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Lucemyra® (Lofexidine): First Non-Opioid Approved for the Management of Acute Opioid Withdrawal

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It is no secret that there is an "opioid use epidemic" in the United States with the CDC reporting opioid misuse costs the United States over $78 billion a year.[1] It is also estimated that 21-29% of chronic pain patients do not use their opioid medications as prescribed.[2] With this misuse, complications of opioid withdrawal are becoming more prevalent and there is a growing need to manage the symptoms. These symptoms include: gastrointestinal symptoms (cramping, diarrhea, nausea/vomiting), flu-like symptoms (diaphoresis, goosebumps, lacrimation, rhinorrhea, and shivering), nervous system involvement (tachycardia, agitation, restless leg syndrome, insomnia, anxiety, and mild hypertension), and myalgias or arthralgias.[3] Withdrawal symptoms can start after 2-3 times the half-life of the withdrawn opioid. Lucemyra® (lofexidine hydrochloride), a central alpha-2 adrenergic agonist, was FDA approved on May 16, 2018 for the indication of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.[4] Prior to the approval of lofexidine, the pharmacological options are opioid withdrawal symptoms were limited. Methadone was the only medication FDA approved for opioid withdrawal.[5] Other treatments used for opioid withdrawal include benzodiazepines, haloperidol, beta blockers, clonidine, and anticonvulsants. Buprenorphine and clonidine are used off-label to manage opioid withdrawal. Lofexidine will fill a gap in care, as it is the first non-opioid FDA approved treatment for opioid withdrawal and the one product approved for the facilitation of completion of opioid discontinuation treatment. The purpose of this article is to provide a review for the safety and efficacy of Lucemyra® (lofexidine hydrochloride) for the treatment of acute opioid withdrawal.

IN THIS ISSUE

Pharmacology

Mechanism of Action

Lofexidine (Lucemyra®) is a selective alpha-2 adrenergic agonist (selective for alpha-2A/C) that reduces the release of norepinephrine from adrenergic neurons in the brain and decreases sympathetic tone.[6] Norepinephrine levels may become excessively elevated when chronic opioids are abruptly discontinued and cause some symptoms of withdrawal. Lofexidine can reduce the release of norepinephrine caused by opioid withdrawal.

Pharmacokinetics

Lofexidine reaches peak concentrations at 3 to 5 hours after administration.[6,7] Lofexadine has a bioavailability of 72% and its absorption is not affected by food. Lofexidine is primarily metabolized hepatically via CYP2D6, but also via CYP1A2 and CYP2C19 to a minor extent. Approximately 30% is converted to inactive metabolites during first-pass metabolism. Lofexidine has a half-life between 17 and 22 hours at steady-state. About 15-20% of lofexidine is eliminated unchanged in the urine.

Clinical Trials

Lofexidine has been available outside of the United States for several decades. However, the FDA required specific phase III trials to evaluate lofexidine's safety and efficacy in the treatment of acute opioid withdrawal. Because lofexidine has been available overseas, several clinical trials are published evaluating its efficacy compared to other medications for the same indication. The following sections will review lofexidine clinical trials relevant to opioid withdrawal and the FDA approval here in the United States.

The studies used many of the same scales for assessing withdrawal and those scales described here. The Short Opiate Withdrawal Scale-Gossop (SOWS-Gossop) scale is a subjective scale which assesses 10 opioid withdrawal symptoms.[8] It is a 10-item questionnaire developed to evaluate opioid withdrawal symptom severity. It is scored from 0 (none) to 3 (severe) with a total range of 0–30. A change in score of 2–4 points is considered a clinically meaningful improvement. The scale was derived from the original 32-item Opiate Withdrawal Scale in order to reduce redundancy while providing an equally sensitive measure of opioid withdrawal symptom severity appropriate for research and clinical practice. The Objective Opiate Withdrawal Scale (OOWS) measures 13 physically observable signs listed as present or absent.[9] The Modified Clinical Global Impression Scale is a scale used for assessing global illness severity and changes in patients with bipolar disorder.[10] The Structure Clinical Interview Axis I (SCID) is a semi-structured interview used to assist in determining DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) Axis I diagnoses.[11] The Visual Analogue Scale (VAS) scale is a subjective scale used to rate opioid craving.[12] VAS is usually a horizontal line

Table 1 | Select Lofexidine Pharmacokinetics[6]

Parameters	Value
Absorption	
Bioavailability	72%
C_{max}	0.82 ng/mL
T_{max}	3 hours
Distribution	
V_d	480 L
Metabolism	
Primary	CYP2D6
Secondary	CYP1A1, CYP2C19
Elimination	
Half-life	17-22 hours
Renal	~93.5% (15-20% unchanged)
Feces	~1.0%

-Values reported represent mean levels

Cmax = maximum concentration; **CYP = cytochrome P450 enxyme; Tmax** = time to maximum concentration; **L** = liter; **mL** = milliliter; **ng** = nanogram; **Vd**=volume of distribution;

anchored by word descriptors at each end. The patient marks on the line the point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimeters from the left hand end of the line to the point that the patient marks.

