



7-1-2017

A Phase III, Randomized, Multi-Center, Double Blind, Placebo Controlled Study of Safety and Efficacy of Lofexidine for Relief of Symptoms in Individuals Undergoing Inpatient Opioid Withdrawal

Charles W. Gorodetzky

Sharon L. Walsh

University of Kentucky, sharon.walsh@uky.edu

Peter R. Martin

Vanderbilt University

Andrew J. Saxon

University of Washington

Kristen L. Gullo

US WorldMeds, LLC

Follow this and additional works at: https://uknowledge.uky.edu/cdar_facpub

 [Open Access](#) next page for additional authors

Part of the [Chemicals and Drugs Commons](#), [Clinical Trials Commons](#), and the [Substance Abuse and Addiction Commons](#)

[Right click to open a feedback form in a new tab to let us know how this document benefits you.](#)

Repository Citation

Gorodetzky, Charles W.; Walsh, Sharon L.; Martin, Peter R.; Saxon, Andrew J.; Gullo, Kristen L.; and Biswas, Kousick, "A Phase III, Randomized, Multi-Center, Double Blind, Placebo Controlled Study of Safety and Efficacy of Lofexidine for Relief of Symptoms in Individuals Undergoing Inpatient Opioid Withdrawal" (2017). *Center on Drug and Alcohol Research Faculty Publications*. 3.

https://uknowledge.uky.edu/cdar_facpub/3

This Article is brought to you for free and open access by the Drug and Alcohol Research at UKnowledge. It has been accepted for inclusion in Center on Drug and Alcohol Research Faculty Publications by an authorized administrator of UKnowledge. For more information, please contact UKnowledge@lsv.uky.edu.

A Phase III, Randomized, Multi-Center, Double Blind, Placebo Controlled Study of Safety and Efficacy of Lofexidine for Relief of Symptoms in Individuals Undergoing Inpatient Opioid Withdrawal

Digital Object Identifier (DOI)

<https://doi.org/10.1016/j.drugalcdep.2017.02.020>

Notes/Citation Information

Published in *Drug and Alcohol Dependence*, v. 176, p. 79-88.

© 2017 The Authors. Published by Elsevier Ireland Ltd.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Authors

Charles W. Gorodetzky, Sharon L. Walsh, Peter R. Martin, Andrew J. Saxon, Kristen L. Gullo, and Kousick Biswas



Full length article

A phase III, randomized, multi-center, double blind, placebo controlled study of safety and efficacy of lofexidine for relief of symptoms in individuals undergoing inpatient opioid withdrawal



Charles W. Gorodetzky^{a,*}, Sharon L. Walsh^b, Peter R. Martin^c, Andrew J. Saxon^d,
Kristen L. Gullo^e, Kousick Biswas^f

^a Consultant in Pharmaceutical Medicine, 433 Ward Parkway, Unit 6S, Kansas City, MO, 64112, USA

^b Center on Drug and Alcohol Research, Department of Behavioral Science, University of Kentucky College of Medicine, 845 Angliana Avenue, Lexington, KY, 40508, USA

^c Department of Psychiatry and Behavioral Sciences, Vanderbilt University School of Medicine, 1601 23rd Avenue South, Suite 3068, Nashville, TN, 37232, USA

^d Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine and VA Puget Sound Health Care System, 1660 S Columbian Way, S-116 Atc, Seattle, WA, 98108, USA

^e US WorldMeds, LLC, 4441 Springdale Rd, Louisville, KY, 40241, USA

^f Cooperative Studies Program Coordinating Center (CSPCC), U.S. Department of Veterans Affairs, Perry Point, MD, 21902, USA

ARTICLE INFO

Keywords:

Lofexidine
Alpha-2-adrenergic receptor agonist
Opioid withdrawal syndrome
Opioid discontinuation
SOWS-Gossop

ABSTRACT

Background: Lofexidine is an alpha-2-adrenergic receptor agonist approved in the United Kingdom (UK) for the treatment of opioid withdrawal symptoms. Lofexidine has demonstrated better efficacy than placebo for reducing opioid withdrawal symptoms in patients undergoing opioid withdrawal with less reported hypotension than clonidine.

Methods: Designed as an FDA registration trial, this 8-day, randomized, double-blind, placebo-controlled, parallel-group study in 264 patients dependent on short-acting opioids evaluated the efficacy of lofexidine hydrochloride in reducing withdrawal symptoms in patients undergoing opioid withdrawal. The primary efficacy measures were SOWS-Gossop on Day 3 and time-to-dropout. Secondary endpoints included the proportion of participants who were completers; area under the 5-day SOWS-Gossop – time curve (i.e., AUC_{1–5}), and daily mean SOWS-Gossop, OOWS-Handelsman, MCGI (subject and rater), and VAS-E scores. Participants received lofexidine HCl 3.2 mg daily in four divided doses or matching placebo on Days 1–5, followed by 2 days of placebo.

Results: Lofexidine significantly decreased mean Day 3 SOWS scores compared to placebo, 6.32 versus 8.67, respectively, $p = 0.0212$. Fewer lofexidine patients were early terminators compared to placebo (59 versus 80, respectively); and non-completers in the lofexidine group remained in the study longer than those assigned to placebo ($p = 0.0034$). Secondary endpoints consistently favored lofexidine. Lofexidine was well tolerated in this trial.

Conclusion: Lofexidine significantly decreased SOWS scores compared to placebo and demonstrated better retention rates in participants undergoing opioid withdrawal. Lofexidine potentially offers a useful non-opioid alternative to treat opioid withdrawal symptoms.

1. Introduction

Opioid dependence (Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition, DSM-IV)/opioid use disorder (OUD; DSM-V) is epidemic in the United States (US). Heroin-related overdose deaths between 2002 and 2013 increased by 286%; in 2014 there were 10,574 heroin overdose deaths and 18,893 deaths from prescription opioids (CDC [ADDR_drug_poisoning_involving_OA_heroin_US_2000-2014](http://www.cdc.gov/drugpoisoning/) CDC

[ADDR_2000](http://www.cdc.gov/drugpoisoning/) CDC [ADDR_drug_poisoning_involving_OA_heroin_US_2000-2014](http://www.cdc.gov/drugpoisoning/)). To combat this epidemic, increased treatment options and access to Medication-Assisted Treatment (MAT) for OUD are essential.

While opioid withdrawal may not be an effective long-term treatment for OUD, withdrawal is often a necessary first step before naltrexone treatment, for patients who are treated with opioids for chronic pain who do not have OUD and need to be withdrawn because

* Corresponding author.

E-mail address: cgoro@kc.rr.com (C.W. Gorodetzky).

<http://dx.doi.org/10.1016/j.drugalcdep.2017.02.020>

Received 9 September 2016; Received in revised form 20 February 2017; Accepted 20 February 2017

Available online 10 May 2017

0376-8716/ © 2017 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

of inefficacy or side effects, and as the final stage after a prolonged period of agonist therapy.

Methadone and buprenorphine are employed as pharmacological withdrawal treatments, but their use can be limited by restricted access (e.g., policy, physician licensing) related to their abuse potential. Use of alpha-2-adrenergic agonists, primarily clonidine, as an alternative treatment to aid withdrawal began in the 1980's (Kleber et al., 1985; Preston and Bigelow, 1985; Gossop, 1988). Although commonly used in the US (Gossop, 1988), clonidine is not approved by the Food and Drug Administration (FDA) for this indication, and its use is limited by sedation and hypotension at doses effective in alleviating opiate withdrawal symptoms (Kleber et al., 1985; Preston and Bigelow, 1985). Lofexidine hydrochloride, also an alpha-2-adrenergic receptor agonist, is approved for this indication in the United Kingdom (UK) and has been used in inpatient and outpatient settings since 1992.

