DISCUSSING

OPIOID WITHDRAWAL MANAGEMENT

A guide to patient communication and support during opioid discontinuation and withdrawal

This guide can help you

- Understand and detect Opioid Withdrawal Syndrome (OWS)
- Identify patients who have physical dependence to opioids and may be at risk for Opioid Use Disorder (OUD)
- Encourage patients to open up about their symptoms
- Explain that OWS is not the patient's fault, and completing withdrawal is key to overcoming physical opioid dependence
- Guide patients to an individualized withdrawal treatment plan
- Review treatment options and determine if LUCEMYRA (lofexidine) is an appropriate choice

Lucemyra®
(lofexidine) tablets 0.18 mg

Relieve the symptoms, retake control

Indication

LUCEMYRA is indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.

Please see the full Important Safety Information on page 10 and the distributed full Prescribing Information.

Doctors may need to more actively manage opioid discontinuation and withdrawal…especially in today's environment

Patients prescribed opioids for pain can rapidly develop physical dependence to opioids—sometimes after only 5 days of use.[1] When physically dependent patients abruptly discontinue opioid use, they experience symptoms of opioid withdrawal, also known as Opioid Withdrawal Syndrome (OWS).[2-4]

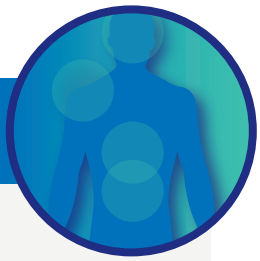
However, patients may not realize or share with their doctor that they have experienced or are experiencing OWS. They may instead ask for more prescriptions or higher doses to avoid withdrawal symptoms, or because they confuse the symptoms with the pain their opioid was prescribed to treat.[5,6] Moreover, physical opioid dependence may also lead to Opioid Use Disorder (OUD), which causes long-term, uncontrollable urges/cravings to keep taking opioids.[3,7]

Growing concern over the social and economic toll of the opioid crisis[8-10] has led to collaborative efforts among doctors, government agencies, insurance providers, employers, and retailers to foster earlier detection of physical dependence to opioids and prevention of OUD.[8,11-13] This may result in policy and management changes regarding how long a patient can continue opioid treatment.

For all these reasons and others, it is especially important for doctors to identify OWS and provide opioid withdrawal management that helps patients discontinue opioids successfully.

Understanding what causes opioid withdrawal

- Opioid use leads to inhibition of an enzyme in the brain, resulting in reduced norepinephrine levels[3]
- The brain responds with compensatory increases of the enzyme, resulting in almost normal norepinephrine levels[3]
- When opioids are discontinued after chronic use, the inhibitory effect on the enzyme that produces norepinephrine is lost[3]
- This results in excessively high levels of norepinephrine[3]
- The surge of norepinephrine causes the clinical symptoms of withdrawal[3]



Some symptoms of opioid withdrawal[14]

- Aches and pains
- Stomach cramps
- Feeling sick
- Muscle spasms/twitching
- Insomnia/problems sleeping
- Feelings of coldness/chills
- Muscular tension
- Heart pounding
- Runny eyes
- Yawning

Opioid withdrawal symptoms often present concurrently.[4] Physical dependence to opioids cannot be resolved without going through withdrawal if opioids are abruptly stopped.

For patients who have developed OUD, completion of withdrawal is one important step in a comprehensive treatment program that will require psychosocial, and possibly, additional medical treatment.

Identifying patients with physical opioid dependence and OWS

Why they may not tell their doctor

Patients experiencing withdrawal symptoms may not share this with their doctor because:

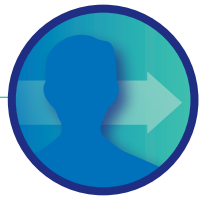
Some may want to continue using opioids to avoid OWS. According to one study, avoidance of withdrawal symptoms is the primary reason patients originally prescribed opioids for chronic pain continued to use them.[5] But they may not share this with their doctor because they may fear that the doctor will simply stop prescribing the opioid.

