

FDA Drug Safety Communication

FDA updates prescribing information for all opioid pain medicines to provide additional guidance for safe use

Includes updates to help reduce unnecessary prescribing

04-13-2023 FDA Drug Safety Communication

What safety concern is FDA announcing?

As part of its ongoing efforts to address the nation's opioid crisis, the U.S. Food and Drug Administration (FDA) is making several updates to the [prescribing information](#) of opioid pain medicines to provide additional guidance on the use of these powerful medicines. Opioid pain medicines are an important treatment option when used as prescribed; however, they also have serious risks, including misuse and abuse, addiction, overdose, and death.

Although there has been a substantial overall decrease in the number of dispensed prescriptions for opioid pain medicines, overdose deaths involving prescription opioids have remained steady. Data also suggest that:

- many acute pain conditions treated in the outpatient setting require no more than a few days of an opioid pain medicine, although the dose and duration of treatment needed to adequately manage pain will vary based on the underlying cause and individual patient factors.
- patients who use opioid pain medicines after surgery often have unused tablets, which may pose a risk of accidental use, misuse and abuse, addiction, and overdose, including by children and teenagers.
- extended-release/long-acting (ER/LA) opioid pain medicines have unique risks and should be used only for those with severe and persistent pain.

Based on our review of available data, FDA has also determined that a new warning is needed about opioid-induced hyperalgesia (OIH), which is when an opioid that is prescribed and taken for pain relief causes an increase in pain (called hyperalgesia) or an increased sensitivity to pain (called allodynia). Although OIH can occur at any opioid dosage, it may occur more often with higher doses and longer-term use. This condition can be difficult to recognize and may result in increased opioid dosages that could worsen symptoms and increase the risk of respiratory depression.

What is FDA doing?

We are requiring several updates to the [prescribing information](#) for both immediate-release (IR) and extended release/long acting (ER/LA) opioid pain medicines (See Table of Key Opioid Label Updates). This includes stating for all opioid pain that the risk of overdose increases as the dose increases. The updates to IR opioids state these products should not be used for an extended period unless the pain remains severe enough to require them and alternative treatments continue to be inadequate, and that many acute pain conditions treated in the outpatient setting require no more than a few days of an opioid pain medicine. This may include pain occurring with a number of surgical conditions or musculoskeletal injuries. We are also updating the approved use for ER/LA opioid pain medicines to recommend they be reserved for severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate.

In addition, we are adding a new warning about opioid-induced hyperalgesia (OIH) for both IR and ER/LA opioid pain medicines. This includes information describing the symptoms that differentiate OIH from opioid tolerance and withdrawal.

Information in the *Boxed Warning*, FDA's most prominent warning, for all IR and ER/LA opioid pain medicines will be updated and reordered to elevate the importance of warnings concerning life-threatening respiratory depression, and risks associated with using opioid pain medicines in conjunction with benzodiazepines or other medicines that depress the central nervous system (CNS). Other changes are also being required to several sections of the prescribing information, including to the *Indications and Usage, Dosage and Administration, and Warnings and Precautions* sections (See Table of Key Opioid Label Updates). We are also requiring updates to the existing patient [Medication Guides](#) to help educate patients and caregivers about these risks.

These changes to the prescribing information are designed to inform about appropriate prescribing of opioid pain medicines while also recognizing that they remain an important treatment option in appropriate situations and that undertreatment of pain (including abrupt discontinuations and forced tapering) carries its own [risks](#), including other morbidities and even the risk of illicit substance use for self-treatment. These changes are designed to provide essential information that prescribers need to prescribe opioid pain medicines appropriately, but the prescribing information itself cannot substitute for individual clinical judgment and talking to patients about their pain control.

What is an opioid and how can it help me?

[Opioid pain medicines](#) are a class of powerful pain medicines prescribed to treat pain that does not respond well to other treatments or non-opioid pain medicines. They activate an area of nerve cells in the brain and body that block pain signals. These medicines have benefits when used appropriately, but they also have serious risks, including misuse and abuse, addiction, overdose, and death. Examples of common opioid pain medicines include codeine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, fentanyl, buprenorphine, and tramadol.

What should health care professionals do?

In assessing the severity of pain, discuss with the patient the impact of the pain on their ability to function and their quality of life. Assessment of pain should consider both the cause of pain and individual patient factors.