Gorodetsky et al. (2017)

Gorodetsky et al. conducted a Phase 3, randomized, multicenter, double blind, placebo controlled study to assess the safety and efficacy of lofexidine for relief of symptoms in individuals undergoing inpatient opioid withdrawal.[13] The study included 264 patients and took place in 15 sites across the US from June 16, 2006 to October 26, 2007. The length of the study was 8 days with 3 phases: screening phase (up to 7 days prior), treatment phase (Days 1-5), post-treatment phase (Days 6-7). Patients were randomly allocated 1:1 to either oral lofexidine group (N=134) or placebo (N=130). During the treatment phase (Days 1 through 5), patients received either oral lofexidine HCl 0.8 mg four times daily (total daily dose of 3.2 mg/day) or matching placebo. During the post-treatment phase (Days 6 and 7), patients in both treatment and placebo groups received placebo (4 tablets) 4 times daily. The co-primary outcomes of the study were the change in SOWS-Gossop score on Day 3 from baseline and time-to-dropout which were analyzed using intention-to-treat method. The secondary outcomes were the proportion of participants who were completers, area under the 5-day SOWS-Gossop – time curve (i.e.,AUC1–5), and daily mean SOWS-Gossop, OOWS-Handelsman, MCGI (subject and rater), and VAS-E scores.

The inclusion criteria for the trial were patients 18 years of age or older and seeking treatment of opioid dependence (DSM-IV), meeting the Structure Clinical Interview Axis I (SCID) criteria for dependence on short-acting opioid, self-reported opioid use of at least 21 of the last 30 days, patients who showed signs of withdrawal just before randomization [Score of 2 or greater on the Handelsman Objective Opiate Withdrawal Scale (OOWS-Handelsman], positive urine screen for opioids but negative for methadone or buprenorphine, 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. The exclusion criteria included any serious medical or psychiatric illness, self-reported Acquired Immune Deficiency Syndrome (AIDS), clinically significant abnormal lab values, dependence or any psychoactive substance other than opioids that required withdrawal, an abnormal cardiovascular exam [Prolonged QTc (>450 msec for males, >470 msec for females), significant hypertension (>160/100 mmHg), significant hypotension (<90/60 mmHg), bradycardia (<45 bpm), history of MI], use of methadone or buprenorphine in the last 14 days, use of psychotropics, prescription analgesics, anticonvulsants, antihypertensives, antiarrhythmics, anti-retroviral, or cholesterol lowering agents in last 4 weeks, donation of blood in the last 8 weeks, participation in another investigational study in the last 3 months, inadequate venous access, active tuberculosis or syphilis, and pregnancy or lactation.

The results of the trial showed lofexidine group was statistically better at reducing withdrawal symptoms compared to placebo. The mean SOWS-Gossop score on Day 3 was 2.4 points lower in the lofexidine group compared to placebo, 6.32 vs 8.67 (p =0.0212).[13] The time to study dropout was compared at different levels of completion in the study: by the protocol, at 5 days of completion and at the full 8 days of completion. Patients that completed the study per protocol (Received the last dose of study medication on Day 5 and completed the SOWS-Gossop on Day 5) was 53% in the lofexidine compared to 34.6% in the placebo group. Patients that completed 5-day treatment (Completed the 5-day treatment phase and discharged in the first time quadrant of Day 6 or later) was 49.3% in the lofexidine group compared to 33.1% in the placebo group. Patients that completed the 8-day study period (completed the 8-day study period and discharged in the morning of Day 8) was 37.3% in the lofexidine group compared to 26.9% in the placebo group. Overall, the patients in the lofexidine group generally stayed in the trial longer than those in placebo and had a higher proportion of patients who completed the trial (p=0.003). The secondary outcome, area under the 5-day SOWS-Gossop – time curve, was lower in both the ITT lofexidine group and with the lofexidine group that completed all 8 days (Completers) when compared to placebo (ITT: p=0.026; Completers: p=0.0188). The SOWS-Gossop, OOWS-Handelsman, MCGI and VAS-E scores were analyzed as Intent-to-Treat population (ITT) and Completers. The ITT population includes all randomized patients. Completers include all randomized patients who received at least one dose of study medication (lofexidine or placebo) on Day 5 and completed the SOWS-Gossop on Day 5 or on any subsequent day. Of the 14 analyses done using these scores 11 of the 14 were statistically significant for lofexidine over placebo.