Others may not be aware that they are experiencing OWS. Patients prescribed opioids for pain may have difficulty distinguishing between their original pain symptoms and withdrawal symptoms. They may think the extreme discomfort they experience when they try to stop or reduce opioid use is caused by the pain for which their opioid was prescribed.[6]

Tips for "reading between the lines"

When patients say...	*What it may really mean...*
"I think I need a higher dose"	The need for higher dosages over time to feel the same pain relief may be a sign that the patient has become physically dependent on the opioid[3]
"I missed a dose, and the next day I felt cramps and nausea"	The patient may actually have become physically dependent on their opioid and experienced withdrawal symptoms when the dose was missed[3,14]
"I tried stopping the medicine, but my pain came back"	If patient's status indicates that the source of the pain should be healed, this suggests possible confusion between pain symptoms and withdrawal symptoms[6]
"I lost my medicine, and I need a new prescription"	If losing medication seems out of character for this patient, he/she may really be using the opioid more frequently than prescribed[15]
"I wouldn't ask for another prescription if I didn't need it for the pain!"	Patient defensiveness when asked questions could indicate that the patient may not want to admit that they are using the opioid to prevent withdrawal symptoms[5]

Understanding physical opioid dependence and OWS from the patient's perspective



Most patients begin use of prescription opioids, under a doctor's care, for a medically appropriate health reason. They are not intentional abusers of opioids and, therefore, may be surprised or offended at the suggestion that they may be experiencing OWS.

"Why am I feeling these symptoms?"

Many patients may not understand what's happening to them. They may not want to accept that they are experiencing OWS, resulting from physical dependence to opioids.

"Drug addicts go through withdrawal—that's not me!"

Physical dependence to opioids may be perceived by many patients as "drug abuse" or "addiction." Hence, these patients may deny they have a problem and may hesitate to confide in anyone, even their doctor, to avoid embarrassment or social stigma.

"I can't be physically dependent—I haven't been on the opioid that long"

Physical opioid dependence can occur after only 5 days of use.[1] Patients using opioids for pain relief following surgery or injury may have trouble understanding that physical dependence can develop quickly.

"I've been using this medication for years—I can't function without it"

Patients using opioids long term for the management of chronic pain may be more likely to understand that they have become physically dependent on their opioid treatment. Some may even have attempted to reduce or discontinue opioid use on their own and failed due to the severity of withdrawal symptoms. Some may also be less likely to share this with their doctor because they may think the doctor will stop prescribing the opioid and put them at risk for OWS.[5]

Helpful reminders about motivational interviewing techniques for productive conversations

*(Adapted from CDC: Communicating Patients. Module 3, 2016)**

Remember to:

Reinforce Trust

Compassion, empathy, and showing that you are not being judgmental will help the patient be open and honest.[16]

Offering practical options that can help the patient get through withdrawal will also help reinforce trust.

Listen

Take time to listen to your patient. Show, verbally and nonverbally, that you genuinely want to help and work with the patient to find a solution.[16]

Check to ensure your patient understands what is being communicated and answer any questions. Educate about treatment options to support recommendations.[16]

Recognize Patient's Uniqueness[16]

Consider the perspective of patients taking opioids to relieve post-surgical/post-injury pain, versus the perspective of patients using opioids long term to manage chronic pain.

Also consider patient's attitudes regarding opioid withdrawal treatment management options (i.e., opioid vs. non-opioid).

Show Empathy

Use empathetic statements, such as[16]:

- "These symptoms are not your fault"
- "We're going to work on managing this together"
- "You have options—there are both opioid and non-opioid treatments for managing withdrawal"
- "Let's create a treatment plan that meets your needs"

Consider your nonverbal communication, such as[16]:

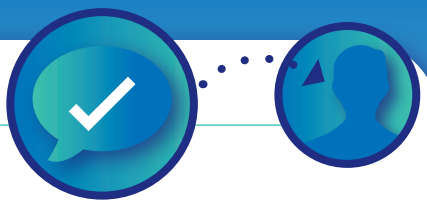
- Making eye contact
- Expressing that you care through your facial expressions and tone of voice

Collaborate and Motivate

Work with each of your patients to create an individualized action plan for managing opioid discontinuation and withdrawal that motivates them to work toward both short-term and long-term goals and gives hope for a successful outcome.[16]

*You can read more about motivational interviewing techniques at **https://www.cdc.gov/drugoverdose/training/communicating/accessible/training.html**