If the patient's pain is severe enough to require an opioid pain medicine and alternative treatment options are insufficient, prescribe the lowest effective dose of an IR opioid for the shortest duration of time to reduce the risks associated with these products. Reserve increasing to higher doses only when lower doses are inadequate and the benefits of using a higher dose outweigh the substantial risks. Many acute pain conditions, such as pain occurring with a number of surgical procedures or musculoskeletal injuries, require no more than a few days of an IR opioid pain medicine.

Reserve ER/LA opioid pain medicines only for severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate. For patients currently on an ER/LA opioid who have pain severe enough to require an opioid but are not assessed as having severe and persistent pain, ensure that a multimodal approach to pain management is available, including mental health support. Discuss options for optimizing their

treatment, which might include moving to an IR opioid or other alternative pain treatment, with the potential to appropriately and carefully taper the opioid but [avoiding any abrupt discontinuation](#). Regularly reevaluate and discuss with your patients the optimum management of pain that appropriately balances the known benefits and risks, and frequently assess for development of addiction, misuse, or abuse. Inform patients of the added risks of using opioid pain medicines with benzodiazepines and other CNS depressants, and educate them on the signs and symptoms of respiratory depression.

For all patients prescribed opioid pain medicines, discuss the availability of naloxone, and consider prescribing it to those at increased risk of overdose. This may include patients who are also using benzodiazepines or other medicines that depress the central nervous system, with a history of opioid use disorder (OUD), or have experienced a previous opioid overdose. Health care professionals should also consider prescribing naloxone if the patient has household members, including children, or other close contacts at risk for accidental ingestion or opioid overdose. In [March 2023](#), FDA approved an inhaled nasal spray version of naloxone to be sold over-the-counter without a prescription.

Be aware that the symptoms of OIH, a condition where opioids cause an increase in pain (called hyperalgesia) or an increased sensitivity to pain (called allodynia), are distinct from opioid tolerance and withdrawal and can be difficult to recognize (see Additional Information for Health Care Professionals). If a patient is suspected to be experiencing OIH, carefully consider an appropriate decrease in dose of the current opioid pain medicine or safely switching them to a different opioid product, if tolerated. Advise patients about the risk of OIH and tell them to never increase the opioid dosage without first consulting a health care professional, because this could worsen the pain and increase the risk of respiratory depression.

What should patients and parents/caregivers do?

Always take your opioid medicines exactly as prescribed. Do not take more of the medicine or take it more often than prescribed without first talking to your health care professional. Talk with them if your pain increases, you feel more sensitive to pain, or if you have new pain, especially from touch or other things that are not usually painful such as combing your hair.

Store your opioid pain medicines securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home. Do not share these medicines with anyone else, and immediately [dispose](#) of unused or expired opioids or take them to a [drug take-back site](#), location, or program. If provided, use the prepaid mail-back envelopes included with the prescription.

Seek emergency medical help or call 911 immediately if you or someone you are caring for experiences symptoms of respiratory problems, which can be life-threatening. Signs and symptoms include serious slowed, shallow, or difficult breathing, severe sleepiness, or not being able to respond or wake up.

Talk to your health care professionals about the benefits of naloxone, which can reverse and opioid overdose, and how to obtain it. Your health care professional can give you a prescription for naloxone. Additionally, in most states and the District of Columbia you can obtain naloxone from a pharmacy under a standing order that takes the place of an individual prescription. Some states also allow you to obtain naloxone without a prescription from a community-based program

or pharmacy. Check with your state [Health Department](#) for more information. In [March 2023](#), FDA approved an inhaled nasal spray version of naloxone to be sold over-the-counter without a prescription while [multiple forms of naloxone](#) remain available as prescription only.

What did FDA find?

Despite substantial declines in the rates for opioid pain medicine dispensing,¹ prescription opioid medicine-involved overdose deaths have remained relatively steady over time, with 16,706 deaths in 2021.² However, these statistics likely underestimate the role of prescription opioids in contributing to overall opioid-related overdose deaths. Data suggest some patients who are prescribed opioid pain medicines may progress to nonmedical use of opioids and other controlled substances, contributing to the number of opioid-related overdoses.³ The impact of the opioid crisis extends beyond deaths and includes health consequences and harm to families.^{4,5}

Evidence suggests that patients getting opioid pain medicines for acute pain are often prescribed a larger quantity than needed,⁶ resulting in unused tablets. When not properly disposed of, these unused opioid tablets provide opportunities for nonmedical use, accidental exposure, and overdose.⁷ Data also strongly suggest that the risk of overdose increases as the prescribed dosage of opioid pain medicines increases,⁸ and this risk can occur at any point during treatment.