Guo et al. (2018)

Guo et al. conducted a single site, randomized, parallel-group, double-blind trial to compare the efficacy of lofexidine to diazepam for the treatment of opioid withdrawal symptoms.[14] The study included 111 patients and took place from August 28, 2012 to July 28, 2015. The length of the study was 14 days composed of two phases: a 10-day medication phase and a 4 day post-medication phase where the patients received cognitive behavioral therapy based counseling, group counseling, art therapy, and psycho-education. The primary outcome of the study was the mean OOWS score on days 3 and 4 from baseline between the diazepam and lofexidine groups. The secondary outcomes of the study

were retention rate, pupil size, SOWS score and VAS rating for opioid craving. Retention rate was defined as the number of days the patient remained in the study from randomization/start of the medication to the last day of study. Pupil size was measure daily by matching against the 8 size examples from 1 mm to 8 mm on the Clinical Institute for Withdrawal Assessment for benzodiazepines (CIWA-B) scale.

Those included in the study were patients aged 21-55, a DSM -IV diagnosis of opioid dependence, a positive urine screen for the presence of opiates, and being able to provide written informed consent. The exclusion criteria for the trial were history of allergy/sensitivity to alpha 2-adrenergic medications, co-dependence on alcohol, benzodiazepines or any other drug that would require detoxification, a history of major physical illness, major psychiatric illness, prescribed opioid analgesics and similar narcotic analgesics, antihypertensive, antiarrhythmic or antiretroviral medication, a baseline blood pressure greater than 140/90 mmHg or lower than 90/65 mmHg, and/or baseline pulse rate <65 beats/min, significant abnormal findings from blood tests or ECG during screening, pregnant or breast-feeding, unable to temporarily stop co-medications that could cause QT-interval prolongation and hypotension in conjunction with lofexidine.

The results of the study showed that the primary outcome, the mean of OOWS scores on days 3 and 4, did not differ significantly between the lofexidine and diazepam groups. The mean difference between the lofexidine and diazepam groups on day 3 was -0.19 from baseline and -0.18 on day 4 from baseline.[14] Patients in the diazepam group had a small change in OOWS scores on days 3 to 4 from baseline compared to those in the lofexidine group (p = 0.52; 95% CI: −0.76, 0.39). The secondary outcome of pupil size was lower in the lofexidine group compared to diazepam up until day 12 (p = 0.02 ; 95% CI: -0.79,-0.09), which was statistically significant in the lofexidine group. The other secondary outcome, retention rate, SOWS score and VAS were not statistically different between groups.

Law et al. (2017)

Law et. al conducted a randomized, double-blind study comparing the efficacy of buprenorphine/naloxone versus methadone/lofexidine for the treatment of low dose, short-term, opiate-dependent patients going through withdrawal.[15] Patients were randomly allocated 1:1 to receive either buprenorphine/naloxone 4 mg/1 mg by mouth daily (in two divided doses) for ten days (n = 40) or methadone 30 mg by mouth daily for three days and concomitant lofexidine 0.18 mg by mouth four times a day as needed for fourteen days (n = 40), during the detoxification phase of the study. The inclusion criteria for the study were age 16-65, a primary diagnosis of DSM-IV opiate dependence, current use of opiates equivalent to 10-30 mg methadone orally (40-240 morphine milliequivalents), and a history of opioid dependence for less than three years (excluding periods of abstinence). The exclusion criteria were other drug dependencies meeting DSM-IV diagnosis, high suicide risk that require hospital admission, clinically significant physical or psychiatric disease, living with other individuals dependent on illicit opiates, benzodiazepine use within five days, pregnancy, lactating, or of childbearing potential without contraception. A total of 40 participants were randomized to the buprenorphine/naloxone treatment arm and 40 were randomized to the methadone/lofexidine treatment arm. Given the time that this study, it is possible that the UK had not adopted the DSM-5 criteria. The primary outcomes of the study were urine drug screens for opiates and withdrawal and craving question-

