Brand Name[1,2,3,4] **:** Lucemyra

Generic Name[1,2,3,4]**:** Lofexidine

Manufacturer[1,2,3,4]**:** US WorldMeds

Drug Class[1,2,3,4]**:** Alpha-2 Adrenergic Receptor Agonist[1,3,4]

Uses:

Labeled[1,2,3,4]**:** Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults

Unlabeled[2]**:** No results available

Mechanism of Action[1,2,3]**:** Lofexidine is a central alpha-2 adrenergic agonist that binds to receptors (alpha-2A and alpha-2C[1])on adrenergic neurons and reduces the release of norepinephrine and decreases sympathetic tone

Pharmacokinetics:

Absorption:

T_{max}[1,2]	3-5 hours
V_d[1,2]	480 L
$t_{1/2}$[1,2,3]	11-13 hours
Clearance[2]	17.6 L/h
Protein Binding[1,2,3]	55%
Bioavailability[1,2,3]	72%

Metabolism[1,2,3,4]**:** Approximately 30% of the administered lofexidine dose is converted to inactive metabolites during the first pass effect associated with drug absorption from the gut. Lofexidine also displays hepatic metabolism with a slight inhibition of CYP2D6, CYP1A2[1,3], and CYP2C19[1,3].

Elimination[1,2,3,4]**:** Lofexidine is primarily excreted through the kidneys (93.5%). The renal elimination of unchanged drug accounts for approximately 15% to 20% of the administered dose. Lofexidine is also excreted 0.92% unchanged in the feces.

Efficacy:

Gorodetzky CW, Walsh SL, Martin PR, Saxon AJ, Gullo KL, Biswas K. 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. Drug Alcohol Depend. 2017 Jul 1;176:79-88.

Study Design: 8-day inpatient, randomized, multicenter, double-blind, placebo-controlled, parallel-group study with three phases

Description of Study: *Methods:* Patients dependent on short-acting opioids were randomized to receive either lofexidine (134 patients) or placebo (130 patients) for reducing opioid withdrawal symptoms during withdrawal. The study consisted of a screening phase (outpatient days -7 to -1), followed by a treatment phase (inpatient days 1 to 5), and ended with a post-treatment phase (days 6-7). Patients were dosed orally with lofexidine HCL 0.8 mg (4 x 0.2 mg lofexidine HCl tablets) four times daily for a total of 3.2 mg/day, or matching placebo on study days 1 through 5 followed by placebo (4 tablets) four times daily on days 6 through 7. The primary efficacy measures were Short Opiate Withdrawal Scale-Gossop (SOWS) on Day 3 and time-to-dropout. Secondary efficacy measures included the proportion of patients who were completers; area under the 5-day SOWS-Gossop- time curve, and daily mean scores for SOWS-Gossop, Objective Opiate Withdrawal Scale-

Handelsman (OOWS), Modified Clinical Global Impression (MCGI), and Visual Analog Scale for Efficacy (VAS-E). *Outcome Results:* The mean Day 3 SOWS-Gossop score was ~2.4 points lower in the lofexidine group (6.32 ± 4.71) than placebo group (8.67 ± 5.54). Fewer participants in the lofexidine group (59, P = 0.0034) were early terminators compared to the placebo group (80, P = 0.0034), and non-completers in the lofexidine group remained in the study longer than those assigned to placebo. Over the 5-day Treatment Phase, AUCs were lower in the lofexidine group compared to the placebo group for the intent-to-treat and Completer populations. A greater proportion of lofexidine-treated participants complemented withdrawal than placebo-treated patients in both the 5-day treatment and the 8-day study periods.

Limitations: This study was sponsored and funded by US WorldMeds (USWM), the manufacture of lofexidine. Two authors were consultants to US WorldMeds and one author was an employee and shareholder of US WorldMeds, introducing multiple conflicts of interest. There was a significantly higher number of males than females who participated in the study. This makes the results difficult to extrapolate to females.
Due to this being an "all comers" study, meaning all participants meeting admission criteria were eligible, regardless of their opioid of choice, it would also be difficult to extrapolate the results to all patients with an opioid use disorder because the authors only report heroin, oxycodone, and hydrocodone as being the illicit substances the study participants were dependent on.

