. Discriminative stimulus and subject-rated effects of methamphetamine, d-amphetamine, methylphenidate, and triazolam in methamphetamine-trained humans. J Pharmacol Exp Ther. 2009;328(3):1007-18.

15. Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. Lancet. 2012;379(9810):55-70.
16. Morley KC, Cornish JL, Faingold A, Wood K, Haber PS. Pharmacotherapeutic agents in the treatment of methamphetamine dependence. Expert Opin Investig Drugs. 2017;26(5):563-78.
17. Kampman KM. The search for medications to treat stimulant dependence. Addict Sci Clin Pract. 2008;4(2):28-35.
18. Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry. 1992;49(11):876-80.
19. O'Malley SS, Jaffe AJ, Chang G, Schottenfeld RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence. A controlled study. Arch Gen Psychiatry. 1992;49(11):881-7.
20. Helstrom AW, Blow FC, Slaymaker V, Kranzler HR, Leong S, Oslin D. Reductions in Alcohol Craving Following Naltrexone Treatment for Heavy Drinking. Alcohol Alcohol. 2016;51(5):562-6.
21. Spanagel R, Zieglgansberger W. Anti-craving compounds for ethanol: new pharmacological tools to study addictive processes. Trends Pharmacol Sci. 1997;18(2):54-9.
22. Meltzer HY. Update on typical and atypical antipsychotic drugs. Annu Rev Med. 2013;64:393-406.
23. Ray LA, Chin PF, Miotto K. Naltrexone for the treatment of alcoholism: clinical findings, mechanisms of action, and pharmacogenetics. CNS Neurol Disord Drug Targets. 2010;9(1):13-22.
24. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Medicine. 2009;6(7):e1000097.