Opioid pain medicines also have been associated with other complications such as OIH. We identified 46 cases describing hyperalgesia and allodynia when opioid pain medicines were being used to treat pain, including eight with short-term use and 38 with longer-term use. These cases include only those submitted to the [FDA Adverse Event Reporting System](#) or those found in the medical literature,⁹ so there may be cases about which we are unaware (see Background and Data Summary). The cases involved a range of opioid pain medicines, including morphine, hydromorphone, and fentanyl/fentanyl analogs most commonly. Other possible causes of the increased pain were excluded, such as worsening of disease. Cancer was the most reported underlying condition being treated. Patients reported improvement in pain after stopping opioid pain medicines. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been suggested.

What is my risk?

Like all medicines, opioid pain medicines can have side effects, even when used correctly as prescribed. It is important to know that people respond differently to medicines depending on their health, the diseases they have, genetic factors, other medicines they are taking, and many other factors. As a result, we cannot determine how likely it is that someone will experience these side effects when taking opioid pain medicines. Talk to your health care professional if you have questions or concerns about the risks of taking opioid pain medicines.

How do I report side effects from opioid pain medicines?

To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving opioid pain medicines or other medicines to the [FDA MedWatch program](#), using the information in the “Contact FDA” box at the bottom of this page.

How can I get new safety information on medicines I’m prescribing or taking?

You can sign up for [email alerts](#) about Drug Safety Communications on medicines or medical specialties of interest to you.

Table of Key Opioid Label Updates

The following tables provide a comparison of the more significant label updates included in this action intended to provide additional guidance on prescribing opioid analgesics. These updates apply to opioid analgesics intended for use in the outpatient setting, although many also apply to opioid analgesics used in the inpatient setting. The below list is not exhaustive. These are representative examples of “former” and “new” labels. Other minor updates were incorporated within this action but are not listed below and will be available once the label updates for each product are approved by the FDA. Updated language is shown **in bold** and will be added to the Boxed Warning (Table 1), Indications and Usage (Tables 2 and 3), Dosage and Administration (Tables 4-7), Warnings and Precautions (Table 8), and Medication Guide (Table 9 - 11) sections of the opioid analgesic labels.

Table 1: Boxed Warning <i>(Applies to both Immediate-Release and Extended-Release/Long-Acting Opioid Analgesics)</i>	
Former Order and Language	New Order and Updated (shortened) Language
<p><u>Addiction, Abuse, and Misuse</u> [TRADENAME] exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk prior to prescribing [TRADENAME] and monitor all patients regularly for the development of these behaviors and conditions [see <i>Warnings and Precautions (5.X)</i>].</p> <p><u>Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)</u> To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products [see <i>Warnings and Precautions (5.X)</i>]. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to</p> <ul style="list-style-type: none"> • complete a REMS-compliant education program, • counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products, • emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and • consider other tools to improve patient, household, and community safety. <p><u>Life-Threatening Respiratory Depression</u> Serious, life-threatening, or fatal respiratory depression may occur with use of [TRADENAME].</p>	<p><u>Addiction, Abuse, and Misuse</u> Because the use of [TRADENAME] exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death, assess each patient’s risk prior to prescribing and reassess all patients regularly for the development of these behaviors and conditions [see <i>Warnings and Precautions (5.X)</i>].</p> <p><u>Life-Threatening Respiratory Depression</u> Serious, life-threatening, or fatal respiratory depression may occur with use of [TRADENAME], especially during initiation or following a dose increase. To reduce the risk of respiratory depression, proper dosing and titration of [TRADENAME] are essential [see <i>Warnings and Precautions (5.X)</i>].</p> <p><u>Accidental Ingestion</u> (no change) Accidental ingestion of even one dose of [TRADENAME], especially by children, can result in a fatal overdose of [active moiety] [see <i>Warnings and Precautions (5.X)</i>].</p> <p><u>Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants</u> Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of [TRADENAME] and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate [see <i>Warnings and Precautions (5.X)</i>, <i>Drug Interactions (7)</i>].</p>

Monitor for respiratory depression, especially during initiation of [TRADENAME] or following a dose increase [see *Warnings and Precautions (5.X)*].