Conclusions: This study showed that lofexidine for alleviation of symptoms of opioid withdrawal is an effective non-opioid treatment option. Overall, lofexidine had favorable outcomes with respect to alleviating symptoms of opioid withdrawal, resulted in longer patient retention in treatment, higher rate of completing the active treatment period, and had a favorable safety profile. An advantage of using lofexidine is that it has no current evidence of abuse potential or addictive properties compared to the opioid agonist medications used for opioid withdrawal in clinical practice. However, more studies need to be conducted to assess the effectives of lofexidine at a dose of 2.4 mg/day (not 3.2 mg/day) and longer durations consistent with 7-14-day withdrawal schedules to further assess the benefit risk profile.

Yu E, Miotto K, Akerele E, Montgomery A, Elkashef A, Walsh R, Montoya I, Fischman MW, Collins J, McSherry F, Boardman K, Davies DK, O'Brien CP, Ling W, Kleber H, Herman BH. A Phase 3 placebo-controlled, double-blind, multi-site trial of the alpha-2-adrenergic agonist, lofexidine, for opioid withdrawal. Drug Alcohol Depend. 2008 Sep 1;97(1-2):158-68.

Study Design: Inpatient, Phase 3, placebo-controlled, double-blind, randomized multi-site trial with three phases

Description of Study: *Methods:* Patients meeting the inclusion criteria were randomized to receive either lofexidine (34 patients) or placebo (33 patients) for opioid withdrawal symptoms. The study consisted of an opioid agonist stabilization phase (days 1-3), a detoxification/medication or placebo phase (days 4-8), and a post detoxification/medication phase (days 9-11). On days 1 through 3, participants received up to 100 mg/day of subcutaneous morphine to account for the variable amount of heroin that the population was dependent on. During days 4 through 7, participants were medicated with 3.2 mg/day of lofexidine or placebo divided into four doses. On day 8, the participants were given 1.6 mg/day of lofexidine or placebo to minimize the risk of rebound hypertension with lofexidine. Finally, the participants received placebo tablets four times a day on days 9 through 11. The primary efficacy measure was the Modified Himmelsbach Opiate Withdraw Scale (MHOWS) including pupil diameter measures which is an objective assessment of the severity of opioid withdrawal signs without reference to subjective symptoms. The MHOWS data was collected during a 10-minute observation period conducted 2 hours after the first administration of morphine or study medication on days 1 through 10. The secondary efficacy measures were both objective and subjective measures to assess opiate withdrawal severity (dropout day, MHOWS peak effect, and OOWS), SOWS-Gossop, MCGI, subject and rater forms, SOWS-Handelsman, VAS-E of the study medications for decreasing withdrawal sickness, and the number of concomitant medications used to treat opioid withdrawal symptoms and signs. *Outcome Results:* The Data and Safety Monitoring Board stopped the study for ethical reasons due to a significant difference in

favor of lofexidine versus placebo on the primary measure MHOWS. Only 35 participants with usable MHOWS scores were used and the results showed lofexidine scores were significantly lower than placebo on study day 5 (LSM = 19.5 ± 2.1 versus 30.9 ± 2.7; p = 0.0019). The lofexidine subjects also had a trend towards significantly fewer early terminations than placebo (log rank test = 6.62, p = 0.01). The secondary measure results show a trend in decreased objective scores for lofexidine vs placebo on peak MHOWS, day 5 OOWS, and peak OOWS. The peak VAS-E showed lofexidine relieved subjects' withdrawal symptoms significantly more than placebo. The other subjective symptoms scales did not show any significant differences between lofexidine versus placebo.