Gowing and colleagues have recently reviewed studies assessing alpha adrenergic agonists for opioid withdrawal (Gowing et al., 2016). A total of 26 studies involving 1728 participants and meeting pre-defined quality criteria were included. Six studies compared adrenergic agonist treatment to placebo but only one assessed lofexidine (Yu et al., 2008). In that double-blind study, opioid dependent participants were initially stabilized on morphine, abruptly withdrawn, and then treated with lofexidine (0.8 mg QID, p.o.) or placebo for 5 days, followed by 2 additional days on placebo. Lofexidine significantly decreased the scores on The Modified Himmelsbach Opiate Withdrawal Scale (MHOWS) on study Day 5 (withdrawal Day 2) compared to placebo. Secondary outcomes favored lofexidine. Lofexidine was associated with significantly fewer early terminations than placebo. Side effects of asthenia, dizziness, hypotension, insomnia and somnolence occurred more frequently with lofexidine compared to placebo.

The remaining five controlled studies compared placebo to clonidine and found less severe withdrawal with clonidine and more participants dropping out early with placebo (Gerra et al., 1995); fewer participants with severe withdrawal in the clonidine groups (Batey et al., 1987; Benos, 1985); and lower withdrawal scores with clonidine versus placebo (Benos, 1985). Side effects with clonidine included sedation and dry mouth (Benos, 1985) and drowsiness and dizziness (Batey et al., 1987). One study reported no difference in side effects between clonidine and placebo (Nazari et al., 2013). Completion of withdrawal treatment was reported more likely with clonidine (Batey et al., 1987; Benos, 1985).

The other studies meeting review qualifications compared alpha-adrenergic agonists (primarily clonidine and lofexidine) with methadone and symptomatic medications and several compared different alpha-adrenergic agonists. The authors concluded that there was no significant difference in efficacy of lofexidine and clonidine compared to methadone reduction (see also Kahn et al., 1997; Carnworth and Hardman, 1998; Lin et al., 1997); methadone had fewer side effects than clonidine; and lofexidine had a better safety profile than clonidine (Gowing et al., 2016). The signs and symptoms of withdrawal occurred and resolved earlier with alpha-2-adrenergic agonists, and the duration of treatment was significantly longer with reducing doses of methadone. Studies suggest that lofexidine has less hypotensive effects than clonidine at doses effective for the alleviation of opioid withdrawal and has no abuse potential (Gowing et al., 2004; Gerra et al., 2001; Strang et al., 1999).

Lofexidine is under development for approval in the US by US WorldMeds, LLC. This report describes a Phase 3 efficacy/safety study designed as a registration study to meet FDA requirements. As recommended by the FDA, it compared lofexidine to placebo in a population undergoing abrupt discontinuation from chronically administered short-acting opioids.

2. Methods

2.1. Participants

Eligible participants included individuals who were at least 18 years of age and seeking treatment for opioid dependence (DSM-IV), met Structured Clinical Interview Axis I (SCID) criteria for dependence on a short-acting opioid, self-reported opioid use ≥ 21 of the last 30 days, showed signs of withdrawal just before randomization (score of ≥ 2 on the Handelsman Objective Opiate Withdrawal Scale [OOWS-Handelsman]), had a urine screen positive for opioids but negative for methadone or buprenorphine, provided written informed consent and completed the Addiction Severity Index (ASI) during screening and all other assessments (Short Opiate Withdrawal Scale [SOWS-Gossop], OOWS-Handelsman, and Modified Clinical Global Impression [MCGI]) during the baseline period.

Exclusion criteria included any serious medical or psychiatric illness, self-reported Acquired Immune Deficiency Syndrome, clinically significant abnormal lab values or dependence on any psychoactive substance (other than opioids) that required withdrawal; abnormal cardiovascular exam, including prolonged QTc (> 450 msec for males, > 470 msec for females); significant hypertension ($> 160/100$ mmHg) or hypotension ($< 90/60$ mmHg); bradycardia (< 45 bpm); history of myocardial infarction; use of methadone or buprenorphine in last 14 days; use of psychotropics, prescription analgesics, anticonvulsants, anti-hypertensives, anti-arrhythmics, anti-retroviral, or cholesterol lowering agents in last 4 weeks; donation of blood in last 8 weeks; participation in another investigational study in last 3 months; inadequate venous access; active tuberculosis or syphilis; and pregnancy or lactation.

2.2. Procedure and medications

This trial was performed by US WorldMeds, LLC, Louisville, KY, in collaboration with the National Institute on Drug Abuse (NIDA) and the Cooperative Studies Program of the Department of Veterans Affairs. This 15-site study was conducted in the US between June 16, 2006 and October 26, 2007 in accordance with the provisions of the Declaration of Helsinki and with the clinical research guidelines embodied in the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. Monitoring for adherence to GCPs was done routinely. The protocol and informed consent were reviewed and approved by each center's Institutional Review Board and the Veterans Administration Cooperative Studies Program Coordinating Center's Human Rights Committee. All participants reviewed and signed written informed consent before any study-related procedures were performed.

Eligible participants were dosed orally with lofexidine HCl 0.8 mg (4×0.2 mg lofexidine HCl tablets) four times daily (QID) for a total daily dose of 3.2 mg/day, or matching placebo on study Days 1 through 5 followed by placebo (4 tablets) QID on Days 6–7. Drug and placebo were supplied by US WorldMeds. Lofexidine HCl 0.2 mg tablets contain 0.18 mg lofexidine base (for a total daily dose per protocol of 2.88 mg).

For ethical reasons and practical considerations, specified non-opioid, symptomatic concomitant medications were allowed when requested by the participants and approved by the study physician including multivitamins, guaifenesin, alumina, magnesia, simethicone, dioctyl sodium sulfosuccinate, psyllium hydrocolloid, bismuth sulfate, acetaminophen, zolpidem, and nicotine replacement therapy.

2.3. Randomization and blinding

Randomization across all sites employed a centralized Interactive Touch Tone Randomization System and allocated patients to treatment groups in a 1:1 ratio. An adaptive randomization procedure was used to allocate treatment assignment based on the assignments and prognostic

variable levels for all previously enrolled patients. Randomization used a “biased coin” procedure, which used randomization probabilities favoring the treatment with the deficit enrollment (Efron, 1971).

2.4. Design

This was an 8-day inpatient, randomized, multicenter, double-blind, placebo-controlled, parallel-group study with three phases.

2.4.1. Screening phase (outpatient days –7 to –1)

Participants meeting eligibility criteria were randomized no later than the morning of the 7th screening day. Participants were admitted to the inpatient unit on the evening of Day 0 or early in the morning of Day 1, with baseline assessments completed just before randomization on Day 1. Screening was completed on an outpatient basis, while baseline data were collected as inpatients just prior to randomization.

2.4.2. Treatment phase (Days 1–5)

Participants received their first dose of study medication (lofexidine or placebo) on Day 1 at 08:00 h and were then dosed with 0.8 mg of lofexidine HCl or matching placebo 4 times daily (QID) for a total daily dose of 3.2 mg on Days 1–5. Daily dosing windows were scheduled at 08:00 h, 13:00 h, 18:00 h, and 23:00 h.

2.4.3. Post-treatment phase (Days 6–7)

All participants received placebo (four tablets QID) on Days 6 and 7. On Day 8, no medication was administered and participants were discharged after completing required assessments.

2.5. Assessments

Co-primary outcome measurements included the SOWS-Gossop scale (Gossop, 1990) on Day 3 of the treatment phase and time to study dropout. Day 3 was chosen to be at or near the anticipated peak of withdrawal as per FDA recommendation. Area-under-the-SOWS-Gossop-time curve (AUC) was the principal secondary outcome measure.

SOWS-Gossop (total score) was chosen because of its sensitivity to symptom relief during acute opioid withdrawal, validation as an opioid withdrawal measure (e.g., Bradley et al., 1987; Vernon et al., 2016) and frequent use in similar drug trials. This subject-rated scale consists of 10 items, scored from 0 (none) to 3 (severe) (total range 0–30). Studies indicate that a change score of 2–4 points is a clinically meaningful improvement (e.g., Vernon et al., 2016). The SOWS was completed at baseline (immediately before first drug administration), 3.5 h after the first dose of study medication on Days 1–7 and at discharge (Day 8).

Time-to-dropout was chosen as a global assessment of efficacy (i.e., treatment retention). Each study day was divided into four 6 h time quadrants (i.e., 6am–12pm; 12pm–6pm; 6pm–12am; and, 12am–6am) and time-to-dropout was measured as the number of 6 h time quadrants until withdrawal or completion of the 5-day Treatment Phase.

