INPLASY PROTOCOL

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None declared.

Pharmacotherapies for opioid withdrawal syndrome: a systematic review and network meta-analysis

Wang, QS[1]; Zhang, L[2]; Jiang, XJ[3]; Fan, WB[4].

Review question / Objective: **Which medications are effective and acceptable for the treatment of opioid withdrawal syndrome among adults? Opioid use disorder carries a significant burden, affecting not only the individual but families and communities as well. It is estimated that 10% of the U.S. population has participated in illicit drug use, with 20 million Americans suffering from substance abuse. It is essential for patients going through withdrawal to have the proper treatment that keeps them comfortable while reducing their likelihood of returning to opioids. Lofexidine, an alpha-2 agonist, can be used to manage acute withdrawal symptoms before starting maintenance treatment with either methadone or buprenorphine. Opiate addiction is increasing and plaguing the western world and specifically the U.S. It takes a large toll on both a personal and societal level and carries a high cost. Withdrawal is difficult, both related to withdrawal symptoms and renewed cravings. Lofexidine has been shown to be effective in reducing the former and could potentially aid in recovery and withdrawal. The objective of this study was to evaluate the RCTS of multiple opioid withdrawal treatment agents for network meta-analysis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 29 May 2023 and was last updated on 29 May 2023 (registration number INPLASY202350108).

INTRODUCTION

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abuse. It is essential for patients going through withdrawal to have the proper treatment that keeps them comfortable while reducing their likelihood of returning to opioids. Lofexidine, an alpha-2 agonist, can be used to manage acute withdrawal symptoms before starting maintenance treatment with either methadone or buprenorphine. Opiate addiction is increasing and plaguing the western world and specifically the U.S. It takes a large toll on both a personal and societal level and carries a high cost. Withdrawal is difficult, both related to withdrawal symptoms and renewed cravings. Lofexidine has been shown to be effective in reducing the former and could potentially aid in recovery and withdrawal. The objective of this study was to evaluate the RCTS of multiple opioid withdrawal treatment agents for network meta-analysis.

Condition being studied: Opioid use disorder (OUD) is a rapidly growing challenge worldwide and is characterized by an increase in dependence on opioids up to a point that a person loses control over the drug use.Multiple drugs are approved for its treatment, including methadone, buprenorphine, and diazepam. Although not approved, clonidine is also used for the treatment of OUD. On May 16,2018, the United States Food and Drug Administration (FDA) approved a new drug lofexidine hydrochloride for the treatment of opioid withdrawal symptoms. Lofexidine is a centrally acting alpha two receptor agonist. It reduces the neurochemical surge by inhibiting the conversion of adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) which in turn decrease the sympathetic outflow. This results in the improvement of withdrawal symptoms.When compared with methadone and buprenorphine, it is equally effective in controlling withdrawal symptoms. Its efficacy is also similar to clonidine with a better side effects profile. The adverse effects of lofexidine include bradycardia, hypotension, orthostasis, somnolence, sedation, dry mouth, and rebound elevations in blood pressure and prolongation of QT interval. Lofexidine is contraindicated in patients who are on beta-blockers and angiotensin converting enzyme inhibitors (ACE inhibitors).

METHODS

Participant or population: Adults (≥18 years old) with dependence on short-acting opioids and self-reported use on ?21 of the past 30 days who voluntarily consented to enter the study were enrolled. Opioid-dependence was determined using the Mini International Neuropsychiatric Interview in Study 1 and the Structured Clinical Interview Axis I in Study 2. Major exclusion criteria included use of methadone or buprenorphine in the past two weeks, unstable/serious medical or psychiatric illness, pregnancy or lactation, self-reported positive HIV status, and use of psychotropics, antihypertensives, antiarrhythmics or anticonvulsants within the past four weeks. An abnormal cardiovascular exam, including prolonged cor-rected QT interval (>450 ms for males, >470 ms for females) and significant hypertension or hypotension was cause for exclusion.

