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Lofexidine versus diazepam for the treatment of opioid withdrawal syndrome: A double-blind randomized clinical trial in Singapore☆

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ABSTRACT

Background: Many individuals leave costly inpatient detoxification programs prematurely because of the severity of withdrawal symptoms experienced. In the absence of opioid-assisted detoxification in Singapore, diazepam is used to manage withdrawal. However since diazepam is addictive, there is a need to explore the effectiveness of alternative medications.

Design and procedures: The study aimed to examine the safety and efficacy of lofexidine, a non-opiate, non-addictive, alpha 2-adrenergic agonist in assisting opioid detoxification in Singapore, using a randomized, double-blind, investigator-initiated placebo-controlled trial comparing lofexidine against diazepam. Opioid dependent patients (n = 111) were randomized to receive a 10-day course of lofexidine (n = 56) or diazepam (n = 55). The primary endpoint was the Objective Opioid Withdrawal Scale (OOWS) score on days 3 and 4 and secondary outcomes were the Short Opioid Withdrawal Scale (SOWS) score, program retention rate, and ratings of opiate craving.

Main findings: The OOWS, SOWS and opiate craving scores were consistently lower in the lofexidine group relative to the diazepam group over the 14-day study period; however no statistically significant differences were found on days 3 and 4 (peak withdrawal). Changes in mean pupil size during peak withdrawal were significantly smaller in the lofexidine group and more participants in the lofexidine group remained in treatment and completed detoxification.

Conclusions: Lofexidine was at least as effective as diazepam in reducing the opioid withdrawal syndrome and increased treatment retention. In addition to its non-addictive and non-abuse properties, lofexidine has several clinical advantages over diazepam. The use of lofexidine is recommended when opioid-assisted medications are not available.

1. Introduction

Opioid dependence remains a major global health and social challenge (Gowing, Farrell, Ali, & White, 2016) with deaths tripling between 1990 and 2013 (Abubakar, Tillman, & Banerjee, 2015). The World Drug Report (United Nations Office on Drugs and Crime, 2016) shows that between 1998 and 2014 opiate use declined in Western and Central Europe and Oceania but remained largely unchanged in Asia,

☆ The trial was registered with ClinicalTrials.gov (NCT number: NCT01675648).

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which has one of the fastest growing populations. While there are no prevalence studies of illicit drug use in Singapore, data on drug-related arrests suggest heroin accounts for almost one-third of all cases (Central Narcotics Bureau, 2016). The treatment of opioid dependence often commences with a period of medically-assisted withdrawal, followed by pharmacological and/or psychosocial interventions (Amato et al., 2008; Veilleux, Colvin, Anderson, York, & Heinz, 2010). However because of the country's 'zero-tolerance' drug use policy, the most widely recommended WHO pharmacotherapies for assisting opioid withdrawal (i.e., methadone and buprenorphine) are not available in Singapore (World Health Organization, 2009). It is therefore necessary for local healthcare agencies to evaluate the efficacy of alternative medications to moderate the symptoms of opioid withdrawal to facilitate successful completion of the detoxification programs. However, the use of medically assisted treatments is also restricted in other jurisdictions due local policies, concerns around abuse potential and medical licensing requirements. A recent systematic review of the global coverage of interventions to prevent and manage blood-borne viruses among people who inject drugs reported that only 86 of the 179 countries examined have evidence of opioid substitution treatment implementation (Larney et al., 2017). Given this, it is important to identify more effective, non-opioid medications to ameliorate the withdrawal syndrome and improve engagement in longer-term follow-up care.

Lofexidine is an alpha 2-adrenergic agonist with no abuse or addiction potential that has shown promising results in several studies (Gowing, Ali, & White, 2009) and has been shown to be superior to clonidine in rapid opioid withdrawal (Gerra et al., 2001).

Opioid withdrawal is thought to involve noradrenergic hyperactivity, and alpha-2-adrenergic agonists can act to ameliorate symptoms of opioid withdrawal by reducing this hyperactivity (Gowing et al., 2016). A recent Cochrane review on alpha 2-adrenergic for the management of opioid withdrawal which included 26 Randomized Controlled Trials (RCTs) involving 1728 opioid-dependent participants (Gowing et al., 2016) concluded that alpha 2-adrenergic agonists are more effective than placebo in managing opioid withdrawal. The review suggest that there are few differences in the efficacy of lofexidine and clonidine compared to reducing doses of methadone over a 10 day withdrawal from heroin, but evidence of an accelerated onset and alleviation of withdrawal symptoms with the alpha 2-adrenergic agonists and reduced hypotensive effects of lofexidine relative to clonidine (Gowing et al., 2016). The majority of trials have been conducted on Western populations and the authors note that in the limited number of Asian studies (two in China, one in India and one in Taiwan) (Howells et al., 2002; Li, Chen, & Mo, 2002; Lin, Strang, Su, Tsai, & Hu, 1997; Zuo-Ning et al., 1993), patients were not all undergoing voluntary detoxification. For this reason, more trials on Asian populations are warranted, particularly in light of the reduced access to opioid substitution therapy in this region (Larney et al., 2017; Stone, 2015).