Limitations: The study was funded by the National Institute on Drug Abuse through the Department of Veterans Affairs Cooperative Studies Program (DVACSP). One author was an employee of the manufacture of the study drug lofexidine, introducing a potential conflict of interest. The study's original sample size was 96 subjects (48 per group) but only 68 patients were randomized after matching the inclusion criteria (35 in lofexidine group versus 33 in placebo group). Due to such a small sample size, only effects with large differences could be detected. For example, only adverse effects such as asthenia, dizziness, hypotension, and insomnia could be detected because there was a large difference identified between the groups. The Data and Safety Monitoring Board stopped the study after reviewing the results of the single planned interim analyses because there was a significant difference in favor of lofexidine versus placebo on the MHOWS measure and it would not have been ethical to continue subjects on placebo. This is a limitation because it does not reflect any data on lofexidine long-term outcomes.

Conclusions: This study showed the lofexidine compared to placebo significantly decrease the signs and symptoms of opioid withdrawal in opioid dependent patients in an inpatient setting. On study day 5 MHOWS (second opioid detoxification treatment day), participants treated with lofexidine had significantly lower scores than placebo subjects (mean 19.5 ± 2.1 versus 30.9 ± 2.7; p = 0.0019). Treatment with lofexidine also had significantly better retention days than placebo subjects (38.2% versus 15.2%; log rank test p = 0.01). However, more studies have to be done that study the efficacy of patients self-medicating with lofexidine for opioid withdrawal symptoms on an outpatient basis, per the instructions of the trial, to add to the existing literature on the tolerability and efficacy of lofexidine as a detoxification agent.

Howells C, Allen S, Gupta J, Stillwell G, Marsden J, Farrell M. Prison based detoxification for opioid dependence: a randomized double-blind controlled trial of lofexidine and methadone. Drug Alcohol Depend. 2002 Jul 1;67(2):169-76.

Study Design: Randomized, double-blind, two-group comparison design

Description of Study: *Methods:* Patients were randomized to receive either methadone (38 patients) or lofexidine (32 patients) for symptoms of opioid withdrawal in a prison setting. The dosage regimen for lofexidine was designed to prevent any rebound hypertension and was given as follows; day 1 0.6 mg, day 2 1.0 mg, day 3 1.4 mg, day 4 2.0 mg, day 5 2.0 mg, day 6 2.0 mg, day 7 1.6 mg, day 8 1.2 mg, day 9 0.8 mg, and day 10 0.4 mg. The methadone regimen was organized by the pharmacist using the standard procedure used in the prison and was given as follows; day 1 30 mg, day 2 25 mg, day 3 25 mg, day 4 20 mg, day 5 20 mg, day 6 15 mg, day 7 15 mg, day 8 10 mg, day 9 10 mg, and day 10 5 mg. The primary efficacy measure was withdrawal symptom severity measured using two withdrawal scales; the 20-item Withdrawal Problems Scale (WPS), and the eight item SOWS. The secondary efficacy measures were rates and timing of withdrawal from the detoxification program and to assess the severity of psychological aspects of drug dependence using the Severity of Dependency Scale (SDS). *Outcome Results:* Complete sets of withdrawal scale data were created from 29 patients from the lofexidine group and 34 patients from the methadone group. The mean total withdrawal scale data score summed over all 10 days of the trial for the lofexidine group was 596.1 ± 208.3 verse the methadone group which was 572.1 ± 184.4 (p = 0.632). Severity of opioid dependence as measured by the SDS was similar in both groups (p = 0.44).

Limitations: The authors of the study never reveal who the primary source of funding was. A number of patients in both groups left the trial due to management reasons in the prison system. Forty-six patients reported using an illicit benzodiazepine during the past month and 36 patients had been prescribed methadone for at least one day before entering the trial. This could have influenced the results. Many of the prisoners who participated in the study were already experiencing withdrawal symptoms when the study started, making it difficult to determine how much lofexidine or methadone really helped relieve the opioid withdrawal symptoms. The initial dosing interval of lofexidine for opioid withdrawal is four times daily. This study started the initial dose interval of lofexidine as twice daily, which could have influenced the results.