Additional assessments included the OOWS (Handelsman et al., 1987), MCGI (patient and rater forms) and Visual Analog Scale for Efficacy (VAS-E) assessing the efficacy of study medication for decreasing withdrawal sickness collected at screening, baseline, once daily at 3.5 h following the 0800 medication dose and before discharge. Also evaluated were: use of concomitant medications to alleviate withdrawal symptoms; requirement for opioid rescue for symptom relief; and withdrawal-related adverse events (AEs).

Adverse events (AEs) were assessed daily at approximately the same time using a non-specific query. Participants could also spontaneously report AEs any time. All AEs were reviewed with the subject by a study physician.

12-lead electrocardiograms (ECGs) were conducted during screening, at clinic admission, 4 h after the first dose of study medication each day, and before discharge. Vital signs were collected at screening, baseline, within 30 min before each dose of study medication, 3 h after

the first dose of study medication each day, and before discharge.

Physical exams were performed at screening, baseline, 3–4 h after randomization on Day 1 and before discharge. Standard clinical laboratory exams were done at screening, before discharge and as needed.

2.6. Data analyses

A sample of 264 participants was needed to provide sufficient power for the analyses of both the primary outcomes. The sample size was calculated based on assumptions derived from an earlier study of lofexidine in a similar patient population (Yu et al., 2008). For SOWS-Gossop on Day 3, a sample size of 264 was estimated, assuming a minimal clinically significant difference (drug versus placebo) of 5 points, a standard deviation of 10, a power level of 90%, statistical significance of 0.05, a 1:1 allocation of participants to lofexidine or placebo, and a 35% attrition rate. For time-to-dropout (the second co-primary outcome variable), a sample size of 224 was estimated based on retention rate data from the earlier study.

The Intent-to-Treat population (ITT) includes all randomized patients. The Evaluable population includes all randomized patients who received at least one dose of study medication and completed the post-medication SOWS-Gossop on Day 1 or on any subsequent day. Completers include all randomized patients who received at least one dose of study medication on Day 5 and completed the SOWS-Gossop on Day 5 or on any subsequent day.

SOWS-Gossop score on Day 3 for the Evaluable population used a prescribed multiple imputation technique to estimate missing data (Alison, 2001; Rubin, 1987). These scores were compared between treatment groups using an analysis of covariance (ANCOVA) model adjusted for baseline SOWS-Gossop scores and using the pre-randomization opioid dependence severity score (SCID) as a covariate, because participants with a range of dependence severities were enrolled. For time to dropout, a log rank test compared the risk-adjusted dropout rates between treatment groups.

The principal secondary analyses of area-under-the-withdrawal-symptoms (i.e., SOWS Gossop scores)-time curve (AUC) for the 5-day Treatment Phase and entire 8-day study were computed using daily SOWS-Gossop scores. Kaplan-Meier curves present the proportion of participants who completed the 5-day Treatment Phase and 8-day study as the survival probability by treatment group over the entire study duration.

Other secondary analyses included: Day 3 SOWS-Gossop (ITT and Completer populations); repeated measures analyses over days (SOWS-Gossop; OOWS-Handelsman; VAS-E; and MCGI severity); and concomitant medication use. Statistical analyses were done using Analysis of Covariance (ANCOVA), *t*-test, Chi-square test, or Fisher's exact test, as appropriate. For repeated measures analyses, $p < 0.01$ was used as a cut-off for statistical significance; otherwise $p < 0.05$ was used.

The proportion of participants with each type of AE was compared between treatment groups using Fisher's exact test. Electrocardiogram variables were analyzed using an ANCOVA model adjusted for baseline readings. Mean changes from baseline in vital signs data were analyzed using *t*-tests. A paired *t*-test was used to compare baseline to end of study clinical laboratory values and an unpaired *t*-test compared treatment groups with respect to change from baseline.

A Data and Safety Monitoring Board reviewed the study annually.

3. Results

3.1. Participant disposition and demographics

Four hundred forty-eight participants were screened for eligibility of which 264 were enrolled and randomized to treatment (134 on lofexidine and 130 on placebo, for a screen fail rate of 40.8%; Fig. 1). Eighty-five participants completed the trial (50/134 [37.3%] lofexidine

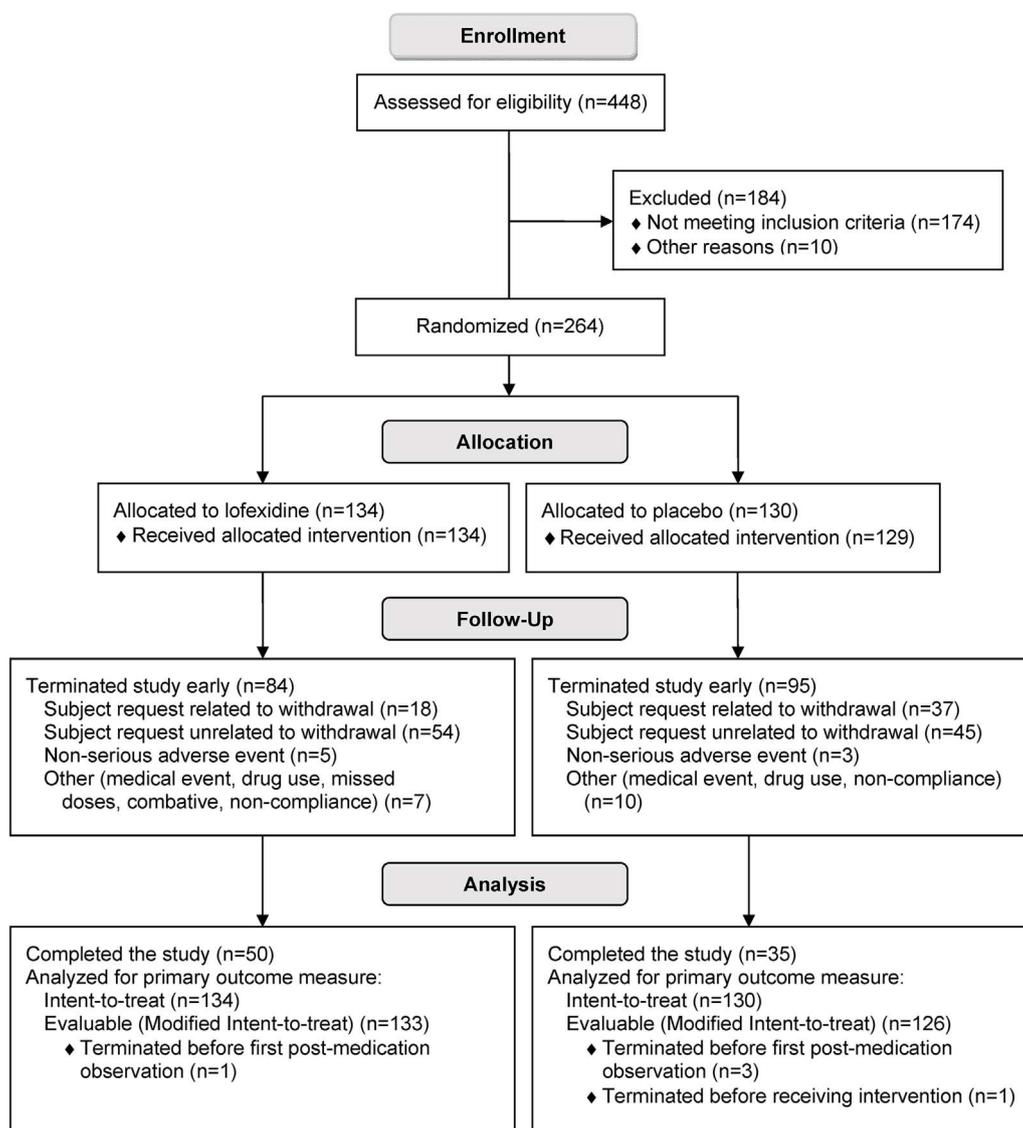


Fig. 1. Flow diagram for the randomized controlled trial of lofexidine.

participants and 35/130 [26.9%] placebo participants) for an overall retention rate of 32.2%. Specific reasons for subject discontinuation are provided in Fig. 1.

