The opioid epidemic in the United States does not appear to be dissipating. From 2000 to 2014, the rate of overdose deaths involving opioids (prescription opioid pain relievers and heroin) has tripled.1 Furthermore, data from the U.S. Centers for Disease Control and Prevention show that anyone can be at risk. Opioid dependence does not discriminate based on sex, age, race, or region of the country.2

This newsletter serves as a primer for recognizing the severity of today’s opioid crisis. Gaining a deeper understanding of opioid dependence—including its prevalence, pathophysiology, and effects—is an important step toward recognizing evidence-based approaches to help combat this chronic, relapsing brain disease.

Opioid Dependence vs. Opioid Use Disorder

In this series of newsletters, the term “opioid” refers to opium-like compounds that bind to opioid receptors, such as prescription opioids (natural, semisynthetic, and synthetic) and heroin.1 Opioids prescribed to treat moderate to severe pain include medications such as oxycodone, hydrocodone, codeine, morphine, and fentanyl.1

The Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) updated the diagnostic criteria for opioid use disorders. The diagnostic criterion of “substance dependence” was combined with “substance abuse” to make one diagnostic category of “substance use disorder,” with the specific substance defining each specific disorder (eg, opioid use disorder).3 The manual also includes a specifier for severity based on the number of symptoms.3 This 2013 update is consistent with the previous edition in citing the “clinically significant impairment or distress” that manifests as a result of substance use disorders, including opioid use disorders.3,4

Substance dependence, including opioid dependence, is characterized by a maladaptive pattern of substance use that leads to clinically significant impairment or distress.4 The Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) defined an individual with substance dependence as experiencing at least 3 of the following criteria:
with a given 12-month period: tolerance; withdrawal; taking the substance in larger amounts or for longer than intended; persistent desire or unsuccessful efforts to curb or control use; excessive time spent obtaining, using, or recovering from use; giving up or reducing important activities because of use; and continued use despite acknowledged physical or psychological problems due to use. This comprehensive definition partially served as the basis for the U.S. Food and Drug Administration to approve most available medication-assisted treatments (MATs) for opioid dependence.5-10

In this newsletter, the term “opioid dependence” is used to be consistent with the approved indication for numerous MAT options.

**A National Crisis**

While the clinical criteria characterizing opioid dependence can help identify an individual affliction, it does not even begin to demonstrate the impact of opioid dependence on the health of Americans.

**Prevalence**

First and foremost, the opioid epidemic in the U.S. is continuing, and the incidence of opioid-associated overdose deaths is on the rise.11 According to the National Survey on Drug Use and Health, nearly 2 million American adults had an opioid use disorder in 2016, of whom about 625,000 had a heroin use disorder.12 There are many factors that contributed to the development of this epidemic; one factor may be the increased availability of prescription opioids. Sales of prescription opioids in the U.S. nearly quadrupled from 1999 to 2014, and heroin use increased 63% from 2002 to 2013.13,14

**Mortality**

It is estimated that, in 2015, 63% of all drug overdose deaths nationwide involved an opioid.11 In total, opioids were responsible for an estimated 33,000 deaths in 2015.11

These fatalities do not appear to be associated with a clear set of demographic criteria. From 2014 to 2015, overdose deaths involving heroin and synthetic opioids other than methadone increased in both men and women, people aged ≥15 years, and all racial/ethnic groups, and overdose deaths involving natural/semisynthetic opioids increased among males overall, both sexes aged 25-44 years, and non-Hispanic whites.11

**Pathophysiology of Opioid Dependence**

Another facet of understanding opioid dependence and its treatment is appreciating its pathophysiology, starting with its effects on the brain. Opioids have many effects on the brain and body; some of the brain regions associated with opioid dependence are the cortex, which is responsible for decision-making, thinking, reasoning, and planning, and the limbic system, which controls basic drives and urges, rewards, and pleasure (Figure 1). As shown in Figure 1, different components of treatment target the different affected brain regions.

The motivation to seek reward and pleasure is considered a natural component of normal human behavior.6 Reward pathways are necessary, as they serve to promote survival (e.g., seeking food and water, engaging in reproductive activities) and influence beneficial behaviors.15

**Nearly 2 million American adults had an opioid use disorder in 2016, of whom about 625,000 had a heroin use disorder.**12

**The pleasure pathway**

Problems with opioids, including dependence, can occur when the brain’s natural mechanisms of pleasure and reward are dysfunctional.17,18 When someone takes an opioid drug, that drug binds to and activates the mu opioid receptors in the limbic system.18 This activation turns on the same “pleasure pathway” as the brain’s own natural opioids but releases 2 to 10 times more dopamine than natural (endogenous) opioids (see Figure 2 on page 3).15 In some cases, this reward response can occur immediately, and the effects can last longer than those produced by natural rewards (i.e., eating, sex).15

Acute exposure to opioids can have a positive reinforcing effect, where the individual may impulsively seek opioids for the pleasurable effects.19 However, prolonged administration of opioids can create neuroadaptations in the dopamine reward system.19 These neuroadaptations are thought to contribute to loss of motivation for natural...
(non-opioid) stimuli and increased sensitivity to opioid-related stimuli or cues. Eventually, opioid addiction can transition to a negative reinforcing effect, where individuals may compulsively begin seeking opioids to avoid the negative effects of withdrawal. The negative reinforcing effects may increase the likelihood of relapse. Chronic relapse, even after prolonged abstinence, is a hallmark of opioid use disorders.

Conclusions

The opioid epidemic in the U.S. has no single solution. However, understanding the prevalence, pathophysiology, and effects of opioid dependence is an important step in addressing this national crisis. It also is important to be action-oriented and examine evidence-based approaches to treatment and rehabilitation.