Accidental Ingestion

Accidental ingestion of even one dose of [TRADENAME], especially by children, can result in a fatal overdose of [active moiety] [see *Warnings and Precautions (5.X)*].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of [TRADENAME] during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Warnings and Precautions (5.X)*].

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions (5.X)*, *Drug Interactions (7)*].

- Reserve concomitant prescribing of [TRADENAME] and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

Neonatal Opioid Withdrawal Syndrome (NOWS)

If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of NOWS, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery [see *Warnings and Precautions (5.X)*].

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) (also shortened)

Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription [see *Warnings and Precautions (5.X)*].

Table 2: Indications and Usage <i>(Applies to Immediate-Release Opioid Analgesics)</i>	
Former	New
<p><u>Limitations of Use:</u> Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [see <i>Warnings and Precautions (5.X)</i>], reserve [TRADENAME] for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or opioid combination products):</p> <ul style="list-style-type: none"> • Have not been tolerated, or are not expected to be tolerated, • Have not provided adequate analgesia, or are not expected to provide adequate analgesia, or are not expected to provide adequate analgesia 	<p><u>Limitations of Use:</u> Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosages or duration [see <i>Warnings and Precautions (5.X)</i>], reserve [TRADENAME] for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or opioid combination products):</p> <ul style="list-style-type: none"> • Have not been tolerated, or are not expected to be tolerated, • Have not provided adequate analgesia, or are not expected to provide adequate analgesia <p>[TRADENAME] should not be used for an extended period of time unless the pain remains severe enough to require an opioid analgesic and for which alternative treatment options continue to be inadequate.</p>

Table 3: Indications and Usage <i>(Applies to Extended-Release/Long-Acting Opioid Analgesics)</i>	
Former	New
<p>[TRADENAME] is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatments are inadequate.</p> <p><u>Limitations of Use:</u></p> <ul style="list-style-type: none"> • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release/long-acting opioid formulations [see <i>Warnings and Precautions (5.X)</i>], reserve [TRADENAME] for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • [TRADENAME] is not indicated as an as-needed (prn) analgesic. 	<p>[TRADENAME] is indicated for the management of severe and persistent pain that requires an extended treatment period with a daily opioid analgesic and for which alternative treatment options are inadequate.</p> <p><u>Limitations of Use:</u></p> <ul style="list-style-type: none"> • Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration, and because of the greater risks of overdose and death with extended-release/long-acting opioid formulations, [see <i>Warnings and Precautions (5.X)</i>], reserve [TRADENAME] for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • [TRADENAME] is not indicated as an as-needed (prn) analgesic.

Table 4: Dosage and Administration Important Dosage and Administration Instructions <i>(Applies to Immediate-Release Opioid Analgesics)</i>	
Former	New
<p>Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals <i>[see Warnings and Precautions (5)]</i>.</p> <p>Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse <i>[see Warnings and Precautions (5.X)]</i>.</p> <p>Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with [TRADENAME] and adjust the dosage accordingly <i>[see Warnings and Precautions (5.X)]</i>.</p>	<p>[TRADENAME] should be prescribed only by healthcare professionals who are knowledgeable about the use of opioids and how to mitigate the associated risks.</p> <p>Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals <i>[see Warnings and Precautions (5)]</i>. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of [TRADENAME] for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.</p> <p>Many acute pain conditions (e.g., the pain that occurs with a number of surgical procedures or acute musculoskeletal injuries) require no more than a few days of an opioid analgesic. Clinical guidelines on opioid prescribing for some acute pain conditions are available.</p> <p>There is variability in the opioid analgesic dose and duration needed to adequately manage pain due both to the cause of pain and to individual patient factors. Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and response, and risk factors for addiction, abuse, and misuse <i>[see Warnings and Precautions (5.X)]</i>.</p> <p>Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with [TRADENAME]. Consider this risk when selecting an initial dose and when making dose adjustments <i>[see Warnings and Precautions (5)]</i>.</p>