Conclusions: The study showed that there were no significant differences in withdrawal scores between the two groups at the beginning of the trial and the two groups showed similar trends of decreasing scores during the 10 days of the trial. Withdrawal symptoms also subsided at the same rate in both treatment groups once started on medication. No severe or serious adverse events with hypotensive effects were reported with lofexidine use during the trial. The investigators conclude that lofexidine has comparable efficacy to methadone in improving the effects of the opioid withdrawal syndrome.

Contraindications[1,2,3,4]**:** Specific contraindications have not been determined

Precautions:

Cardiovascular[1,2,3]	Hypotension, orthostasis, bradycardia, and syncope can occur; dose adjustments may be warranted; monitoring and hydration recommended.
	Avoid use in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, and in patients with marked bradycardia.
	QT interval prolongation has been reported; monitoring recommended in patients with congestive heart failure, bradyarrhythmia, hepatic or renal impairment, or electrolyte abnormalities and in patients taking other medications known to increase QT interval. In patients with electrolyte abnormalities, correct abnormality first, then monitor ECG before initiating lofexidine[1].
	Avoid use in patients with congenital long QT syndrome.
Concomitant Use[2]	Avoid concomitant use with drugs that decrease pulse or blood pressure.
Opioid Overdose[1,2,3]	Increase risk of fatal overdose with resumed opioid use; treatment for opioid use disorder should only be performed in conjunction with a comprehensive management program. Patients should be aware that they may be more sensitive to lower doses of opioids after lofexidine treatment is discontinued, after a missed dose, or near the end of the dosing interval[1].
Withdrawal[1,2,3]	Abrupt discontinuation can cause a marked rise in blood pressure; gradually reduce dose. Discontinuing lofexidine abruptly may result in additional adverse events such as anxiety, chills, diarrhea, extremity pain, hyperhidrosis and insomnia[1].
CNS Depression[1,3]	May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks that require mental alertness.
Hepatic/Renal Impairment[1,3]	Prolongation of the QTc interval is more pronounced in these patients. Use caution in patients with hepatic or renal impairment.
CYP2D6 Poor Metabolizers[1,3]	Exposure to lofexidine may be increased; monitor for orthostasis and bradycardia.

Adverse Effects:

Cardiovascular Effects[1,2,3,4]	Bradyarrhythmia (24% to 32%)
	Hypotension (30%)
	Orthostatic hypotension (29% to 42%)
	Prolonged QT interval
	Syncope (0.9% to 1.4%)
	Torsades de points (<1%)[1,3]
Gastrointestinal Effects[1,2,3]	Xerostomia (10% to 11%)
Neurologic Effects[1,2,3,4]	Dizziness (19% to 23%)
	Insomnia (51% to 55%)
	Sedation (12% to 13%)
	Somnolence (11% to 13%)
Otic Effects[1,2,3]	Tinnitus (0.9% to 3.2%)
Other [2,3]	Withdrawal symptom

Drug Interactions:

Increased Risk of CNS Depressant Effects[2]
Lofexidine may enhance the CNS depressant effects of other CNS depressant drugs.

Increased Risk of QT Interval Prolongation[2]
Lofexidine may enhance the QT interval of other QT interval prolongation drugs.

Increased Risk of Torsades de Pointes[2]
Amisulpride

Increased Risk of Bradycardia[1]
Ceritinib

Increased Risk of Hypotension[1]
Bromperidol

Increased Plasma Levels of Lofexidine[2]
Bupropion, Fluoxetine*, Paroxetine*, Quinidine*, Terbinafine

Inaccurate Dosimetry Calculations or Reduced Efficacy[2]
Iobenguane I 131

Reduced Efficacy of Oral Drug[2]
Naltrexone

Dosing/Administration[1,2,3,4]:
Initial Oral Dose: 0.54 mg (3 0.18 mg tablets) QID (every 5-6 hours) during peak withdrawal symptoms (generally the first 5-7 days after last opioid use). Adjust dosing based on tolerability and withdrawal symptoms and may continue for up to 14 days if needed. Maximum dose 0.73 mg/dose or 2.88 mg/day.