Please refer to Issues 2 and 3 in this newsletter series for more information about opioid dependence as well as an antagonist treatment option.


Figure 2. The Brain and Opioid Use: Understanding the Effects of Opioids. 

The negative reinforcing effects of opioid addiction may increase the likelihood of relapse.

References

VIVITROL® (naltrexone for extended-release injectable suspension) is indicated for:

- Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL. Patients should not be actively drinking at the time of initial VIVITROL administration.
- Prevention of relapse to opioid dependence, following opioid detoxification.
- VIVITROL should be part of a comprehensive management program that includes psychosocial support.

**CONTRAINDICATIONS**

VIVITROL is contraindicated in patients:

- Receiving opioid analgesics
- With current physiologic opioid dependence
- In acute opioid withdrawal
- Who have failed the naloxone challenge test or have a positive urine screen for opioids
- Who have exhibited hypersensitivity to naltrexone, polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other components of the diluent

**WARNINGS AND PRECAUTIONS**

**Vulnerability to Opioid Overdose:**

- After opioid detoxification, patients are likely to have a reduced tolerance to opioids. VIVITROL blocks the effects of exogenous opioids for approximately 28 days after administration. As the blockade wanes and eventually dissipates completely, use of previously tolerated doses of opioids could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.).

- Cases of opioid overdose with fatal outcomes have been reported in patients who used opioids at the end of a dosing interval, after missing a scheduled dose, or after discontinuing treatment. Patients and caregivers should be told of this increased sensitivity to opioids and the risk of overdose.

- Although VIVITROL is a potent antagonist with a prolonged pharmacological effect, the blockade produced by VIVITROL is surmountable. The plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. This poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids.

- Any attempt by a patient to overcome the VIVITROL blockade by taking opioids may lead to fatal overdose. Patients should be told of the serious consequences of trying to overcome the opioid blockade.

**Injection Site Reactions:**

- VIVITROL must be prepared and administered by a healthcare provider.
- VIVITROL injections may be followed by pain, tenderness, induration, swelling, erythema, bruising, or pruritus; however, in some cases injection site reactions may be very severe.
- Injection site reactions not improving may require prompt medical attention, including, in some cases, surgical intervention.
- Inadvertent subcutaneous/adipose layer injection of VIVITROL may increase the likelihood of severe injection site reactions.
- Select proper needle size for patient body habitus, and use only the needles provided in the carton.
- Patients should be informed that any concerning injection site reactions should be brought to the attention of their healthcare provider.

**Precipitation of Opioid Withdrawal:**

- When withdrawal is precipitated abruptly by administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe. Some cases of withdrawal symptoms have been severe enough to require hospitalization, and in some cases, management in the ICU.

- To prevent occurrence of precipitated withdrawal, opioid-dependent patients, including those being treated for alcohol dependence, should be opioid-free (including tramadol) before starting VIVITROL treatment:
  - An opioid-free interval of a minimum of 7-10 days is recommended for patients previously dependent on short-acting opioids.
  - Patients transitioning from buprenorphine or methadone may be vulnerable to precipitated withdrawal for as long as two weeks.

- If a more rapid transition from agonist to antagonist therapy is deemed necessary and appropriate by the healthcare provider, monitor the patient closely in an appropriate medical setting where precipitated withdrawal can be managed.

- Patients should be made aware of the risk associated with precipitated withdrawal and be encouraged to give an accurate account of last opioid use.

**Hepatotoxicity:**

- Cases of hepatitis and clinically significant liver dysfunction have been observed in association with VIVITROL. Warn patients of the risk of hepatic injury; advise them to seek help if experiencing symptoms of acute hepatitis. Discontinue use of VIVITROL in patients who exhibit acute hepatitis symptoms.

**Depression and Suicidality:**

- Alcohol- and opioid-dependent patients taking VIVITROL should be monitored for depression or suicidal thoughts. Alert families and caregivers to monitor and report the emergence of symptoms of depression or suicidality.

**When Reversal of VIVITROL Blockade Is Required for Pain Management:**

- For VIVITROL patients in emergency situations, suggestions for pain management include regional analgesia or use of non-opioid analgesics. If opioid therapy is required to reverse the VIVITROL blockade, patients should be closely monitored by trained personnel in a setting staffed and equipped for CPR.

**Eosinophilic Pneumonia:**

- Cases of eosinophilic pneumonia requiring hospitalization have been reported. Warn patients of the risk of eosinophilic pneumonia and to seek medical attention if they develop symptoms of pneumonia.

**Hypersensitivity Reactions:**

- Patients should be warned of the risk of hypersensitivity reactions, including anaphylaxis.

**Intramuscular Injections:**

- As with any intramuscular injection, VIVITROL should be administered with caution to patients with thrombocytopenia or any coagulation disorder.

**Alcohol Withdrawal:**

- Use of VIVITROL does not eliminate nor diminish alcohol withdrawal symptoms.

**ADVERSE REACTIONS**

The adverse events seen most frequently in association with VIVITROL therapy for alcohol dependence (ie, those occurring in ≥5% and at least twice as frequently with VIVITROL than placebo) include nausea, vomiting, injection site reactions (including induration, pruritus, nodules, and swelling), arthralgia, arthritis, or joint stiffness, muscle cramps, dizziness or syncope, somnolence or sedation, anorexia, decreased appetite or other appetite disorders.

The adverse events seen most frequently in association with VIVITROL in opioid-dependent patients (ie, those occurring in ≥2% and at least twice as frequently with VIVITROL than placebo) were hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.

You are encouraged to report side effects to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying Prescribing Information and Medication Guide. Review the Medication Guide with your patients.