Table 5: Dosage and Administration Initial Dosage <i>(Applies to Immediate-Release Opioid Analgesics)</i>	
Former	New
<p><u>Use of [TRADENAME] as the First Opioid Analgesic</u></p> <p>Initiate treatment with [TRADENAME] in a dosing range of X mg to X mg every Y to Y hours as</p>	<p><u>Use of [TRADENAME] as the First Opioid Analgesic</u></p> <p>Initiate treatment with [TRADENAME] in a dosing range of X mg to X mg every Y to Y hours as</p>

needed for pain.	needed for pain, at the lowest dose necessary to achieve adequate analgesia. Titrate the dose based upon the individual patient's response to their initial dose of [TRADENAME].
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Table 6: Dosage and Administration Important Dosage and Administration Instructions <i>(Applies to Extended-Release/Long-Acting Opioid Analgesics)</i>	
Former	New
<p>[TRADENAME] should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.</p> <p>... (product-specific information)...</p> <p>Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals <i>[see Warnings and Precautions (5)]</i>.</p> <p>Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse <i>[see Warnings and Precautions (5.X)]</i>.</p> <p>Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with [TRADENAME] and adjust the dosage accordingly <i>[see Warnings and Precautions (5.X)]</i>.</p>	<p>[TRADENAME] should be prescribed only by healthcare professionals who are knowledgeable about the use of extended-release/long-acting opioids and how to mitigate the associated risks.</p> <p>... (product-specific information)...</p> <p>Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals <i>[see Warnings and Precautions (5)]</i>. Because the risk of overdose increases as opioid doses increase, reserve titration to higher doses of [TRADENAME] for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.</p> <p>Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse <i>[see Warnings and Precautions (5.X)]</i>.</p> <p>Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with [TRADENAME]. Consider this risk when selecting an initial dose and when making dose adjustments <i>[see Warnings and Precautions (5)]</i>.</p>

Table 7: Dosage and Administration Initial Dosage <i>(Applies to Extended-Release/Long-Acting Opioid Analgesics)</i>	
Former	New
<p><u>Conversion from Other Opioids to [TRADENAME]</u> Discontinue all other around-the-clock opioid drugs when [TRADENAME] therapy is initiated.</p>	<p><u>Conversion from Other Opioids to [TRADENAME]</u> When [TRADENAME] therapy is initiated, discontinue all opioid analgesics other than those used on an as needed basis for breakthrough pain when appropriate.</p>

Table 8: Warnings and Precautions <i>(Applies to both Immediate-Release and Extended-Release/Long-Acting Opioid Analgesics)</i>	
Former	New
(n/a)	<p>5.X Opioid-Induced Hyperalgesia and Allodynia</p> <p>Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect [see <i>Dependence (9.3)</i>]. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.</p> <p>Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic, or opioid rotation (safety switching the patient to a different opioid moiety) [see <i>Dosage and Administration (2.X)</i>; <i>Warnings and Precautions (5.X)</i>].</p>

Table 9: Medication Guide <i>(Applies to <u>Extended-Release/Long-Acting Opioid Analgesics</u>)</i>	
Former	New
<p>[TRADENAME] is:</p> <ul style="list-style-type: none"> • A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily, around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them. • A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death. • Not for use to treat pain that is not around-the-clock 	<p>[TRADENAME] is:</p> <ul style="list-style-type: none"> • A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage severe and persistent pain that requires an extended treatment period with a daily opioid medicine, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them. • A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death. • Not to be taken on an “as needed” basis.

Table 10: Medication Guide <i>(Applies to <u>both Immediate-Release and Extended-Release/Long-Acting Opioid Analgesics</u>)</i>	
Former	New
<p>Tell your healthcare provider if you:</p> <ul style="list-style-type: none"> • are pregnant or planning to become pregnant. Prolonged use of [TRADENAME] during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. 	<p>Tell your healthcare provider if you:</p> <ul style="list-style-type: none"> • are pregnant or planning to become pregnant. Use of [TRADENAME] for an extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated. • notice your pain getting worse. If your pain gets worse after you take [TRADENAME], do not take more of [TRADENAME] without first talking to your doctor. Talk to your doctor if the pain you have increases, if you feel more sensitive to pain, or if you have new pain after taking [TRADENAME].

