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A Phase 3 placebo-controlled, double-blind, multi-site trial of the alpha-2-adrenergic agonist, lofexidine, for opioid withdrawal☆

Elmer Yu[a,*], Karen Miotto[b], Evaristo Akerele[c], Ann Montgomery[d], Ahmed Elkashef[d], Robert Walsh[d], Ivan Montoya[d], Marian W. Fischman[c,1], Joseph Collins[e], Frances McSherry[e], Kathy Boardman[f], David K. Davies[g], Charles P. O'Brien[a], Walter Ling[b], Herbert Kleber[c], Barbara H. Herman[d]

[a] *University of Pennsylvania & Philadelphia Veterans Affairs Medical Center, Philadelphia VAMC 116, University & Woodland Avenues, Philadelphia, PA 19104, United States*
[b] *University of California at Los Angeles & Long Beach Veterans Affairs Medical Center, David Geffen School of Medicine at UCLA, 11075 Santa Monica Blvd., Suite 200, Los Angeles, CA 90025, United States*
[c] *Columbia University College of Physicians and Surgeons & New York State Psychiatric Institute, 1051 Riverside Drive, Room 3713, Unit 66, New York, NY 10032, United States*
[d] *Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDA), National Institute on Drug Abuse (NIDA), National Institute of Health (NIH), 6001 Executive Boulevard, Room 4123, MSC-9551, Bethesda, MD 20892-9551, United States*
[e] *Department of Veterans Affairs Cooperative Studies Program (VACSP), Building 362T, P.O. Box 1010, VA Medical Center, Perry Point, MD 21902, United States*
[f] *Veterans Administration Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (VACSPCRPCC), 2401 Centre Avenue SE, Albuquerque, NM 87106, United States*
[g] *Britannia Pharmaceuticals Limited, 41 Brighton Road, Redhill, Surrey RH1 6YS, United Kingdom*

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Abstract

Context: Lofexidine is an alpha-2-adrenergic receptor agonist that is approved in the United Kingdom for the treatment of opioid withdrawal symptoms. Lofexidine has been reported to have more significant effects on decreasing opioid withdrawal symptoms with less hypotension than clonidine.
Objective: To demonstrate that lofexidine is well tolerated and effective in the alleviation of observationally defined opioid withdrawal symptoms in opioid dependent individuals undergoing medically supervised opioid detoxification as compared to placebo.
Design: An inpatient, Phase 3, placebo-controlled, double-blind, randomized multi-site trial with three phases: (1) opioid agonist stabilization phase (days 1–3), (2) detoxification/medication or placebo phase (days 4–8), and (3) post detoxification/medication phase (days 9–11).
Subjects: Sixty-eight opioid dependent subjects were enrolled at three sites with 35 randomized to lofexidine and 33 to placebo.
Main outcome measure: Modified Himmelsbach Opiate Withdrawal Scale (MHOWS) on study day 5 (second opioid detoxification treatment day).
Results: Due to significant findings, the study was terminated early. On the study day 5 MHOWS, subjects treated with lofexidine had significantly lower scores (equating to fewer/less severe withdrawal symptoms) than placebo subjects (least squares means 19.5 ± 2.1 versus 30.9 ± 2.7; $p = 0.0019$). Lofexidine subjects had significantly better retention in treatment than placebo subjects (38.2% versus 15.2%; Log rank test $p = 0.01$).
Conclusions: Lofexidine is well tolerated and more efficacious than placebo for reducing opioid withdrawal symptoms in inpatients undergoing medically supervised opioid detoxification.
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Keywords: Lofexidine; Alpha-2-adrenergic agonist; Opioid withdrawal treatment; Phase 3; Placebo-controlled; Double-blind; Multi-site trail

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* Corresponding author. Tel.: +1 215 823 4672; fax: +1 215 823 5919.
E-mail address: yu_e@mail.trc.upenn.edu (E. Yu).

[1] Dr. Fischman's untimely death coincided with the creation of this manuscript.

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1. Introduction

Opioid dependence is a medical condition associated with severe health and social consequences (Hser et al., 2001). The Office of National Drug Control Policy estimates the number of individuals addicted to heroin in the United States is between 750,000 and 1,000,000 users (Office of National Drug Control Policy, 2003). According to the 2006 National Survey on Drug Use and Health (NSDUH), approximately 3.8 million Americans aged 12 or older reported trying heroin at least once during their lifetimes, representing 1.5% of the population aged 12 or older. Approximately 560,000 (0.2%) reported past year heroin use and 338,000 (0.1%) reported past month heroin use. According to the NSDUH survey, across age groups, an estimated 5.2 million persons were current nonmedical users of prescription pain relievers in 2006, which is more than the estimated 4.7 million in 2005. The growing population of people with prescription opioid dependence increases the need for a range of evidence-based treatments.