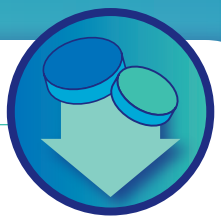
Communicating the right messages to patients



Key Messages

I Recognize That You Are Still Experiencing Symptoms	• They may be caused by opioid withdrawal, rather than by your original condition[6]
You're Experiencing Opioid Withdrawal Syndrome (OWS)	• OWS can occur when someone stops taking opioids and experiences multiple unpleasant symptoms like the ones you've described[14,16]
OWS Is Not Your Fault	• Physical dependence to opioids often develops in people taking opioids—sometimes after just a few days of treatment[1-3,16]
OWS Is a Physical Response to a Chemical Imbalance Caused by Opioid Use	• Opioid use causes your body to produce lower levels of norepinephrine, a naturally occurring hormone[3] • When opioids are taken away suddenly, there is an imbalance of norepinephrine[3] • The excessive release of norepinephrine causes withdrawal symptoms[3]
We Are in This Together and Can Solve It Together	• I will work with you to get you through OWS or refer you to specialists who can help you • It can also help you to engage a friend or family member for added support
Let's Create a Withdrawal Management Plan That Works for You	• Meeting your personal/physical needs (if possible, treatment at home to maintain privacy and reduce lifestyle disruption) • Going at a pace you can handle, ensuring that you know what to expect and when to ask for help[16]

Approaches to opioid withdrawal management



Symptoms of opioid withdrawal can be managed with or without opioids. Ideally, the decision to discontinue or taper opioid use should be made by the patient in collaboration with the doctor, and should be based on what is most likely to work for the individual patient.[17]

	Management Approach	
	Abrupt discontinuation from opioids	**Tapering/maintaining on opioids**
Treatment Options	Non-opioid medications to help alleviate symptoms of opioid withdrawal,* including[17-19]: • OTC options to relieve specific symptoms (such as NSAIDs to treat pain or antiemetics to relieve nausea and vomiting) • **LUCEMYRA™ (lofexidine)**, the first and only FDA-approved, non-opioid, non-addictive prescription treatment for relief of multiple symptoms of opioid withdrawal to facilitate abrupt opioid discontinuation[19]	• Maintenance opioids, such as methadone and buprenorphine[17] • Medications should be combined with behavioral counseling for a "whole patient" approach, known as Medication Assisted Treatment (MAT)[20] • Some patients will need to continue to receive maintenance treatment indefinitely to prevent relapse or withdrawal symptoms[18] **LUCEMYRA is indicated in abrupt opioid discontinuation. LUCEMYRA is *not* indicated for use during opioid taper or opioid maintenance.**
Inpatient/Outpatient	Generally outpatient; can also be used as part of a larger inpatient program	Generally inpatient until patient is stabilized on maintenance treatment
Patient Selection	Appropriate for: • Patients with physical dependence to opioids only • Patients with OUD who need withdrawal symptom relief when stopping opioids, as part of a comprehensive treatment program that will require behavioral counseling and additional medical treatment that will continue after LUCEMYRA treatment is completed **LUCEMYRA is not a treatment for OUD** • **Successful OWS management can help both physically dependent patients and patients with OUD through opioid withdrawal** • **When treating patients with OUD, LUCEMYRA should only be used in conjunction with a comprehensive management program for the treatment of Opioid Use Disorder**	Appropriate for: • Patients with OUD • Patients with physical opioid dependence who require an opioid substitute to manage cancer pain or intractable physical pain

*Abstinence-based treatment options do not address the psychological aspect of OUD (such as cravings) and may therefore be easier to use in patients with a physical opioid dependence[2]

Indication

LUCEMYRA is indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.