Table 11: Medication Guide <i>(Applies to Immediate-Release Opioid Analgesics)</i>	
Former	New
<p>When taking [TRADENAME]:</p> <ul style="list-style-type: none"> Do not change your dose. Take [TRADENAME] exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed. Take your prescribed dose every 4 to 6 hours. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time. Call your healthcare provider if the dose you are taking does not control your pain. If you have been taking [TRADENAME] regularly, do not stop taking [TRADENAME] without talking to your healthcare provider. Dispose of expired, unwanted, or unused [TRADENAME] by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines. 	<p>When taking [TRADENAME]:</p> <ul style="list-style-type: none"> Do not change your dose. Take [TRADENAME] exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed. For acute (short-term) pain, you may only need to take [TRADENAME] for a few days. You may have some [TRADENAME] left over that you did not use. See disposal information at the bottom of this section for directions on how to safely dispose of [TRADENAME]. Take your prescribed dose every 4 to 6 hours. Do not take more than your prescribed dose. If you miss a dose, take your next dose at your usual time. Call your healthcare provider if the dose you are taking does not control your pain. If you have been taking [TRADENAME] regularly, do not stop taking [TRADENAME] without talking to your healthcare provider. Dispose of expired, unwanted, or unused [TRADENAME] by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

NOTE: FDA defines *misuse* as the intentional use, for therapeutic purposes, of a drug in a manner other than as prescribed or by an individual for whom it was not prescribed. FDA defines *abuse* as the intentional, nontherapeutic use of a drug for its desirable psychological or physiological effects. The term *abuse* is used in this document to describe a specific behavior that confers a risk of adverse health outcomes; it is not intended to imply moral judgment. FDA is committed to reducing stigma, expanding therapeutic options, and ensuring access to evidence-based treatment for individuals with substance use disorders.

Facts about Opioid Pain medicines

- Opioid pain medicines are powerful prescription medicines that can help manage pain when other treatments and medicines are not able to provide enough relief. However, opioid pain medicines also carry serious risks, including [misuse and abuse](#), addiction, overdose, and death.

- There are two main categories of prescription opioid pain medicines. Immediate-release (IR) products are usually intended for use every 4-6 hours as needed for acute pain. Extended-release/long-acting (ER/LA) opioid pain medicines are intended to be taken only once or twice a day for severe and persistent pain that requires an extended treatment period and for which alternative treatment options are inadequate, depending on the individual product and patient.
- Opioid pain medicines are available in many different forms, including tablets, capsules, lozenges, sublingual tablets, transdermal patches, nasal sprays, and injections.
- Common side effects of opioid pain medicines include drowsiness, dizziness, nausea, vomiting, constipation, physical dependence, and slowed or difficult breathing.
- The risk of opioid addiction, misuse, or abuse is increased in patients with a personal or family history of substance use disorder or mental illness.
- [Naloxone](#) is an opioid reversal medicine used to treat an opioid overdose or possible overdose and can help prevent death. Naloxone is widely available according to individual [state's](#) requirements or guidelines. Consider co-prescribing naloxone with all opioid prescriptions for those at increased risk of opioid overdose. In [March 2023](#), FDA approved the inhaled nasal spray version of naloxone to be sold over-the-counter without a prescription.

Additional Information for Health Care Professionals

- As part of its ongoing efforts to address the nation's opioid crisis, FDA is making several updates to the opioid analgesics' [prescribing information](#) to provide additional guidance on prescribing these powerful medicines. Although there has been a substantial overall decrease in the number of dispensed prescriptions for opioid analgesics, prescription opioid-related overdoses have not similarly decreased. Data suggest that:
 - many acute pain conditions treated in the outpatient setting, such as pain occurring with a number of surgical procedures or musculoskeletal injuries, require no more than a few days of an opioid pain medicine, although dose and duration of treatment needed to adequately manage pain will vary based on the underlying cause and individual patient factors.
 - outpatient opioid pain medicine use after surgery often results in unused tablets, and when not properly disposed of these unused medicines provide opportunities for nonmedical use, accidental exposure, and overdose.
 - extended-release/long-acting (ER/LA) opioid pain medicines have unique risks due to their properties and should be reserved for those with severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate.
- We are also adding a new warning about opioid-induced hyperalgesia (OIH), a condition where opioids cause an increase in pain (called hyperalgesia) or an increased sensitivity to pain (called allodynia). This condition, which can occur at any dosage but may occur more often with higher doses and longer-term use, can be difficult to recognize and may result in increasing the opioid pain medicine dosage, which could worsen the OIH and increase the risk of respiratory depression. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid or safely switching to a different opioid product, if tolerated. Symptoms of OIH can include:
 - increased pain intensity despite increasing opioid pain medicine doses
 - decreased pain intensity in response to a decrease in opioid pain medicine doses
 - hypersensitivity to non-painful stimuli (in the absence of opioid tolerance or withdrawal)