No significant differences were found between treatment groups on any demographic parameter. The mean (Standard Deviation, SD) age of study participants was 36.8 ± 10.9 years; the majority were male (75.8%) (Table 1).

All participants met DSM-IV Revised criteria for opioid dependence. The primary opioid of abuse for the lofexidine and placebo groups, respectively, were: heroin (63.8%, 61.2%); oxycodone (19.4%, 23.1%); and hydrocodone (17.2%; 11.5%). Approximately 71% and 75% of patients in the lofexidine and placebo groups, respectively, were taking other medications before study start (most commonly analgesics, sleep aids, and benzodiazepines).

As per FDA recommendation, this was an “all comers” study; all participants meeting admission criteria were eligible, regardless of their particular opioid of choice, amount or duration of use. At randomization all participants were in early withdrawal (with OOWS score of at least 2). The large N was chosen to account for expected variability.

3.2. Co-primary outcome measures

Statistical significance was achieved for both co-primary endpoints

(SOWS-Gossop and time-to-dropout) favoring lofexidine.

3.2.1. SOWS-Gossop on day 3 (3rd day of medically supervised opioid withdrawal)

The mean Day 3 SOWS-Gossop score was approximately 2.4 points lower in the lofexidine group than the placebo group, ($p = 0.0212$) (Table 2). The peak difference in mean SOWS-Gossop scores between treatment groups occurred on Day 2 and placebo scores remained higher than lofexidine scores throughout the 5-day Treatment Phase (Fig. 2). Upon treatment discontinuation, some rebound in lofexidine group scores occurred indicating a mild withdrawal syndrome persisted beyond five days.

3.2.2. Time-to-dropout

Fewer participants in the lofexidine group were early terminators compared to the placebo group, and non-completers in the lofexidine group remained in the study longer than those assigned to placebo ($p = 0.0034$; Table 3).

3.3. Principal secondary outcome analyses

3.3.1. AUC

Over the 5-day Treatment Phase, AUCs were lower in the lofexidine

Table 1
Baseline demographics.

Demographic	Lofexidine (N = 134)	Placebo (N = 130)	Total (N = 264)	p-Value
Age (in years)				
Mean ± S.D.	36.1 ± 11.2	37.6 ± 10.7	36.8 ± 10.9	0.2749 ^a
Race (N, %)				
White	63 (47.0)	76 (58.5)	139 (52.7)	0.1796 ^b
Black	37 (27.6)	27 (20.8)	64 (24.2)	
Hispanic	34 (25.4)	27 (20.8)	61 (23.1)	
Total	134 (100.0)	130 (100.0)	264 (100.0)	
Gender (N, %)				
Male	101 (75.4)	99 (76.2)	200 (75.8)	0.8870 ^b
Female	33 (24.6)	31 (23.8)	64 (24.2)	
Total	134 (100.0)	130 (100.0)	264 (100.0)	
Education (in years)				
Mean ± S.D.	12.0 ± 1.9	12.1 ± 1.9	12.1 ± 1.9	0.6917 ^a
Employment past 3 years (N, %)				
Employed	97 (72.4)	88 (67.7)	185 (70.1)	0.7731 ^b
Student	1 (0.7)	2 (1.5)	3 (1.1)	
Retired/Disability	5 (3.7)	5 (3.8)	10 (3.8)	
Unemployed	31 (23.1)	35 (26.9)	66 (25.0)	
Total	134 (100.0)	130 (100.0)	264 (100.0)	
Marital Status (N, %)				
Ever Married	70 (52.2)	72 (55.4)	142 (53.8)	0.6234 ^b
Never Married	64 (47.8)	58 (44.6)	122 (46.2)	
Total	134 (100.0)	130 (100.0)	264 (100.0)	

^a t-Test.^b Chi-Square.**Table 2**
SOWS-Gossop scores (Evaluable Population Analyses).

Analysis/Time Point	Lofexidine		Placebo		p-Value ^a
	n	Mean ± S.D.	n	Mean ± S.D.	
Multiple Imputation Analysis					
Day 3	133	6.32 ± 4.71	126	8.67 ± 5.54	0.0212

^a Based on analysis of covariance model adjusted for baseline SOWS-Gossop scores and using the pre-randomization opioid dependence severity based on SCID (Structured Clinical Interview for DSM-IV-TR Axis I Disorders) as a covariate.

group than the placebo group for the ITT and Completer populations ($p = 0.0260$ and $p = 0.0188$, respectively) (Table 4). Over the entire 8-day study, AUCs were also significantly lower in the lofexidine versus placebo group for the Completer population ($p = 0.0306$) and showed a trend for the ITT population ($p = 0.0979$).

3.3.2. Proportion of completers

Lofexidine-treated participants stayed in the trial longer than placebo-treated participants for the 5-day Treatment Phase and entire 8 days (Fig. 3). Likewise, a greater proportion of lofexidine-treated participants completed withdrawal than placebo-treated participants, which was statistically significant for those meeting the Completer definition ($p = 0.0030$) and those completing the entire 5-day Treatment Phase ($p = 0.0087$), with a trend for completion of the entire 8 days ($p = 0.0867$) (Table 5).

3.4. Other secondary analyses

Lofexidine consistently demonstrated a positive effect versus placebo on relief of opioid withdrawal over a variety of measures. Of the listed analyses of opioid withdrawal symptoms in Table 6, 11 of the 14 analyses showed either a statistically significant difference or a trend favoring lofexidine over placebo. The average number of withdrawal-

related AEs was less in the lofexidine group than the placebo group for the 5-days of active treatment, but greater than placebo when lofexidine was discontinued (Days 6, 7 and 8). During the study, only two participants in the lofexidine group and three participants in the placebo group were given opioid rescue medications.

3.5. Safety monitoring variables

3.5.1. Blood pressure and heart rate

No differences in pre-dose sitting blood pressure or heart rate were apparent between the treatment groups at baseline. On initiation of lofexidine, blood pressure dropped and remained relatively constant throughout the 5-day Treatment Phase (Fig. 4). Mean systolic pressure dropped about 15 mmHg and diastolic pressure dropped approximately 9 mmHg in lofexidine-treated participants, with a statistically significant difference ($p < 0.01$) between the treatment groups on Days 1–6, but not on Day 7. The same pattern of blood pressure changes was seen for the other three measurement conditions (predose standing and 3 h post initial daily dose both sitting and standing). Orthostatic measurements showed about a 50% greater decrease with lofexidine compared to sitting values. Likewise, the 3 h post-dose measurements showed slightly greater drops than the pre-dose measurements.

Mean sitting heart rate was lower following lofexidine administration over the first 3 days of treatment, then gradually increased above baseline value after lofexidine discontinuation on Day 6, (Fig. 4). In the placebo group, heart rate steadily increased over the course of the study. The difference between treatment groups was statistically significant for Days 1–5 ($p < 0.0001$ for all 5 days). The same general pattern of heart rate changes was seen in the other three treatment assessments; however, in standing conditions, a reflex tachycardia mitigated some of the bradycardic effects of lofexidine and the magnitude of pulse decreases were less compared to sitting conditions. In general, all mean changes were less than 10 bpm versus baseline with the maximum mean change of 14 bpm (baseline versus Day 7) seen in the placebo group in the 3 h post-dose standing condition.

Although adverse events were not directly linked to vital sign assessments, 22.4% of lofexidine participants reported dizziness (versus 6.9% on placebo), many of which were likely caused by hypotension or orthostatic hypotension. One subject on the fifth day of lofexidine treatment had a syncopal episode, which resolved quickly with no treatment or sequelae.

3.5.2. QTc prolongation

The study was not designed for robust assessment of cardiac repolarization effects. However, on daily ECGs, obtained at approximately peak lofexidine concentration, no meaningful difference was found in mean QTc values (using the Bazett correction) between the treatment groups for any population (ITT, Evaluable, and Completer) evaluated. Means varied between approximately 402 and 410 msec. There was no clinically meaningful difference in change from baseline between treatment groups on any day. Mean QTc values decreased over the course of the study for both groups except for a mean increase from baseline of 0.7 msec on Day 1 in the lofexidine group.