Discontinuation of Therapy: decrease dose gradually over 2-4 days (reduce by 0.18 mg per dose every 1-2 days).

Use in Special Circumstances:
Geriatric[1,2,3]: same as adult dosing; use with caution; consider lower doses similar to those in renal impairment

Adult Renal Impairment[1,2,3]:
- eGFR ≥90 mL/minute: no dosage adjustment necessary
- eGFR 30 to 89.9 mL/minute: 0.36 mg (2 tablets) QID (total daily dose 1.44 mg)
- eGFR <30 mL/minute: 0.18 mg (1 tablet) QID (total daily dose 0.72 mg)
- ESRD or on Hemodialysis: 0.18 mg QID; minimally dialyzable; administer without regard to timing of dialysis

Adult Hepatic Impairment[1,2,3]:

Mild (Child-Pugh Class A): no dosage adjustment necessary
Moderate (Child-Pugh Class B): 0.36 mg (2 tablets) QID (total daily dose 1.44 mg)
Severe (Child-Pugh Class C): 0.18 mg (1 tablet) QID (total daily dose 0.72 mg)

Adolescents[3]: safety and efficacy have not been established

Children[3]: safety and efficacy have not been established

Infants[3]: safety and efficacy have not been established

Conclusion:

Lofexidine is an effective therapy for patients experiencing symptoms of opioid withdrawal and shows possible efficacy in both inpatient and outpatient management. More studies need to be conducted to evaluate lofexidine's most effective length of treatment for opioid withdrawal. Lofexidine is safe to use as monotherapy with important drug interactions to be aware of such as agents that prolong QTc interval and blood pressure lowering agents. Studies determining lofexidine's place in treatment of withdrawals from prescription opioid drugs, instead of illicit substances, also need to be completed. The side effects and adverse events of the drug appear to be minimal, compared to the symptoms of withdrawal, except in patients with cardiovascular problems. It is difficult to assess to what degree lofexidine may affect cardiovascular status at the start of therapy.

Recommended References:

1. Lofexidine. Lexi-Drugs [database online]. Lexi-Comp, Inc; Accessed: August 15, 2018.
2. Lofexidine. In: IBM Micromedex System [database online]. Greenwood Village, Colo: Thompson Micromedex. Accessed: August 15, 2018.
3. Lofexidine. Clinical Pharmacology [database online]. Gold Standard, Inc., 2007. Accessed: August 15, 2018.
4. Lofexidine (Lucemyra) for Opioid Withdrawal. The Medical Letter on Drugs and Therapeutics. 2018 Jul 16; 60 (1551): 115-117.
5. Gorodetzky CW, Walsh SL, Martin PR, Saxon AJ, Gullo KL, Biswas K. 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. Drug Alcohol Depend. 2017 Jul 1;176:79-88. doi: 10.1016/j.drugalcdep.2017.02.020. Epub 2017 May 10. PubMed PMID: 28527421.
6. Yu E, Miotto K, Akerele E, Montgomery A, Elkashef A, Walsh R, Montoya I, Fischman MW, Collins J, McSherry F, Boardman K, Davies DK, O'Brien CP, Ling W, Kleber H, Herman BH. A Phase 3 placebo-controlled, double-blind, multi-site trial of the alpha-2-adrenergic agonist, lofexidine, for opioid withdrawal. Drug Alcohol Depend. 2008 Sep 1;97(1-2):158-68. doi: 10.1016/j.drugalcdep.2008.04.002. Epub 2008 May 27. PubMed PMID: 18508207; PubMed Central PMCID: PMC2613766.
7. Howells C, Allen S, Gupta J, Stillwell G, Marsden J, Farrell M. Prison based detoxification for opioid dependence: a randomised double blind controlled trial of lofexidine and methadone. Drug Alcohol Depend. 2002 Jul 1;67(2):169-76. PubMed PMID: 12095666.

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