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Lofexidine for acute opioid withdrawal: A clinical case series

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Abstract

Introduction: Maintaining abstinence through the opioid withdrawal period is a substantial barrier to treatment for patients with opioid use disorder. The alpha-2 agonist lofexidine has demonstrated efficacy and safety in clinical trials, but pragmatic studies describing its use in clinical practice are lacking. This case series describes the use of lofexidine for opioid withdrawal symptoms in an inpatient addiction treatment facility.

Methods: Seventeen patients receiving at least 1 dose of lofexidine during inpatient treatment for opioid withdrawal were included in this study. A retrospective chart review was conducted for clinical, subjective, and objective data. Adverse events, total daily dose, clinical opioid withdrawal scale (COWS) scores, vital signs, and reasons for early discontinuation of lofexidine are reported.

Results: Patients treated with lofexidine experienced mild withdrawal symptoms throughout treatment. Most patients (65%) experienced a decrease in their average daily COWS scores from intake to discharge. Two patients (12%) left treatment against medical advice, and 5 patients (29%) discontinued treatment prior to day 7 due to resolution of symptoms. Average daily blood pressure readings remained stable, and daily average heart rate decreased over time.

Discussion: Lofexidine can be successfully incorporated into a conventional withdrawal management protocol. The cost of lofexidine and its recent introduction to the market remain barriers to accessibility in the United States. Studies evaluating patient-reported outcomes as well as direct comparisons with other alpha-2 agonists are needed to inform optimal clinical use of lofexidine.

Keywords: opioid withdrawal, lofexidine, safety

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Introduction

In 2018, the National Survey on Drug Use and Health estimated that more than 2 million people in the United States had a diagnosis of opioid use disorder (OUD).[1] Opioid use disorder treatment frequently begins with management of the opioid withdrawal syndrome (OWS).[2] Opioid withdrawal syndrome typically appears within 6 to 12 hours after the use of a short-acting opioid, such as heroin or fentanyl, but this can be delayed in patients using long-acting opioids, such as methadone.[3] Several validated scales, including the 11-item Clinical Opiate Withdrawal Scale (COWS), may be used to measure the severity of opioid withdrawal symptoms.[4] A common goal of medically supervised withdrawal is to safely wean a

patient off opioids for subsequent transition to an abstinence-based residential treatment or housing program. These patients are often transitioned to antagonist treatment with naltrexone although some patients may initiate long-term opioid substitution with an agonist or partial agonist.

Alpha-2 agonists, such as clonidine and lofexidine, have demonstrated efficacy for the management of opioid withdrawal symptoms.[5,6] Lofexidine (Lucemyra®, Louisville, KY) is the first alpha-2 agonist to be approved for the treatment of OWS by the US Food and Drug Administration (FDA) based on success in multiple randomized, placebo-controlled trials.[7-9] Furthermore, a 2016 Cochrane review[5] found that lofexidine has a better side effect profile than clonidine, possibly due to its selectivity for alpha-2A and alpha-2C receptors. The most commonly reported adverse reactions for lofexidine, including hypotension, orthostatic hypotension, bradycardia, dizziness, somnolence, sedation, and dry mouth, are similar to those reported with clonidine.[6] However, the frequency and severity of hypotension is lower for lofexidine. A recently published systematic literature review[10] of comparative studies conducted from 1997 to 2002 primarily outside of the United States reveals great variability in reported hypotension rates among trials. Reported rates of hypotension varied from as low as 3.9% to as high as 53% with lofexidine and from 4.6% to 93% with clonidine.[11-13]

The typical starting dose for lofexidine is three 0.18-mg tablets (0.54 mg) taken orally 4 times daily for 7 days.[8] Although this is the recommended dose and duration in the labeling, lofexidine is approved by the FDA for use up to 14 days.[6] One barrier to treatment with lofexidine in clinical practice is its cost in comparison to clonidine. The average wholesale price per 0.18-mg lofexidine tablet is $24.83, and clonidine tablets (0.1, 0.2, and 0.3 mg) are priced at under 50 cents each.[14,15] One day of treatment with lofexidine can be priced up to $297.96, and clonidine dosed at the same 6-hour dosing interval is a fraction of the cost at $1.80.[14,15] The objective of this case series is to report the number of lofexidine treatment completions, the number of successful transitions to medication for OUD, and any challenges associated with lofexidine use for OWS in an inpatient facility offering medically supervised withdrawal.