Six participants (two on lofexidine, four on placebo) had prolonged QTc intervals reported as AEs. Of the lofexidine-treated participants, one was discontinued from the trial because QTc interval readings on day 1 (471–483 msec) exceeded the protocol-specified cut-off. The other lofexidine-treated subject had prolonged QTc interval on Days 2, 3, and 4, but this observation was subsequently found to be likely due to an error in the machine reading. In those participants with QTc prolongation, the QTc interval rapidly returned to within normal limits and in no case did the PI or consultant feel that additional cardiovascular studies were necessary.

3.5.3. Adverse events

Overall, 130 participants (97.0%) in the lofexidine group and 122

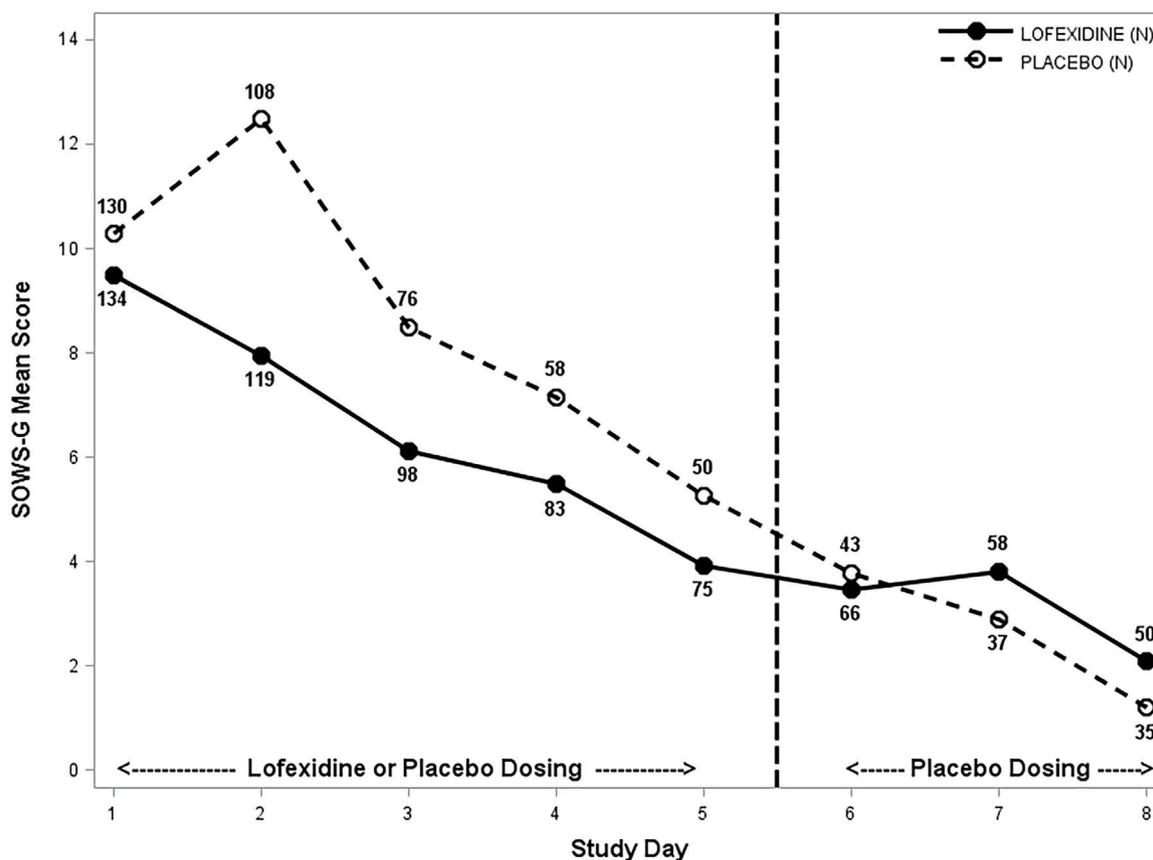


Fig. 2. Effects of lofexidine versus placebo on SOWS-Gossop scores (ITT population).

Table 3
Number of early terminators during the 5-day treatment phase (Evaluable Population analyses).

Variable	Lofexidine	Placebo	Log-Rank p-Value
Number of early terminators ^a	59	80	
Mean time quadrants to early termination ^b	6.9	6.4	0.0034

^a Defined as any subject who withdrew before taking at least one dose of study medication on Day 5 and before completing the Day 5 or any subsequent day’s SOWS-Gossop assessment.

^b Number of 6 h time quadrants until early termination.

Table 4
Area under the withdrawal symptoms-time curves (AUC).

Analysis Population Time Point	Lofexidine		Placebo		p-Value ^a
	n	Mean ± S.D.	n	Mean ± S.D.	
ITT population					
5-day active treatment period	114	20.84 (15.13)	99	25.75 (16.80)	0.0260
8-day study period	114	26.04 (21.28)	99	29.63 (20.64)	0.0979
Completer population					
5-day active treatment period	71	23.97 (16.20)	45	31.86 (17.85)	0.0188
8-day study period	71	32.32 (23.33)	45	40.38 (22.19)	0.0306

^a Wilcoxon test.

participants (93.8%) in the placebo group reported AEs (p = 0.2496) All reported AEs, regardless of attribution, occurring in at least 5% of participants are shown in Table 7. AEs considered withdrawal-related were reported for 85.1% and 87.7% of patients in the lofexidine and

placebo groups, respectively (p = 0.5928). AEs occurring at a significantly (p < 0.01) higher rate in the lofexidine group compared to the placebo group were hypotension, dizziness, dry mouth, and bradycardia, whereas vomiting and lacrimation were significantly (p < 0.01) higher in the placebo group. Other notable differences include pain in extremity, sedation, stomach discomfort, malaise, and sinus bradycardia in the lofexidine group and rhinorrhea, feeling hot and cold, and hypertension in the placebo group. The majority of AEs were classified as mild to moderate in severity with no significant differences between treatment groups. AEs of severe intensity occurred in 23.1% and 29.2% of patients in the lofexidine and placebo groups, respectively.

Sixteen participants (8 on lofexidine, 8 on placebo) experienced AEs classified as serious (SAEs). Of these 16 SAEs, 9 (4 lofexidine, 5 placebo) were due to severe opioid withdrawal and required study discontinuation. These 9 required prolonged hospitalization beyond their discontinuation to achieve stabilization (typically not more than 1 day) and thus met FDA’s SAE definition. The remaining 4 lofexidine SAEs were for hypotension and/or bradycardia, requiring additional inpatient monitoring. All 4 participants were discharged after not more than 1 day of continued assessment. The other 3 SAEs on placebo were persistent hypertension, second degree heart block and prolonged QTc (471 msec in a female subject). All of the SAEs reported during the study resolved rapidly and were without sequelae.

4. Discussion

The present study demonstrates significant efficacy of lofexidine versus placebo for alleviation of symptoms of opioid withdrawal and confirms and extends the finding of Yu et al. (2008). The current study was performed in a similar patient population with differences in study design and primary outcomes to meet the requests of the FDA. The morphine lead-in was eliminated and lofexidine was abruptly discontinued after 5 days of administration (0.8 mg QID) with continued