Intervention: In this study, the following RCTS for opioid withdrawal intervention were selected: Lofexidine Buspirone Venlafaxine Diazepam Buprenorphine NaloxoneMethadone Dronabinol ClonidineJinniu capsules Naltrexone placebo-controlled.

Comparator: Buspirone Venlafaxine Diazepam Buprenorphine Naloxone Methadone Dronabinol Clonidine Jinniu capsules Naltrexone placebo-controlled.

Study designs to be included: RCT study on opioid withdrawal therapy. Men or women≥ 18 years old seeking treatment for opioid use disorder were eligible. Participants were required to have current DSM-IV dependence according to the Mini International Neuropsychiatric Interview (MINI) on any opioid with a half-life similar to heroin or morphine with use for ≥21 of the past 30 days, a baseline score ≥2 on the Objective Opiate Withdrawal Scale (OOWS–Handelsman), and iffemale,

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agreement to use an acceptable method of contraception.

Eligibility criteria: Exclusion criteria: non-controlled studies of opioid withdrawal treatment, reviews, animal experiments, conference communications, etc. Exclude pregnant or lactating women. Patients under 18 years of age.

Information sources: Randomized clinical trials up to January 2023 were searched in four databases. To search PubMed, Embase, Cochrane Library,Web of Science, we used the following search terms: randomized controlled trial,opioid withdrawal syndrome, Lofexidine, Buspirone,Venlafaxine, Diazepam, Buprenorphine, Naloxone, Methadone, Dronabinol, Clonidine, Naltrexone, placebo-controlled. The trial was included after a blind review by two independent reviewers.

Main outcome(s): One study demonstrated a statistically significant reduction in opioid withdrawal symptom severity with lofexidine compared with clonidine, whereas the other 4 studies showed no significant difference. Three studies reported the completion of opioid detoxification treatment, with no significant differences seen. In 1 study that compared lofexidine with placebo, lofexidine caused significant hypotension, bradycardia, and pupillary constriction. Three studies showed significant adverse effects of hypotension and symptoms of feeling unwell with clonidine compared with lofexidine. Conclusion: Lofexidine appears equivalent in efficacy to clonidine, with fewer adverse effects, and it may have a limited role in the management of opioid withdrawal symptoms. However, cost, detoxification venue, and value of other preferred treatment modalities may affect the comparative efficacy of lofexidine to other agents.

Quality assessment / Risk of bias analysis: We will use the Cochrane Collaboration's tool which is recommended by the Cochrane Reviewer's Handbook to assess risk of bias for quality assessment of the included studies. The studies will be graded based on: (i) random sequence generation; (ii) allocation concealment; (iii) blinding; (iv) incomplete outcome data; (v) selective outcome reporting; (vi) other sources of bias.

Strategy of data synthesis: The data of the study included may be divided into two cases, depending on whether the data are suitable for meta-analysis. If the meta-analysis will not be performed because of heterogeneity, interventions, comparisons, outcomes etc., we will make forms for a qualitative description. If the data is suitable for meta-analysis, we will perform the meta-analysis using software RevMan 5.3 (Review Manager). For dichotomous data, we will present the results as risk ratios (RR) with 95% confidence intervals (CIs). For continuous data, the mean difference (MD) will be presented. If outcome variables are measured on different scales, standard mean differences (SMD) analysis with 95% CIs will be performed. For the datas will be done with the meta-analysis, the heterogeneity will be tested by a standard I^2 test. If there is no statistic heterogeneity among the results, the fixed effects model is employed for meta-analysis. If there is a statistic heterogeneity, the source of the heterogeneity should be further analyzed. If there is obvious clinical heterogeneity, the subgroup or sensitivity analysis, or only descriptive analysis can be performed.

Subgroup analysis: We will conduct a subgroup analysis of lofexidine versus other agents for the treatment of opioid withdrawal syndrome.

Sensitivity analysis: We will conduct a sensitivety analysis to verify the robustness of the research conclusions, assess the methodological quality, the study design, the effect of sample size and missing data, and the effect of the analysis method on the results of this review . the meta-analysis will be repeated ,and lower-quality studies will be excluded. These results will then be compared and discussed.

Country(ies) involved: China.

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