- Prescribe the lowest effective dose for the shortest duration for all opioid pain medicines consistent with a patient’s individual treatment goals. Because the risk of overdose increases as opioid pain medicine doses increase, reserve titrating to higher doses for patients who have an inadequate response to lower doses and when the benefits of a higher dose clearly outweigh the substantial risks.
- Periodically reassess the continued need for opioid pain medicine use regardless of the dose and for signs of addiction, [misuse, or abuse](#).
- Educate patients and caregivers that taking an opioid pain medicine other than how it is prescribed or with alcohol or benzodiazepines and other CNS depressants could increase the risk of overdose, and how to recognize the signs and symptoms of respiratory depression.
- Naloxone is used to treat an opioid emergency, such as an overdose or possible overdose. Consider co-prescribing naloxone with all opioid prescriptions for those at risk of opioid overdose or talk to patients about options for obtaining naloxone according to their [state](#) requirements or guidelines. Prescription and non-prescription forms of naloxone are FDA approved.
- Encourage patients to read the patient [Medication Guide](#) they receive with their filled prescription(s). Important, new information will be included. The Medication Guide explains the important things they need to know about the medicine. These include the side effects, what the medicine is used for, how to take and store it properly, and other things to watch out for when you are taking the medicine.
- To help FDA track safety issues with medicines, report adverse events involving opioid pain medicines or other medicines to the [FDA MedWatch program](#), using the information in the “Contact FDA” box at the bottom of this page.
- You can sign up for [email alerts](#) about Drug Safety Communications on medicines and medical specialties of interest to you.

Additional Information for Patients and Caregivers

- As part of its ongoing efforts to address the nation’s opioid crisis, FDA is making several updates to the [prescribing information](#) of opioids used for pain to provide additional guidance to health care professionals prescribing these powerful medicines, which have serious risks, including [misuse and abuse](#), addiction, overdose, and death.
- FDA is also adding a new warning about opioid-induced hyperalgesia (OIH), which is when an opioid that is prescribed and taken for pain relief causes an increase in pain (called hyperalgesia) or an increased sensitivity to pain (called allodynia).
 - OIH is a condition that can occur at any dosage of an opioid, but it may occur more often with higher doses and longer-term use
 - Talk to your health care professional if your pain increases, if you feel more sensitive to pain, or if you have new pain after taking your opioid pain medicine
- We are also updating the patient [Medication Guide](#) with this information. Read the Medication Guide and other information that comes with your filled prescription(s). Important, new information will be included. The Medication Guide explains the important things you need to know about the medicine. These include the side effects, what the medicine is used for, how to take and store it properly, and other things to watch out for when you are taking the medicine.
- Always take opioid pain medicines as prescribed. Do not take more doses or take them more often than prescribed.

- For many acute pain conditions such as pain occurring with a number of surgical procedures or musculoskeletal injuries, you may only need to take your opioid pain medicine for a few days. You may have some medicine left over that you did not use. Never give anyone else your opioid pain medicine. They could die from taking it. Selling or giving away your opioid pain medicine is against the law. Immediately [dispose](#) of unused or expired opioids or take them to a [drug take-back site](#), location, or program. See disposal information in the [Medication Guide](#) on how to safely dispose of your opioid pain medicine. If provided, use the prepaid mail-back envelopes included with the prescription.
- Store your opioid pain medicines securely, out of sight and reach of children, and in a location not accessible by others, including visitors. Every year thousands of children are hospitalized, and some die, after taking medicine not meant for them. Millions of people misuse prescription opioid pain medicines each year, and thousands die from overdoses involving prescription opioids.
- Signs of an opioid overdose include breathing problems, severe sleepiness, or not being able to respond or wake up. Seek medical attention immediately if you or someone you are caring for experiences these life-threatening symptoms.
- Naloxone is used to treat an opioid emergency, such as an overdose or possible overdose. Talk to your health care professional about how to use the naloxone product and options for obtaining naloxone according to your [state's](#) requirements or guidelines. In [March 2023](#), FDA approved an inhaled nasal spray version of naloxone to be sold over-the-counter without a prescription while [multiple forms of naloxone](#) remain available as prescription only.
- To help FDA track safety issues with medicines, report side effects from opioid pain medicines or other medicines to the [FDA MedWatch program](#), using the information in the “Contact FDA” box at the bottom of this page.
- You can sign up for [email alerts](#) about Drug Safety Communications on medicines and medical specialties of interest to you.