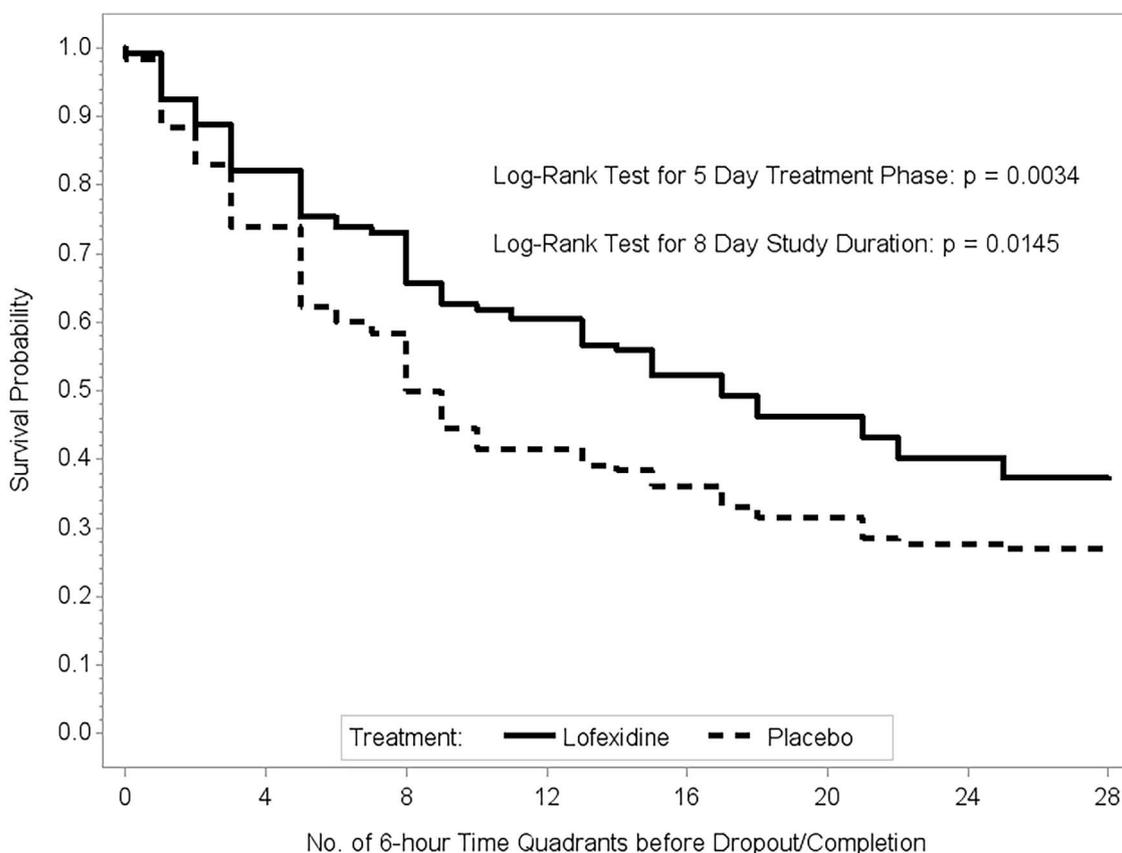


Fig. 3. Effects of lofexidine versus placebo on subject retention rate.

Table 5
Proportion of participants completing the study (ITT population).

Variable	Lofexidine (N = 134) n (%)	Placebo (N = 130) n (%)	p-Value ^a
Participants completing per protocol ^b	71 (53.0)	45 (34.6)	0.0030
Participants completing 5-day treatment ^c	66 (49.3)	43 (33.1)	0.0087
Participants completing 8-day study period ^d	50 (37.3)	35 (26.9)	0.0867

^a Fisher’s exact test.
^b Received the last dose of study medication on Day 5 and completed the SOWS-Gossop on Day 5.
^c Completed the 5-day treatment phase and discharged in the first time quadrant of Day 6 or later.
^d Completed the 8-day study period and discharged in the morning of Day 8.

blinded dosing of placebo for 2 days to assess the degree, if any, of rebound effects. Opioid dependence was determined by history, positive urine toxicology and a minimal score on the OOWS (Handelsman et al., 1987) of at least 2 just prior to randomization. Use of the SOWS-Gossop (Gossop, 1990), a subjective scale completed by participants on Day 3 of withdrawal, better reflected the subjective withdrawal experience based on symptom severity compared to an observer rating (MHOWS in the Yu study). Time-to-dropout was introduced as a co-primary outcome variable.

Despite these differences in study design, there was consistency between the results of MHOWS and SOWS, as well as results for retention and the other secondary outcome measures. Differences in the co-primary outcome measures reached statistical significance ($p = 0.0212$ and $p = 0.0034$) favoring lofexidine over placebo for both Day 3 SOWS Gossop score and time-to-dropout, respectively. Sensitivity analyses confirmed the SOWS-Gossop observations. SOWS scores peaked on Day 2 of withdrawal but remained lower in the lofexidine group throughout the 5 days of treatment as demonstrated in the area-

Table 6
Secondary Efficacy Analyses.

Analysis	Analysis Population	P value, lofexidine versus placebo
SOWS-Gossop, Day 3	ITT	$p = 0.0482$
SOWS-Gossop, Day 3	Completer	$p = 0.1045$
SOWS, Repeated Measures	ITT	$p = 0.0058$
SOWS, Repeated Measures	Completer	$p < 0.0001$
OOWS, Repeated Measures	ITT	$p < 0.0001$
OOWS, Repeated Measures	Completer	$p < 0.0001$
VAS-E, Repeated Measures	ITT	$p = 0.0016$
VAS-E, Repeated Measures	Completer	$p = 0.0118$
MCGI Severity, Subjects, Repeated Measures	ITT	$p = 0.0119$
MCGI Severity, Subjects, Repeated Measures	Completer	$p = 0.2777$
MCGI Severity, Rater, Repeated Measures	ITT	$p = 0.1123$
MCGI Severity, Rater, Repeated Measures	Completer	$p = 0.2444$
Concomitant Meds Given (All), No. Subjects	ITT	$p = 0.0855$
Concomitant Meds Given (All), Daily Meds Used	ITT	$p = 0.0003-0.0007$ for days 1,2 and 3 $p = 0.0730$ for day 4 $p = 0.0221$ for day 5

under-the-SOWS versus days curve. Fewer patients in the lofexidine group were early terminators, and early terminators stayed longer if they were taking lofexidine ($p = 0.0034$). Consistent with this finding, the proportion of patients who completed the 5-day active treatment period was greater for the lofexidine group than the placebo group ($p = 0.0087$). Results from the current study are also in agreement with other trials of lofexidine (see Introduction), demonstrating that lofexidine effectively reduced withdrawal symptoms compared to placebo