The standard pharmacological treatment to assist opioid withdrawal at Singapore's National Addictions Management Service (NAMS) is 7 to 10 days of oral diazepam, combined with other supportive medications. Diazepam is prescribed for its anxiolytic and muscle-relaxant effects and addresses some of the symptoms of the opioid withdrawal such as insomnia. However, both opioids and benzodiazepines are among the most frequently abused psychoactive drugs worldwide (Joranson, Ryan, Gilson, & Dahl, 2000). Abundant evidence shows that their combined abuse is extremely common and among people with substance use disorders, benzodiazepines have high abuse liability (Gudin, Mogali, Jones, & Comer, 2013; Jones, Mogali, & Comer, 2012).

The severity of withdrawal symptoms is associated with poor treatment retention and failure to complete withdrawal (Fishman, 2008; Kanof, Aronson, & Ness, 1993) and indeed the local experience is that many opioid dependent patients undergoing the 2-week inpatient detoxification program leave prematurely (i.e. self-discharge) because of the unpleasant withdrawal symptoms. As a result, patients fail to receive the psychosocial rehabilitation component of treatment where they learn relapse prevention skills and psychological techniques to improve functioning and re-integration into society. Thus in order to improve retention in the inpatient program there is a critical need to identify alternative non-addictive medications to assist in opioid detoxification. A Taiwanese RCT comparing lofexidine with clonidine (Lin et al., 1997) found lofexidine to be equally effective, but with superior tolerance over clonidine.

Since the 2016 Cochrane review on alpha 2-adrenergic agonists, there have been three further studies of lofexidine, with predominantly Caucasian populations. A US randomized, double-blind, placebo-controlled multi-site trial of the safety and efficacy of 5 days of lofexidine (3.2 mg per day) among 264 inpatients undergoing opioid withdrawal (Gorodetzky et al., 2017) demonstrated significantly lower mean scores on the Short Opiate Withdrawal Scale (Gossop, 1990) and greater treatment retention relative to placebo, with evidence lofexidine was tell-tolerated. The authors concluded that lofexidine was therefore a potentially useful, non-opioid alternative medication for the management of opioid withdrawal syndrome.

A pragmatic RCT comparing buprenorphine/naloxone with methadone/lofexidine during outpatient stabilization and detoxification among opiate-dependent individuals in the UK (Law et al., 2017) reported an earlier peak withdrawal and more severe subjective withdrawal symptoms among the methadone/lofexidine group but with no group differences in the proportion of positive urine screens detected, craving nor treatment drop-out during the detoxification phase. The authors concluded that both medication regimes were effective at reducing opiate withdrawal symptoms.

The third recent addition to the literature is a study describing the findings of a retrospective case series of 84 patients treated with a non-opioid and benzodiazepine-free protocol for opioid withdrawal and transitioning to antagonist treatment, using the alpha 2-adrenergic receptor agonist 'tizanidine' in combination with gabapentin and hydroxyzine (Rudolf et al., 2017). The authors found that 94% of patients on this novel protocol completed withdrawal, with low scores mean scores on the Clinical Opiate Withdrawal Scale (COWS) on days 1–4 reported, no serious adverse events and a mean inpatient stay of 3.6 days out of the planned 4-day stay, suggesting it is a promising regime for effective opioid withdrawal management.

Finally, a 2009 commentary on emerging pharmacotherapies for opioid addiction called for future research to assess subjective withdrawal symptoms using scales such as the Short Opiate Withdrawal Scale or the COWS (Ling et al., 2011). While recent studies have adopted the recommended measures, the assessment of opioid withdrawal with tools such as the Objective Opioid Withdrawal Scale (Handelsman et al., 1987) are important in advancing the literature, particularly in the context of open-label or sponsored trials. Nonetheless, recent studies revisiting the potential for lofexidine as an opioid-withdrawal medication address the need to identify candidate, non-opioid and non-addictive medications for use with this population. Indeed this year lofexidine was approved for the United States Food and Drug Administration (FDA) 'fast-track program' - a process to expedite the review of drugs to treat serious conditions and to fill an unmet medical need (FDA, 2017) and recently (March 2018) the FDA advisory committee voted to approve lofexidine to treat symptoms of opioid withdrawal and increase treatment retention thus further studies on its safety and efficacy with more diverse populations are warranted.

The objective of this RCT was to examine the efficacy and safety of lofexidine as a non-opioid, non-addictive alternative to diazepam during detoxification from heroin in a non-Caucasian population of opioid-dependent inpatients in Singapore.

2. Methods

2.1. Study overview

This was an investigator-initiated clinical trial in the National