Methods

This study was performed at an inpatient facility offering medically supervised withdrawal in Austin, Texas. In July 2019, a retrospective chart review was conducted to collect pertinent clinical data for each of the 17 patients treated with lofexidine from November 2018 through June 2019. All patients were diagnosed with OUD and admitted to the facility for treatment of OWS.

Patients who refused induction with buprenorphine, an opioid partial agonist, or who preferred to transition to naltrexone, an opioid antagonist, were placed on a comfort medication protocol. This protocol included scheduled doses of either clonidine or lofexidine along with the following medications on days 1 through 7: acetaminophen 500 mg 4 times daily for pain/inflammation, methocarbamol 750 mg 4 times daily for myalgia, and ondansetron 4 mg 3 times daily for nausea/vomiting. Additional medications included in a separate protocol for use as needed were dicyclomine 20 mg every 8 hours for abdominal cramping, trazodone 100 mg nightly for insomnia, loperamide 4 mg following each loose stool (not to exceed 4 doses in 24 hours), propranolol 10 mg every 4 hours for heart rate (HR) >100, hydroxyzine 50 mg every 4 hours for severe anxiety/agitation, diazepam 10 mg every 4 hours for COWS >8, and clonidine 0.1 mg every 4 hours for systolic blood pressure (SBP) >160 mm Hg or diastolic blood pressure (DBP) >110 mm Hg. Patients initiated on lofexidine were able to transition to clonidine, and patients initiated on clonidine could be transitioned to lofexidine under the facility protocol and at the prescriber's discretion. The dosing protocol for clonidine was 0.2 mg by mouth 4 times daily for 7 days, and the dosing protocol for lofexidine was 0.54 mg by mouth 4 times daily for 7 days. Patients were to be dosed every 6 hours around the clock but were given the opportunity to refuse their dose at any time. Lofexidine was held when SBP ≤85 mm Hg, DBP ≤55 mm Hg or resting heart rate ≤50 beats per minute.

The COWS scores were the primary measure used to monitor the severity of OWS and effectiveness of lofexidine. The instrument is an 11-item scale designed for clinicians to rate objective symptoms of opioid withdrawal.[4] Based on the assessment score, a patient is categorized as experiencing *mild* (5 to 12), *moderate* (13 to 24), *moderately severe* (24 to 36), or *severe* (greater than 36) withdrawal symptoms. The COWS scores and vital signs, including HR and BP, were measured every 2 hours for the first 24 hours and every 4 hours thereafter.

The following information was obtained from patient charts: age, sex, ethnicity, employment status, marital status, co-occurring diagnoses, number of days on treatment, reason for discontinuation, transition to treatment with naltrexone or buprenorphine, total daily lofexidine dose, HR, BP, and COWS scores. Continuous data were tested for normality using the Shapiro-Wilk test and were found to be normally distributed ($P > .05$); therefore, data were presented as means. The case series was deemed exempt research by The University of Texas at Austin Institutional Review Board. Additionally, the

TABLE: Total daily doses of lofexidine, daily average clinical opioid withdrawal scale (COWS) scores, and transition to medication-assisted treatment

		Day													
#	Sex, Age	1 (mg)	1 COWS	2 (mg)	2 COWS	3 (mg)	3 COWS	4 (mg)	4 COWS	5 (mg)	5 COWS	6 (mg)	6 COWS	7 (mg)	7 COWS
1[a]	M, 20	0.54	9	1.62	4	1.08	3	2.16	4.8	1.62	5	0.54	5.67	0	2.67
2	F, 28	1.26	4	1.26	5.33	0.54	8.16	0	...	0	...	0	...	0	...
3[a]	M, 21	1.08	5.2	1.62	4.4	2.16	3.5	2.16	1.4	0	...	0	...	0	...
4[b]	M, 23	0	3.5	2.16	3	2.16	4.6	2.16	2.25	2.16	3.6	0	...	0	...
5	M, 41	0.54	3.9	2.16	2.3	1.62	1.7	1.62	4	2.16	3	1.08	...	0	...
6[b]	F, 35	1.08	6.25	0.54	8.5	0	...	0	...	0	...	0	...	0	...
7[a]	M, 22	2.16	4	2.16	4.2	2.16	4	2.16	5.3	2.16	2.3	1.08	3.3	0	5
8[c]	M, 26	0.54	7	1.62	3.7	1.62	6.2	2.16	5.2	2.16	6.2	1.08	5.3	1.08	2.2
9[a]	M, 51	1.62	4	1.62	5.7	1.62	4.7	1.62	5.8	1.08	5.8	0.54	...	0.54	5.7
10	M, 54	0.54	...	2.16	5.2	1.08	4.8	1.62	9.2	1.08	3	1.08	3.3	0	...
11	F, 39	1.08	3	2.16	1.6	0	...	0	...	0	...	0	...	0	...
12[c]	F, 28	1.08	4.25	1.08	4.8	0.54	5	1.08	5	0	4.16	1.62	3.4	0.54	0.8
13[a]	M, 32	0.54	5	0.54	5	0	...	0	...	0	...	0	...	0	...
14	M, 25	1.08	5	2.16	7.25	1.62	6.25	1.08	3	2.16	7	1.08	2	0	...
15[a]	M, 28	1.62	5.16	1.08	6.4	0	5.4	0	4.2	0	1	0	...	0	...
16	F, 64	0.54	2	1.62	0.2	0	...	0	...	0	...	0	...	0	...
17[a]	M, 58	1.08	3.3	2.16	2.6	1.62	4.4	2.16	8	1.62	6.2	2.16	4.8	1.62	1.6