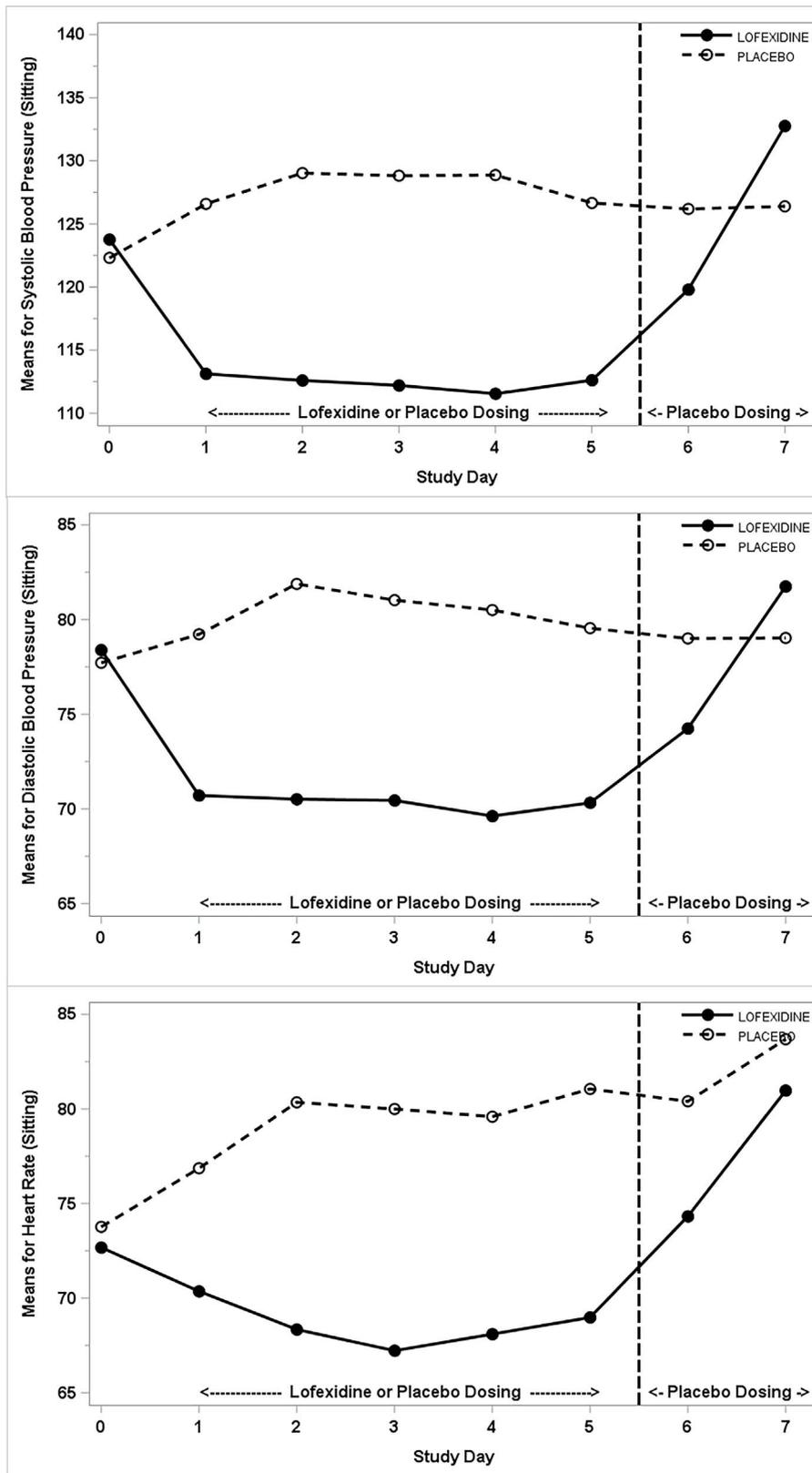


Fig. 4. Effects of lofexidine on systolic (top graph) and diastolic (middle graph) average predose sitting blood pressure and heart rate (bottom graph).

and was generally well tolerated.

Safety outcomes were generally favorable, and, consistent with the findings of the Yu study, lofexidine was well tolerated in this trial. Due, in part, to opioid withdrawal symptoms, AEs were reported for the majority of study participants with withdrawal-related AEs reported for

85.1% of lofexidine-treated participants and 87.7% of placebo-treated participants ($p = 0.5928$).

Those AEs significantly higher ($p < 0.01$) in the lofexidine group versus the placebo group included hypotension, dizziness, dry mouth, and bradycardia. Based on lofexidine mechanism of action, a reduction

Table 7

Number of participants experiencing any adverse event during the 8-day study period with $\geq 5\%$ occurrence in total and/or lofexidine-treated participants^a.

Adverse event MedDRA term	Lofexidine (N = 134) ^b	Placebo (N = 130) ^b	Total (N = 264) ^b	Fisher's p- Value
Insomnia	59 (44.0)	55 (42.3)	114 (43.2)	0.80
Headache	47 (35.1)	45 (34.6)	92 (34.8)	1.00
Diarrhea	36 (26.9)	45 (34.6)	81 (30.7)	0.18
Anxiety	35 (26.1)	30 (23.1)	65 (24.6)	0.57
Nausea	35 (26.1)	42 (32.3)	77 (29.2)	0.28
Hypotension	34 (25.4)	1 (0.8)	35 (13.3)	< 0.01
Dizziness	30 (22.4)	9 (6.9)	39 (14.8)	< 0.01
Dry mouth	19 (14.2)	2 (1.5)	21 (8.0)	< 0.01
Restlessness	18 (13.4)	19 (14.6)	37 (14.0)	0.86
Pain	17 (12.7)	25 (19.2)	42 (15.9)	0.18
Abdominal pain upper	16 (11.9)	20 (15.4)	36 (13.6)	0.47
Chills	16 (11.9)	22 (16.9)	38 (14.4)	0.29
Dyspepsia	15 (11.2)	15 (11.5)	30 (11.4)	1.00
Hyperhidrosis	15 (11.2)	19 (14.6)	34 (12.9)	0.46
Muscle spasms	15 (11.2)	16 (12.3)	31 (11.7)	0.85
Back pain	14 (10.4)	18 (13.8)	32 (12.1)	0.45
Fatigue	14 (10.4)	11 (8.5)	25 (9.5)	0.68
Bradycardia	13 (9.7)	2 (1.5)	15 (5.7)	< 0.01
Myalgia	13 (9.7)	21 (16.2)	34 (12.9)	0.14
Somnolence	13 (9.7)	6(4.6)	19 (7.2)	0.15
Constipation	12 (9.0)	5 (3.8)	17 (6.4)	0.13
Pain in extremity	12 (9.0)	2 (1.5)	14 (5.3)	0.011
Rhinorrhea	12 (9.0)	22 (16.9)	34 (12.9)	0.07
Abdominal pain lower	11 (8.2)	15 (11.5)	17 (9.8)	0.41
Sedation	11(8.2)	2 (1.5)	13 (4.9)	0.02
Yawning	10 (7.5)	14 (10.8)	24 (9.1)	0.40
Tremor	9 (6.7)	15 (11.5)	24 (9.1)	0.20
Muscle twitching	8 (6.0)	9 (6.9)	17 (6.4)	0.81
Musculoskeletal stiffness	8 (6.0)	5 (3.8)	13 (4.9)	0.57
Nasal congestion	8 (6.0)	6 (4.6)	14 (5.3)	0.79
Depression	7 (5.2)	6 (4.6)	13 (4.9)	1.00
Lacrimation increased	7 (5.2)	20 (15.4)	27 (10.2)	< 0.01
Muscle tightness	7 (5.2)	3 (2.3)	10 (3.8)	0.33
Stomach discomfort	7 (5.2)	1 (0.8)	8 (3.0)	0.07
Vomiting	7 (5.2)	27 (20.8)	34 (12.9)	< 0.01
Feeling hot and cold	5 (3.7)	15 (11.5)	20 (7.6)	0.02

^a In order of decreasing occurrence in the lofexidine group.

^b N (%) of participants.

in blood pressure was expected. On initiation of lofexidine, mean systolic and diastolic pressure dropped ~ 15 mmHg and 9 mmHg, respectively, remaining relatively stable throughout the treatment phase. Most instances of hypotension were non-symptomatic and did not require intervention. On abrupt lofexidine discontinuation, blood pressure rose slightly above placebo levels, but there was no clinically significant rebound hypertension.

The safety profile observed for lofexidine in this study was consistent with other lofexidine clinical studies for treatment of opioid withdrawal. In the systematic review by Gowing et al. (2016), hypotensive or other adverse effects were more likely with alpha-2-adrenergic agonists, but this did not translate into a significant difference in withdrawal treatment completion rates. Despite the occurrence of hypotension in the current study, completion rates remained higher for those on lofexidine than placebo. Available data suggest that lofexidine has a better safety profile with a smaller reduction in blood pressure than clonidine (Gowing et al., 2016); however, a comparative study has not been performed with the dose of lofexidine administered in the current trial.

In the present study, lofexidine significantly alleviated symptoms of opioid withdrawal, resulted in longer patient retention in treatment, a higher rate of completing the active treatment period, and demonstrated a favorable safety profile, providing evidence of the potential benefits of lofexidine as a non-opioid treatment for this indication.

Although the 3.2 mg/day dose has been identified as the maximum effective dose, future studies may be warranted at a dose of 2.4 mg/day (consistent with the registered dose in the U.K.) and for longer durations consistent with 7–14 day withdrawal schedules to further assess the lofexidine benefit risk profile.

Few medications are approved by the FDA for treating opioid withdrawal, and there are no current, approved non-opioid treatments for this use. There is no current evidence that lofexidine has abuse potential or addictive properties; and thus, it may represent a meaningful advantage over currently employed opioid agonist medications. Lofexidine potentially offers a safe alternative when a non-opioid agent or augmentation of an opioid agent is desired or in areas where methadone or buprenorphine assisted withdrawal are unavailable (Rosenblatt et al., 2015; Lembke and Chen, 2016).

Role of funding source

US WorldMeds (USWM), LLC, Louisville, KY funded the study. USWM participated in design of the study, monitoring study sites, overall administration of the trial, writing the report and submission for publication.