OWS can affect any patient dependent on opioids, regardless of how they started

LUCEMYRA is the first and only FDA-approved, non-opioid, non-addictive treatment indicated for the relief of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults[19]:

- A central α-2 adrenergic agonist that binds to receptors in the brain
  - This reduces the release of norepinephrine and moderates the symptoms of noradrenergic hyperactivity (withdrawal symptoms) that occur when the inhibitory effect of opioids is removed[19]

Even after patients with OUD get through withdrawal, they still face a high risk of relapse and are strongly encouraged to seek appropriate treatment.[2,3]

Successful OWS management can help both physically dependent patients and patients with OUD through opioid withdrawal. When treating patients with OUD, LUCEMYRA should only be used in conjunction with a comprehensive management program for the treatment of OUD.[2,3]

Important Safety Information

LUCEMYRA may cause hypotension, bradycardia, and syncope. Avoid using LUCEMYRA in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, or marked bradycardia. LUCEMYRA should be used with caution with any medications that decrease pulse or blood pressure to avoid the risk of excessive bradycardia and hypotension. Patients using LUCEMYRA should be monitored for symptoms related to bradycardia and orthostasis.

Please see the full Important Safety Information on page 10 and the distributed full Prescribing Information.

Lucemyra®
(lofexidine) tablets 0.18 mg

Relieve the symptoms, retake control

Indication

LUCEMYRA is indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.

Important Safety Information

LUCEMYRA may cause hypotension, bradycardia, and syncope. Avoid using LUCEMYRA in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, chronic renal failure, or marked bradycardia. LUCEMYRA should be used with caution with any medications that decrease pulse or blood pressure to avoid the risk of excessive bradycardia and hypotension. Patients using LUCEMYRA should be monitored for symptoms related to bradycardia and orthostasis.

LUCEMYRA prolongs the QT interval and should be avoided in patients with congenital long QT syndrome. Monitor ECG in patients using LUCEMYRA who have renal or hepatic impairment, known QT prolongation, metabolic disturbances, pre-existing cardiovascular disease, relevant family history, or those taking drugs known to prolong the QT interval.

LUCEMYRA potentiates the depressant effects of benzodiazepines and may potentiate the CNS depressant effects of alcohol, barbiturates, and other sedating drugs.

During and after opioid discontinuation, patients are at an increased risk of fatal overdose should they resume opioid use; patients and caregivers should be informed of this increased risk. In patients with opioid use disorder, LUCEMYRA should be used in conjunction with a comprehensive treatment program.

LUCEMYRA treatment should be discontinued with gradual dose reduction.

The most commonly reported adverse reactions associated with LUCEMYRA treatment (incidence ≥10% and notably more frequent than placebo) are orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.

Dose adjustment of LUCEMYRA is required in patients with hepatic or renal impairment. Before prescribing, see dosage recommendation tables in Full Prescribing Information.

There are no contraindications for taking LUCEMYRA.

To report SUSPECTED ADVERSE REACTIONS or product complaints, contact US WorldMeds at 1-833-LUCEMYRA. You may also report SUSPECTED ADVERSE REACTIONS to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the full Important Safety Information above and the distributed full Prescribing Information.