The medication treatment for opioid addiction can include short-term detoxification, longer-lasting opioid maintenance and the opioid relapse prevention therapy, such as naltrexone (Herman et al., 1995). The predominant treatment for opioid dependence is methadone for maintenance or detoxification. Another opioid, buprenorphine, has recently been approved for the same indication (Gonzalez et al., 2004). Some patients find maintenance or detoxification with an opioid unacceptable and prefer non-opioid treatment. No single treatment modality is currently effective, and opioid dependence requires adequate access to a wide range of options.

The alpha-2-adrenergic agonist clonidine is currently used "off label" for the treatment of withdrawal (Gossop, 1988). However, clonidine can produce problematic side effects, such as sedation and hypotension, generally restricting its use in the outpatient setting (Kleber et al., 1985; Preston and Bigelow, 1985). Lofexidine is an alpha-2-adrenergic agonist, structurally related to clonidine, which has been used in the United Kingdom primarily in an outpatient setting for opioid detoxification since 1992 under the label BritLofex® (Jarrott et al., 1983; Aigner and Schmidt, 1982). One advantage of lofexidine over clonidine is it is believed to have less hypotensive effects than clonidine (Kahn et al., 1997).

The preclinical neurobiology of the mechanism of alpha-2-adrenergic agonists in opioid withdrawal has been well studied. Early studies suggested that chronic opioid exposure leads to tonic inhibition of noradrenergic cells and cessation of opioid use results in disinhibition of noradrenergic cells in the locus coeruleus (Aghajanian, 1982; Aston-Jones et al., 1997). The therapeutic action of alpha-2-adrenergic agonists stemmed from the ability to reduce firing in the locus coeruleus (Freedman and Aghajanian, 1985; Aghajanian, 1978). In addition to the central actions of alpha-2-adrenergic agonists, a study by Buccafusco and Marshall (1985) also suggest spinal mediated anti-withdrawal effects.

In vitro receptor binding studies have identified three subtypes of the alpha-2-adrenergic receptor: 2A, 2B, and 2C (Marjamaki et al., 1993; Uhlen and Wikberg, 1991). Clonidine is a nonspecific alpha-2-adrenergic receptor agonist with equal affinity for all three of these subtypes (cited in prior reference) while lofexidine appears to bind specifically to the subtype 2A alpha-2-adrenergic receptor (Marjamaki et al., 1993; Uhlen and Wikberg, 1991; Herman and O'Brien, 1997). Higher affinity 2A subtype agents have been shown in nonhuman primates to have less hypotensive effects and to have efficacy on processes such as memory enhancement in aged animals (Arnsten et al., 1998).

Results of clinical studies indicate that alpha-2-adrenergic agonists such as lofexidine are effective in the alleviation of opioid withdrawal. There have been a number of double-blind (DB), controlled studies indicating that the efficacy of lofexidine is comparable to that of clonidine (Carnwath and Hardman, 1998; Kahn et al., 1997; Lin et al., 1997). All studies concluded that there was less problematic hypotension with lofexidine than with clonidine. Two controlled studies comparing lofexidine and short-term methadone taper suggested no significant difference in the withdrawal intensity or blood pressure between the groups (Howells et al., 2002; Bearn et al., 1996). A recent report also indicated that the signs and symptoms of withdrawal occur and resolve earlier with treatment with an alpha-2-adrenergic agonist compared to methadone withdrawal treatment (Gowing et al., 2002). In addition, a large retrospective lofexidine use survey of patients and health care providers in the United Kingdom suggested a common 10-day outpatient treatment protocol without significant reports of adverse effects (Akhurst, 1999). As expected, lofexidine alleviates opioid withdrawal symptoms in the rat (Shearman et al., 1980).

Early open clinical studies supported the dose-dependent use of lofexidine as a treatment to decrease opioid withdrawal signs and symptoms (Gold et al., 1981; Washton et al., 1982; Gowing et al., 2004). The dose of lofexidine required to control withdrawal symptoms varies for each patient depending on the amount, frequency and duration of opioid used. In the U.K., lofexidine treatment is initiated at 0.2 mg twice daily, increasing daily by 0.2–0.4 mg with a recommended final dose of 2.4 mg/day. An inpatient, dose-response analysis of the safety and efficacy of lofexidine in the U.S. evaluated four different divided doses: 1.6 mg/day, 2.4 mg/day, 3.2 mg/day and 4.0 mg/day groups. There was a dose-dependent decrease in objective opiate withdrawal symptoms using the Modified Himmelsbach Opiate Withdrawal Scale (MHOWS). However, transient orthostatic systolic blood pressure changes were more frequent in the higher dose groups (Yu et al., 2001).

Here we report on the results of the first Phase 3, inpatient, randomized, placebo-controlled (PC), multi-site study designed to evaluate the efficacy of lofexidine for the treatment of opioid withdrawal.

2. Methods

2.1. Participants

All enrolled participants met the following inclusion criteria: (1) minimum 18 years of age; (2) current dependence on heroin, morphine, or hydromorphone according to DSM-IV criteria; (3) participants reported use of heroin, morphine, or hydromorphone for at least 21 of the past 30 days; (4) a urine toxicology screen