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Update on Medications Used to Manage Opioid Use Disorder and Opioid Withdrawal

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The widespread use of opioids has resulted in an unprecedented increase in the number of patients who struggle with opioid addiction. Opioid use disorder (OUD) is used to define this condition, which applies to patients with a problematic pattern of opioid use. Effective treatment strategies to assist patients to successfully taper off opioids are widely sought. Methadone, buprenorphine, and naltrexone are Food and Drug Administration (FDA)-approved to manage OUD. The purpose of this newsletter is to provide an update on newer buprenorphine formulations approved by the FDA for treatment of OUD and to review the evidence for lofexidine, a new medication approved to manage opioid withdrawal symptoms for patients who are detoxifying.

Guidance on the Management of Opioid Use Disorder

For patients with a diagnosis of OUD, the Veterans Affairs and Department of Defense (VA/DoD) guideline strongly recommends using methadone in an Opioid Treatment Program (OTP) or buprenorphine/naloxone depending on patient preferences.[1] Also, buprenorphine without naloxone is strongly recommended to be used in patients who are pregnant.[1] Extended-release injectable naltrexone is recommended as an option for patients for whom buprenorphine/naloxone or methadone is contraindicated or unavailable, and who have established opioid abstinence for a sufficient period of time.[1] While shown to have similar efficacy as methadone in clinical trials, buprenorphine/naloxone has several advantages over methadone, including a reduced risk of fatal overdose because of its lower potential for respiratory depression.[2] In May 2018, lofexidine (Lucemyra™) received FDA approval for short-term mitigation of severe opioid withdrawal symptoms in adults to facilitate abrupt opioid discontinuation.[3]

In the Oregon Health Plan (OHP) Fee-For-Service (FFS) program, preferred agents to manage OUD include: buprenorphine/naloxone film and sublingual tablets, naltrexone extended-release injection, and naltrexone tablets.

Long Acting Monotherapy Buprenorphine Products

In 2016, the FDA approved Probuphine®, a monotherapy buprenorphine product administered via subdermal implant for management of OUD.[4] The implant embeds buprenorphine in four matchstick-size rods in a patient's upper arm that release medication over a 6 month period.[4] The buprenorphine implant is designed only for patients who have received buprenorphine/naloxone maintenance therapy for at least 3 months.[4]

Efficacy

The efficacy of the Probuphine® implant is based on evidence from one double-blind, 6-month randomized controlled trial (RCT) that compared the 4 simultaneous 80 mg buprenorphine implants with sublingual buprenorphine in adults who met criteria for opioid dependence.[5] All patients in the trial were clinically stable for at least 6 months on sublingual (SL) buprenorphine at 8 mg per day or less.[5] The primary efficacy end point was the proportion of responders, defined as participants with at least 4 of 6 months without evidence of illicit opioid use (based on urine drug screen and self-report composites) by treatment group.[5] A significant proportion of patients in the implant group responded to therapy compared to the SL group (Number Needed to Treat (NNT) = 12).[5] Therapy beyond 1 year is not feasible with Probuphine®, as a second insertion of the implants cannot be placed into a previously used arm.

In 2017, the FDA approved Sublocade™ a once-monthly buprenorphine extended-release subcutaneous injection for management of OUD.[6] Sublocade™ uses a proprietary delivery system that induces the drug to form a solid deposit under the skin, gradually biodegrading into the active therapeutic agent.[6] The safety and efficacy of Sublocade™ were evaluated in two clinical studies in adults with a diagnosis of moderate-to-severe OUD who began treatment with buprenorphine/naloxone sublingual film for at least 7 days before transitioning to the extended-release subcutaneous injection.[6] Response to buprenorphine therapy compared to placebo was measured by urine drug screening and self-reporting of illicit opioid use during the six-month treatment period. The proportion of patients achieving treatment success (defined as patients with ≥80% opioid-free weeks) was statistically significantly higher in groups treated with buprenorphine 300 mg subcutaneously once a month for 6 doses compared to the placebo group (29.1% vs. 2%; $p<0.05$; NNT = 4).[6]

Safety

Probuphine® is not available in retail pharmacies and must be inserted and removed by the certified prescriber.[4] The implants can only be obtained through a restricted Risk Evaluation and Mitigation Strategy (REMS) program that requires specialized training for physicians on insertion and removal techniques, the risks for accidental overdose, and misuse/abuse of opioids.[4]

Sublocade™ has a boxed warning regarding the risks of intravenous self-administration.[6] If the product were to be administered intravenously rather than subcutaneously, the solid deposit containing the drug could cause occlusion, tissue damage or embolus.[6] Sublocade™ must be prescribed and dispensed as part of a REMS program to ensure that the product is not distributed directly to patients.[6] Sublocade™ is provided to health care providers (HCPs) through a restricted program and must be administered to patients in a health care setting. Pharmacies that dispense Sublocade™ are required to complete an enrollment form attesting that they have procedures in place to ensure that Sublocade™ is dispensed only to HCPs and not directly to patients.[6] The safety and efficacy of extended-release buprenorphine have not been established in children or adolescents less than 17 years of age or adults over the age of 65 years.[6]

To date, no systematic reviews comparing the various buprenorphine formulations have been identified.[7] The data from clinical trials indicates that newer long-acting buprenorphine formulations may be

safe for treatment of OUD, but the trials were relatively short in duration (26 weeks or less) and were not powered to detect rare adverse effects.[7] Larger studies with longer treatment durations are required to better understand the safety profile of these newer buprenorphine formulations.[7]