Contributors

All authors have approved the final article. The authors contributed as follows:

- Charles W. Gorodetzky – Was Principal Investigator and Medical Monitor of the study. Participated in study design, site monitoring and interpretation of the data. Was the primary author of the manuscript.
- Sharon L. Walsh – Was a Site Principal Investigator. Participated in preparation of the manuscript.
- Peter R. Martin – Was a Site Principal Investigator. Participated in preparation of the manuscript.
- Andrew J. Saxon – Was a Site Principal Investigator. Participated in preparation of the manuscript.
- Kristen L. Gullo – Participated in study design, site monitoring, interpretation of the data, overall trial administration and preparation of the manuscript.
- Kousick Biswas – Was principal person involved in data collection and analysis. Participated in study design, data interpretation and preparation of the manuscript.

Conflict of interest

- Charles W. Gorodetzky is a consultant to US WorldMeds.
- Sharon L. Walsh has no conflict to declare.
- Peter R. Martin is a consultant to US WorldMeds.
- Andrew J. Saxon has no conflict to declare.
- Kristen L. Gullo is an employee and shareholder of US WorldMeds.
- Kousick Biswas has no conflict to declare.

Acknowledgements

This trial was fully funded and performed by US WorldMeds, Louisville, KY, in collaboration with the National Institute on Drug Abuse (NIDA) and the Cooperative Studies Program of the U.S. Department of Veterans Affairs.

This study was conducted at 15 sites in the United States and the authors thank the following individuals who served as the Principal Investigator at their study site: Susan Stine, MD (Wayne State University, Detroit, MI); Sharon Walsh, PhD (University of Kentucky, Lexington, KY); Robert Riesenber, MD (Atlanta Center for Medical Research, Atlanta, GA); Adam Lowy, MD (CNS Psychiatric Institute, Washington, DC); Peter R. Martin, MD (Vanderbilt University,

Nashville, TN); Richard Pearlman, MD (Richmond Medical Center, Staten Island, NY); Lance Longo, MD (Aurora Psychiatric Hospital, Wauwatosa, WI); Alipio Mascarenhas, MD (Research Across America, Dallas, TX); Mark Lerman, MD (Alexian Center for Psychiatric Research, Hoffman Estates, IL); John Roache, PhD (University of Texas, San Antonio, TX); Mark Willner, MD (North Miami Research, North Miami, FL); Kashinath Yadalam, MD (Lake Charles Clinical Trials, Lake Charles, LA); Robert Swift, MD (Providence Veterans Affairs Medical Center, Providence, RI); Christopher Stock, PharmD (Salt Lake City VA Healthcare System, Salt Lake City, UT); Andrew Saxon, MD (VA Puget Sound Healthcare System, Seattle, WA).

References

- Alison, P.D., 2001. Missing data. Sage University Paper Series on Quantitative Applications in the Social Sciences 7–136. Sage Publications, Thousand Oaks, CA, pp. 1–84.
- Batey, R., Liddle, C., Craig, P., 1987. A placebo controlled trial of clonidine in the outpatient management of heroin. *Aust. Drug Alcohol Rev.* 6, 11–14.
- Benos, V.J., 1985. Clonidine in opiate withdrawal syndrome. *Fortschr. Med.* 103, 991–995.
- Bradley, B.P., Gossop, M., Phillips, G.T., Legarda, J.J., 1987. The development of an opiate withdrawal scale (OWS). *Br. J. Addict.* 82, 1139–1142.
- CDC AADR drug poisoning involving OA Heroin US 2000–2014 from www.cdc.gov/nchs/data/health_policy/AADR_drug_poisoning_involving_OA_Heroin_US_2000–2014.pdf (Accessed 28 July 16).
- Carnworth, T., Hardman, J., 1998. Randomized double-blind comparison of lofexidine and clonidine in the outpatient treatment of opiate withdrawal. *Drug Alcohol Depend.* 50, 251–254.
- Efron, B., 1971. Forcing a sequential experiment to be balanced. *Biometrika* 58, 403–417.
- Gerra, G., Marcato, A., Caccavari, R., Fontanesi, B., Delsignore, R., Fertonani, G., Avanzini, P., Rustichelli, P., Passeri, M., 1995. Clonidine and opiate receptor antagonists in the treatment of heroin addiction. *J. Subst. Abuse Treat.* 12, 35–41.
- Gerra, G., Zaimovica, A., Giusti, F., Di Gennaro, C., Zambelli, U., Gardini, S., Delsignore, R., 2001. Lofexidine versus clonidine in rapid opiate detoxification. *J. Subst. Abuse Treat.* 21, 11–17.
- Gossop, M., 1988. Clonidine and the treatment of the opiate withdrawal syndrome. *Drug Alcohol Depend.* 21, 253–259.
- Gossop, M., 1990. The development of a short opiate withdrawal scale (SOWS). *Addict. Behav.* 15, 487–490.
- Gowing, L., Farrell, M., Ali, R., White, J., 2004. Alpha 2-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst. Rev.* 4 (CD002024).
- Gowing, L., Farrell, M.F., Ali, R., White, J.M., 2016. Alpha2-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst. Rev.* 5 (CD002024).
- Handelsman, L., Cochrane, K.J., Aronson, M.J., Ness, R., Rubinstein, K.J., Kanof, P.D., 1987. Two new rating scales for opiate withdrawal. *Am. J. Drug Alcohol Abuse* 13, 293–308.
- Kahn, A., Mumford, J.P., Ash Rogers, G., Beckford, H., 1997. Double-blind study of lofexidine and clonidine in the detoxification of opiate addicts in hospital. *Drug Alcohol Depend.* 44, 57–61.
- Kleber, H.D., Riordan, C.E., Rounsaville, B., Kosten, T., Charney, D., Gaspari, J., Hogan, I., O'Connor, C., 1985. Clonidine in outpatient detoxification from methadone maintenance. *Arch. Gen. Psychiatr.* 42, 391–394.
- Lembke, A., Chen, J.H., 2016. Use of opioid agonist therapy for medicare patients in 2013. *JAMA Psychiatry* 73, 990–992.
- Lin, S.K., Strang, J., Su, L.W., Tsai, C.J., Hu, W.H., 1997. Double-blind randomized controlled trial of lofexidine versus clonidine in the treatment of heroin withdrawal. *Drug Alcohol Depend.* 48, 127–133.
- Nazari, S.M., Naseri, M., Mokri, A., Davati, A., Kamalinejad, M., 2013. Hab-o-Shefa (an Iranian traditional medicine compound) in withdrawal syndrome and its effects in acute detoxification of opiate addicts: a randomized, double blind, clinical trial. *J. Med. Plant Res.* 7, 1628–1635.
- Preston, K.L., Bigelow, G.E., 1985. Pharmacological advances in addiction treatment. *Int. J. Addict.* 20, 845–867.
- Rosenblatt, R.A., Andrilla, C.H.A., Catlin, M., Larson, E.H., 2015. Geographic and specialty distribution of US physicians trained to treat opioid use disorder. *Ann. Fam. Med.* 13, 23–26.
- Rubin, D.B., 1987. Multiple imputation for nonresponse in surveys. *Wiley Series in Probability and Statistics*, vol. 17. John Wiley and Sons Inc, New York, NY, pp. 1–228.
- Strang, J., Bearn, J., Gossop, M., 1999. Lofexidine for opiate detoxification: review of recent randomized and open controlled trials. *Am. J. Addict.* 8, 337–348.
- Vernon, M.K., Reinders, S., Mannix, S., Gullo, K., Gorodetzky, C.W., Clinch, T., 2016. Psychometric evaluation of the 10-item short opiate withdrawal scale-Gossop (SOWS-Gossop) in patients undergoing opioid detoxification. *Addict. Behav.* 60, 109–116.
- Yu, E., Miotto, K., Akerele, E., Montgomery, A., Elkashef, A., Walsh, R., Montoya, I., Fischman, M.W., Collins, J., McSherry, F., Boardman, K., Davies, D.K., O'Brien, C.P., Ling, W., Kleber, H., Herman, B.H., 2008. A phase 3 placebo-controlled, double-blind, multi-site trial of the alpha 2 adrenergic agonist, lofexidine, for opioid withdrawal. *Drug Alcohol Depend.* 97, 158–168.