F = female; M = male.

[a]Transitioned to depot naltrexone.

[b]Left against medical advice.

[c]Transitioned to buprenorphine.

Board waived the requirements to obtain subject authorization for use and disclosure of protected health information.

Results

Seventeen patients were treated with lofexidine during the 8-month study period. White (88.2%) and male (71%) patients were the majority. The mean age of patients was 35 years (range 20 to 64). Fifteen participants (88.2%) had a diagnosis of severe OUD. Most patients (76.5%) reported heroin as their primary opioid used. Substance use and psychiatric comorbidity was common with 76% having a nonopioid substance use disorder and 29% having a mood disorder. Common co-occurring substance use disorder diagnoses included sedative, anxiolytic, or hypnotic use disorder (n = 8), alcohol use disorder (n = 4), stimulant use disorder (n = 4), cocaine use disorder (n = 3), sedative use disorder (n = 2), and cannabis use disorder (n = 2). Documented mood disorders included anxiety disorder (n = 3) and depressive disorder (n = 2).

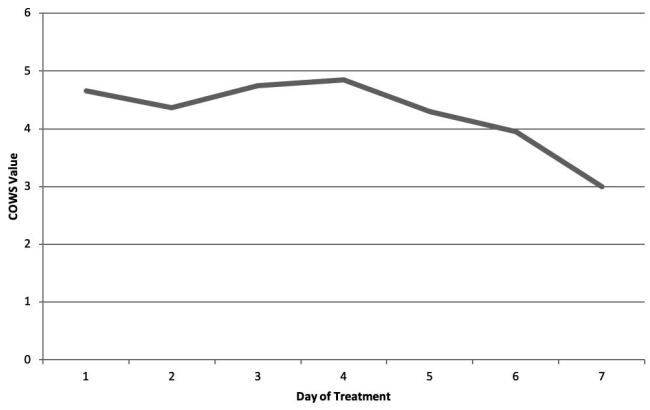

FIGURE 1: Daily averages of clinical opioid withdrawal (COW) scale scores

Dosing patterns varied greatly among the 17 patients with just over half ever receiving the maximum daily dose (2.16 mg, n = 10) identified in the protocol (Table). Six patients (35%) had their lofexidine dose held at least once due to hypotension (SBP <85 mm Hg, DBP <65 mm Hg). All clinician-reported COWS scores remained within the *mild withdrawal* range throughout treatment with lofexidine. Eleven patients (65%) had a decrease in their average daily COWS score from intake to discharge (Figure 1). Five patients (29%) discontinued treatment early due to a resolution of withdrawal symptoms. Three of these patients transitioned to oral buprenorphine or naltrexone.