Lucemyra®
(lofexidine) tablets 0.18 mg

Relieve the symptoms, retake control

References: **1.** Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use—United States, 2006-2015. *MMWR Morb Mortal Wkly Rep.* 2017;66(10):265-269. **2.** Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain–Misconceptions and Mitigation Strategies. *N Engl J Med.* 2016;374(13):1253-1263. **3.** Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. *Sci Pract Perspect.* 2002;1(1):13-20. **4.** Shigakova F. Clinical manifestations of the opiate withdrawal syndrome. *Int J Biomed.* 2015;5(3):151-154. **5.** Weiss RD, Potter JS, Griffin ML, McHugh RK, et al. Reasons for opioid use among patients with dependence on prescription opioids: the role of chronic pain. *J Subst Abuse Treat.* 2014;47(2):140-145. **6.** Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. *Exp Clin Psychopharmacol.* 2008;16(5):405-416. **7.** American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5™). Arlington, VA, American Psychiatric Association, 2013. **8.** US Department of Health and Human Services. Facing Addiction in America. *The Surgeon General's Report on Alcohol, Drugs, and Health.* November 2016. **9.** The Council of Economic Advisors. The underestimated cost of the opioid crisis. November 2017. https://www.whitehouse.gov/sites/whitehouse.gov/files/images/The%20Underestimated%20Cost%20of%20the%20Opioid%20Crisis.pdf. Accessed June 13, 2018. **10.** Kirson NY, Scarpati LM, Enloe CJ, Dincer AP. The economic burden of opioid abuse: updated findings. *J Manag Care Spec Pharm.* 2017;23(4):427-445. **11.** Centers for Disease Control and Prevention. CDC releases guideline for prescribing opioids for chronic pain. https://www.cdc.gov/media/dpk/prescription-drug-overdose/opioid-prescription-guidelines/dpk-opioid-prescription-guidelines.html. Accessed August 19, 2017. **12.** Davis JH. *The New York Times.* October 27, 2017. Trump declares opioid crisis a 'health emergency' but requests no funds. https://www.nytimes.com/2017/10/26/us/politics/trump-opioid-crisis.html. Accessed November 3, 2017. **13.** Save Our Society (SOS) from Drugs. Trump administration announces opiate epidemic task force. http://www.saveoursociety.org/uncategorized/trump-administration-announces-opiate-epidemic-task-force/. Accessed June 13, 2018. **14.** Vernon MK, Reinders S, Mannix S, et al. Psychometric evaluation of the 10-item Short Opiate Withdrawal Scale-Gossop (SOWS-Gossop) in patients undergoing opioid detoxification. *Addict Behav.* 2016;60:109-116. **15.** Munzing T. Physician guide to appropriate opioid prescribing for noncancer pain. *Perm J.* 2017;21:1-7. **16.** Centers for Disease Control and Prevention. Module 3: communicating with patients. Transcript. 2016. https://www.cdc.gov/drugoverdose/training/communicating/accessible/training.html. Accessed June 13, 2018. **17.** Kleber H. Opioids: detoxification. In: Galanter M, Kleber, HD, eds. *Textbook of Substance Abuse Treatment.* 2nd ed. Washington, DC: American Psychiatric Press;1999:251-269. **18.** Schuckit MA. Treatment of Opioid-Use Disorders. *N Engl J Med.* 2016;375(4):357-368. **19.** LUCEMYRA® (lofexidine) [Prescribing Information]. USWM, LLC; 2018. **20.** Substance Abuse and Mental Health Services Administration (SAMHSA). Medication and counseling treatment. https://www.samhsa.gov/medication-assisted-treatment/treatment#medications-used-in-mat. Accessed June 13, 2018.

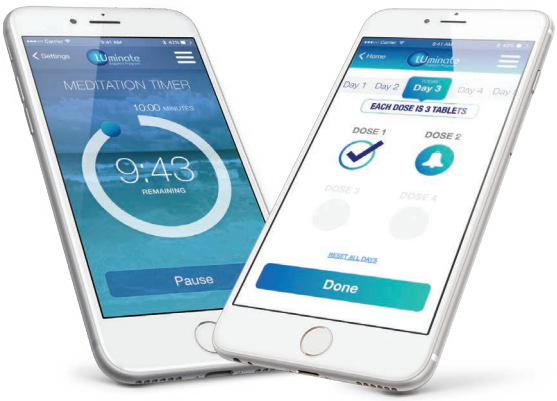
Lucemyra is the only FDA-approved, non-opioid, non-addictive treatment indicated for the relief of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults[19]

- Significantly reduces the severity of withdrawal symptoms
  - In one study, LUCEMYRA demonstrated significant improvement over placebo on Days 2 and 3 when symptoms were most severe ($P<0.05$)[19]
- Improves the success rates for completing treatment
  - In the 5-day treatment study, 49% of patients who received LUCEMYRA completed the study, versus 33% of patients who received placebo ($P=0.0087$)[19]
- Features a demonstrated safety profile[19]
- Offers integrated patient support

LUminate® Support Program

LUminate Support App

Offer your patients "hands-on" support while going through opioid withdrawal with the LUminate Support App. Your patients can download the app for free and access a variety of useful features, including:



- Dose Tracking/Reminders
- Supportive messages each day of treatment
- Symptom Library (including advice and tips for relief)
- Meditation Timer

Download on the App Store

GET IT ON Google Play

Patients do not need to sign up—they simply download the app to start immediately!

Lucemyra®
(lofexidine) tablets 0.18 mg

US WorldMeds®

USWM, LLC
4441 Springdale Road
Louisville, KY 40241

Under license from Britannia Pharmaceuticals Ltd.

USWM, LLC is the exclusive licensee and distributor of LUCEMYRA in the United States and Its territories.

USWMLUC-00368