Lofexidine for Opioid Withdrawal Symptoms

In May 2018, lofexidine (Lucemyra™) received FDA approval for management of severe opioid withdrawal symptoms for up to 14 days of treatment.[3] Lofexidine is an alpha2-adrenergic agonist similar to clonidine which reduces the release of norepinephrine and decreases sympathetic tone and lessens the symptoms of withdrawal.[3] Lofexidine may not completely prevent withdrawal symptoms and is not a treatment for OUD as a single agent, but can be used as part of a broader, long-term treatment plan for managing OUD.[3]

Lofexidine Evidence

The safety and efficacy of lofexidine were assessed in one double-blind RCT conducted at 15 U.S. inpatient sites. Patients meeting criteria for opioid dependence were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, or oxycodone).[8] Subjects were randomized 1:1 to receive lofexidine 2.88 mg/day (n=134) or placebo (n=130) for 5 days, followed by an additional 2 days of treatment with placebo prior to discharge on Day 8.[8]

The co-primary efficacy endpoints were mean Short Opioid Withdrawal Scale (SOWS)-Gossop total score on day 3 of treatment and time to study dropout. The SOWS-Gossop assessment is a 10 item, patient-reported outcome instrument. Each item represents a symptom and is evaluated on a scale ranging from a total score of 0 (no symptoms) to 30 (severe symptoms).[9] Studies indicate that a change score of 2 to 4 points on the SOWS-Gossop scale may represent a clinically meaningful improvement.[10] For this trial, the investigators assumed a minimal clinically significant difference of 5 points.[8] The mean SOWS-Gossop scores on day 3 were 8.67 and 6.32 for placebo and lofexidine, respectively, which demonstrated a statistically significant difference between the 2 arms [least squares mean difference (LSMD) = -2.24, 95% Confidence Interval (CI) -3.88 to -0.6; p=0.009].[11] While there was a statistically significant difference, there was no clinical difference between lofexidine and placebo.

Comparative Evidence for Acute Opioid Withdrawal Symptom Management

A high quality systematic review evaluated evidence on safety and efficacy of alpha2-adrengeric agonists (lofexidine and clonidine) in managing the acute phase of opioid withdrawal.[12] Moderate quality evidence from three studies comparing alpha2-adrenergic agonists and placebo showed completion of withdrawal treatment was significantly more likely with an adrenergic agonist (Risk Ratio (RR) 1.95; 95% confidence interval (CI) 1.34 to 2.84) and severe withdrawal was significantly less likely with an adrenergic agonist (RR 0.32; 95% CI 0.18 to 0.57).[12] Upon comparison of alpha2-adrenergic agonists with a methadone taper, moderate quality evidence suggests there is no significant difference in severity of the withdrawal episode (Standardized Mean Difference [SMD] 0.13; 95% CI -0.24 to 0.49).[12] Moderate quality evidence also shows no significant differences were observed in completion rates of withdrawal treatment (RR 0.91; 95% CI 0.75 to 1.11) for the adrenergic agonist versus methadone comparisons.[12]

Comparative Evidence for Withdrawal Completion Rates

A meta-analysis of 5 moderate quality trials supports a conclusion of no difference between buprenorphine and methadone for withdrawal completion rates.[13] In a meta-analysis of 14 trials, buprenorphine was associated with a lower average withdrawal score (indicating less severe withdrawal) compared to lofexidine or clonidine during the treatment episode.[13] Patients receiving buprenorphine were more likely to complete withdrawal treatment compared to adrenergic agonists.[13] Specific results from these trials are summarized in **Table 1**.

Table 1. Comparative Evidence for Buprenorphine in OUD[13]

Comparison	Outcome	Results
Buprenorphine vs. Methadone	Withdrawal Completion Rates	RR 1.04 95% CI 0.91 to 1.20
Buprenorphine vs. Adrenergic Agonists	Average Withdrawal Score	SMD -0.43 95% CI -0.58 to -0.28 Favors buprenorphine
Buprenorphine vs. Adrenergic Agonists	Withdrawal Completion Rates	RR 1.59 95% CI 1.23 to 2.06 Favors buprenorphine

Abbreviations: CI = confidence interval; RR = risk ratio; SMD = standardized mean difference

Table 2. Comparative Costs of OUD Therapies (Acute Phase and Maintenance Phase)

Product	Cost per 30 days*
Buprenorphine 8 mg Sublingual Tablets	$140-$420
Buprenorphine/Naloxone 8/2mg Sublingual Tablets	$250-$750
Suboxone® (Buprenorphine/Naloxone) Film 8/2mg	$245-$735
Probuphine® (Buprenorphine) 80 mg Implants: 6 months	$4950**
Sublocade™ (Buprenorphine) Injection 300-100mg	$1580-$3160
Clonidine 0.1 mg Tablets	$3-$6
Lucemyra™(Lofexidine) 0.18 mg Tablets: 7-14 days	$1740-$4635**
Naltrexone 50 mg Tablets	$85
Vivitrol® (Naltrexone) 380 mg Injection	$1309

*Costs based on Wholesale Acquisition Cost (WAC) and vary based on prescribed dosing regimen.
**Cost is for duration of therapy.

In summary, buprenorphine for the treatment of OUD is available in several formulations: tablet, sublingual film, long-acting injection and implant. Buprenorphine sublingual tablets are restricted for use in pregnant females and all buprenorphine monotherapy products require prior authorization (PA) for the OHP FFS PDL. Lofexidine also requires prior authorization to insure medically appropriate use in FDA-approved indications. Relative costs for the various medications used to manage OUD are outlined in **Table 2.**

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