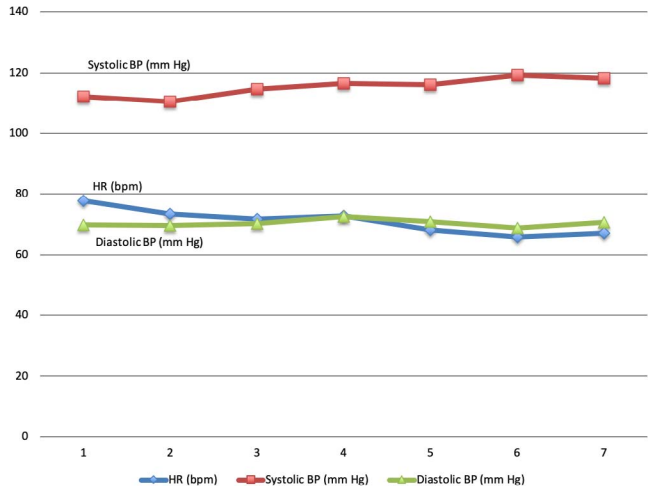

FIGURE 2: Daily averages of vital signs (HR = heart rate; BP = blood pressure)

Three patients (17.6%) reported side effects noted as *foggy, lightheaded, and dizzy*. One adverse event led to early treatment discontinuation. Mean BPs remained stable, averaging below 120 mm Hg for SBP and below 80 mm Hg for DBP readings (Figure 2). Two patients experienced significant BP reduction, defined as greater than 20 mm Hg below baseline SBP or DBP, leading to lofexidine doses being withheld (1 male patient 4 times, 1 female patient 9 times). There was an overall decrease in average HR values (Figure 2) with a majority (58.8%) of participants having a lower HR upon discharge compared to admission.

Nine patients (52.9%) were still taking lofexidine on day 6, and 4 patients (23.5%) were still taking it on day 7 (Table). Under a clinician's guidance, 1 patient began treatment with lofexidine on day 3 and another on day 4 after trialing clonidine without adequate resolution of symptoms or due to adverse reactions. Reasons for early lofexidine treatment discontinuation included absence of withdrawal symptoms (n = 5), medication unavailable (n = 2), patient dropout (n = 2), side effects (n = 1), and transitioned back to clonidine prescribed for hypertension prior to admission (n = 1).

Nine patients (52.9%) transitioned to maintenance medications for treatment of OUD following medically supervised withdrawal. Four of these patients were able to transition within 1 week of admission (1 on day 4, 1 on day 5, and 2 on day 7). Seven patients were initiated on naltrexone and 2 patients on buprenorphine. Eight patients (47.1%) were transitioned to the level of care deemed appropriate by the clinical staff, 5 were discharged to home without following a recommended step-down treatment plan, and 2 left treatment against medical advice.

Discussion

To our knowledge this is the first postmarketing case series reporting the use of lofexidine in a conventional withdrawal management protocol. In this case series, 15 out of 17 participants (88.2%) completed the recommended length of stay with 53% starting either naltrexone or buprenorphine upon completion. Overall, lofexidine was tolerated by the study population. Because lofexidine is an alpha-2 agonist, reductions in BP and HR were expected.[4] Vital-sign changes were monitored and assessed throughout the course of treatment. Mean BP remained stable over the course of treatment with lofexidine, and mean HR decreased over time.

This case series demonstrates that lofexidine can be used in conjunction with other medications commonly used to treat OWS. The high rate of completion allowed patients time to transition to medication therapy and ongoing structured residential, partial hospital, and intensive outpatient programming.[16] Additionally, the case series reveals 1 model of executing a clinical protocol including lofexidine in an inpatient treatment center serving patients with severe OUD.

Our study has several limitations that call for attention. First, the case reports were retrospective; therefore, we were unable to compare lofexidine treatment to other options, such as no pharmacotherapy or treatment with clonidine for OWS. We were unable to assess if our results were confounded by utilization of concurrent supportive medications available to patients in the comfort medication and as-needed medication protocols. In addition, adverse events and reasons for discontinuation were reported by different raters in different sections of patients' electronic health records. Last, fragmented data availability for patients after leaving treatment led to difficulties reporting important clinical outcomes, such as transition to maintenance medications and rates of rebound hypertension. Rebound hypertension has been reported as an adverse effect of abrupt discontinuation of clonidine but has been reported less frequently with lofexidine and was not observed in patients who discontinued treatment before day 7.[7]

Conclusion

This study demonstrated positive real-world safety and showed that a majority transitioned to medication for OUD postlofexidine treatment. Lofexidine was tolerated by most patients and successfully incorporated in a standard withdrawal management protocol with excellent patient retention. Currently, the cost of lofexidine and its recent introduction to the market remain barriers to treatment accessibility in the United States. Further studies including patient-reported outcomes, direct com-

parisons with other alpha-2 agonists, and evaluating the use of lofexidine in ambulatory settings are needed to further inform clinical use.

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