Table 2 | Summary of Lofexidine Withdrawal Treatment Clinical Trials—Primary Endpoints

Trial	Intervention	Primary Endpoint	Results
Gorodetzky et al.[13]	Lofexidine 0.8 mg PO QID for 5 days (n=133) -vs- Placebo for 5 days (n=126)	Co-primary outcomes: • Change from baseline in SOWS-Gossop[a] score on day 3 of treatment • Mean time quadrants to early treatment termination[b]	**SOWS-Gossop score:**[a] 6.32 ± 4.71 vs 8.67 ± 5.54 P = 0.0212 for comparison **Time-to-dropout:**[b] 6.9 (41.4 h) vs 6.4 (38.4) P = 0.0034
Guo et al.[14]	Lofexidine (in 3 divided doses): 0.8 mg/day on day 1, increased by 0.4 to 0.8 mg per day, up to 2.2 mg per day on days 3-4 (n=55)[c] -vs- Diazepam 10 mg days 1-2, 15 mg days 3-4 (n=53)	Difference from baseline in the mean OOWS[d] score measured on treatment days 3 and 4	Mean difference on days 3 and 4: diazepam – lofexidine -0.187 (95% CI, -0.763 to 0.39)

a: SOWS-Gossop: This subject-rated scale consists of 10 items, scored from 0 (none) to 3 (severe) (total range 0–30). A change score of 2–4 points is a clinically meaningful improvement. The SOWS was completed at baseline, 3.5 h after the first dose of study medication on days 1–7 and at discharge (day 8).[3]

b: measured as number of 6 hour time quadrants until early termination

c: In the trial, the peak dose of lofexidine was reduced to 2.2 mg instead of the recommended maximum of 2.4 mg because of lower doses studied in Asian populations and a general lower body mass index of Asian patients.

d: The Objective Opiate Withdrawal Scale (OOWS) is an objective assessment of the severity of opioid withdrawal signs and assesses 13 signs. Scores range from 0-13, with a higher score indicating more withdrawal symptoms. Data were collected during a 5-minute observation of the participant.

95% CI = 95% confidence interval; **mg** = milligram; **PO** = by mouth; **QID** = four times daily;

naires.

During the study, patients attended the clinic daily for 2 to 6 weeks for opiate use stabilization, then investigator induced opiate withdrawal, followed by 2.5 weeks of opiate detoxification. During the induction phase, patients were given either 30 mg methadone or buprenorphine/naloxone 2 mg/0.5 mg twice daily for 2 weeks. Then, within the next 4 weeks, patients started the detoxification phase once they provided 3 consecutive urine samples free of illicit opiates within 1 week. Once in the detoxification phase, the buprenorphine/naloxone group was medicated for 10 days and the buprenorphine dose was decreased titrated 1 mg every 3 to 4 days and discontinued on day 10. In the methadone/lofexidine group, methadone 30 mg was given for only 3 days while lofexidine was given regularly for 14 days and provided as needed for an additional 3 days. During the detoxification phase, patients in both groups were also allowed to use other adjunctive treatments as needed. These included zopiclone 7.5-15 mg by mouth at night for sedation, ibuprofen 400 mg four times a daily as needed for aches and pains, promethazine 10-20 mg a day as needed for anxiety, and hyoscine 20 mg a day as needed for stomach cramps and spasms. A total of 90% of the participants completed the induction phase and 58% completed stabilization, and of that group, 96% of the participants completed the detoxification phase.

The results of the induction and stabilization phase are shown below in **Table 2**. During the induction phase of the study, withdrawal symptoms resolved slower in the buprenorphine/naloxone group and these patients had higher opiate cravings ($p < 0.05$, 95% confidence interval -3.5, -0.38).[15] During the detoxification phase, the onset of action was quicker and the intensity of withdrawal symptoms was greater in the methadone/lofexidine group ($p < 0.01$, 95% confidence interval 3.0, 8.3). The study showed that the methadone/lofexidine group had significantly lower scores on the Opiate Craving Scale compared to the buprenorphine/naloxone group. The scale is scored from 0-18, with higher scores indicating a higher level of craving. The methadone/lofexidine group had higher scores on the 'Normal' dimension of the Single Dose Opiate Questionnaire (mean difference 10.1; p=0.01). The peak level of withdrawal symptoms occurred at day 8 for the methadone/lofexidine group and day 12 of the buprenorphine/naloxone group were 29.0 and 23.1, respectively, based on the Opiate Withdrawal Scale. This scale measures the subjective withdrawal symptoms using 32-item questionnaire that asks how strong each symptoms is on a four point scale (0= none, 4= severe) during the past 24 hours. The scores range from 0 to 96, with higher scores indicating worse symptoms. No significant differences were observed between groups in terms of cravings, proportion of negative urine samples, or blood pressure. Additionally, there were no differences in the number of participants successfully completing the induction/stabilization or detoxification phase between the groups. Overall, there was no difference in positive drug screens between the two treatment arms.