Background and Data Summary

Opioid-involved overdose deaths have risen steadily over the past 15 years, with a dramatic increase between 2017 (47,600 deaths) and 2021 (80,411 deaths).² Although most opioid-involved deaths are due to illicit fentanyl and fentanyl analogs,² several statistics help frame the context in which FDA is taking action to update the prescribing information for opioid pain medicines. Despite substantial declines in the rates of opioid pain medicine dispensing, falling from 81.3 prescriptions per 100 persons in 2012 to 43.3 prescriptions per 100 persons in 2020,¹ prescription opioid-involved overdose deaths have remained relatively steady over time, with 16,706 deaths in 2021.² These mortality statistics likely underestimate the role of prescription opioid pain medicines in contributing to overall opioid-related overdose deaths.

Data suggest that some patients prescribed opioid pain medicines may transition to nonmedical use of opioids and other controlled substances. In one study conducted between 2019 and 2021, researchers led in-depth interviews with 148 participants from three different states who reported using heroin, illicit fentanyl, or prescription opioid pain medicines nonmedically.³ Of those participants, 90 percent reported their initial exposure involved prescription opioid pain medicines, nearly half (48%) of whom

obtained them through a prescription. Many reported using opioids nonmedically for many years. Some study participants reported that their use of illicit opioids may have been influenced by policies and prescribing practices that unintentionally limited access to prescription opioids in inappropriate ways, e.g., rapid discontinuation of prescribed opioids.

The impact of the opioid crisis extends beyond mortality and includes associated morbidity and societal costs. Among Americans 12 and older, 5.6 million (2%) reported in 2021 having an opioid use disorder (OUD) in the past year.⁷ Health consequences of non-fatal, opioid-involved overdoses may include acute complications, such as opioid-induced respiratory depression, and more serious, chronic complications, such as brain injury.⁴ The impacts on children and their families include an increased risk of mental health problems, drug use, development of substance use disorder, accidental opioid poisoning, and loss of a parent to an opioid overdose.⁵

Evidence suggests opioid pain medicines continue to be overprescribed for many patients with some acute pain conditions. A systematic review of studies published through 2019 examined patient-reported outpatient opioid pain medicine use after surgery, finding that among studies that reported on excess tablets, 25 percent to 98 percent of total tablets prescribed were reported as excess, with most studies reporting between 50 percent and 70 percent excess tablets.⁶ Studies show that many patients report having leftover opioids after surgery.^{11,12,13} For many acute and chronic pain conditions, other non-opioid treatments, including both non-pharmacologic and pharmacologic, have been found to be effective. For a number of conditions, non-opioid medicines may be just as effective as opioid pain medicines.^{14,15}

Opioid-induced Hyperalgesia (OIH)

Opioid pain medicines have been associated with opioid-induced hyperalgesia (OIH), a condition where opioids cause an increase in pain (called hyperalgesia) or an increased sensitivity to pain (called allodynia). Increases in pain typically occur following a dose increase and resolve quickly following proper diagnosis and management of the condition.

We identified 46 patients describing hyperalgesia and allodynia when opioid pain medicines were being used to treat pain, including eight with short-term and 38 with longer-term use. These cases include only those submitted to the [FDA Adverse Event Reporting System](#) or those found in the medical literature,⁹ so there may be cases about which we are unaware. The cases involved a range of opioid pain medicines, including most commonly morphine, hydromorphone, and fentanyl/fentanyl analogs. Cancer was the most reported underlying condition being treated. Other possible causes were excluded such as worsening of disease. Patients reported improvement in pain after stopping opioid pain medicines. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been suggested.

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Related Information

- [FDA Overdose Prevention Framework](#)
- [Opioid Medications](#)
- [Opioid Overdose](#)
- [Misuse of Prescription Pain Relievers](#)
- [Information about Naloxone](#)
- [State Health Departments](#)
- [Naloxone Access by State](#)
- [Disposal of Unused Medicines: What You Should Know](#)
- [Lock it Up: Medicine Safety in Your Home](#)
- [The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)
- [Think It Through: Managing the Benefits and Risks of Medicines](#)