The authors stated that the possible non-equivalence of doses in the different treatment arms could have potentially confounded the findings during the withdrawal phase of the study. Overall, they concluded that buprenorphine/naloxone may produce a delayed but more comfortable detoxification compared with lofexidine, and lofexidine may be advantageous for expediting detoxification but with more discomfort than buprenorphine/naloxone.

Adverse Effects and Precautions

The most common adverse effects, seen in more than 10% of patients, were bradycardia (24% to 32% of patients), dizziness, drowsiness, hypotension (about 30% of patients) including orthostatic hypotension (about 29% to 42% of patients), insomnia, and xerostomia.[6] Lofexidine can cause a decrease in blood pressure, a decrease in pulse, and syncope. Lofexidine prolongs the QT interval and should be avoided in patients with congenital long QT syndrome, because of this when used with methadone the clinician should monitor ECG. Lofexidine also potentiates the CNS depressant effects so should be used with extreme caution with benzodiazepines, alcohol, barbiturates, and other sedating drugs. Lofexidine alters the pharmacokinetics of oral naltrexone at steady state and may reduce its efficacy. This interaction is not expected with non-oral naltrexone. Concomitant use of lofexidine and paroxetine increases the absorption of lofexidine and increases the risk of orthostatic hypotension and bradycardia.

Dosing and Administration

Lofexidine is available in a 0.18 mg tablet and may be administered with or without food.[6] The usual dose for the treatment of opioid withdrawal symptoms is 0.54 mg (3 tablets) 4 times daily during peak withdrawal symptoms (typically the first 5 to 7 days after last opioid use) and a single dose should not exceed 0.72 mg. The total daily dose of lofexidine should not exceed 2.88 mg (16 tablets). Lofexidine may be continued for up to 14 days. Treatment for longer than 14 days has not been evaluated by clinical trials. Doses may be tapered up or down based on patient tolerability and as opioid withdrawal symptoms start to wane. Abrupt discontinuation of lofexidine may cause withdrawal symptoms such as a marked rise in blood pressure, diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain. When discontinuing lofexidine, it should be tapered by gradually reducing the dose by 1 tablet (0.18 mg) every 1 to 2 days over a 2 to 4 day period.

For patients with an eGFR ≥90 mL/minute/1.73 m2: No dosage adjustment necessary. For an eGFR of 30 to 89.9 mL/minute/1.73 m2: 0.36 mg (2 tablets) 4 times daily. For an eGFR <30 mL/minute/1.73 m2: 0.18 mg (1 tablet) 4 times daily. For patients in end-stage renal disease (ESRD) or on hemodialysis: 0.18 mg (1 tablet) 4 times daily. Lofexidine is minimally dialyzable and can be administered without regard to the timing of dialysis. Hepatic dose adjustments are based on Childs-Pugh class scores for hepatic impairment. For Child-Pugh class A (score: 5-6): No dosage adjustment necessary. For Child-Pugh class B (score: 7-9): 0.36 mg (2 tablets) 4 times daily. For Child-Pugh class C (score >9): 0.18 mg (1 tablet) 4 times daily. The safety and effectiveness of lofexidine has not been established in pediatric or geriatric patients.

Conclusion

In conclusion, lofexidine is a new FDA approved drug for the management of opioid withdrawal. One benefit of this medication over methadone, the only other agent with an FDA indication for opioid withdrawal, is that lofexidine is not an opioid. Moreover, there have been multiple trials studying lofexidine for the management of opioid withdrawal symptoms and these studies showed positive results in reducing these symptoms; however, there is some research showing a lack of significant effect.[13,14,15] A potential limitation of this agent is its potent hypotensive properties, which can make it difficult to tolerate in the recommended doses and limit its use in patients. However, lofexidine has shown

to have less blood pressure effects compared to clonidine. In clinical practice, prescribing lofexidine as a withdrawal treatment should not be difficult, as it is not an opioid nor does it have many contraindications. Overall, lofexidine is a viable option in the treatment of the symptoms of patients experiencing opioid withdrawal.

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