U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA Drug Safety Communication: FDA warns about several safety issues with opioid pain medicines; requires label changes

Safety Announcement

[3-22-2016] The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. We are requiring changes to the labels of all opioid drugs to warn about these risks.

More specifically, the labels will warn about the following:

- Opioids can interact with antidepressants and migraine medicines to cause a serious central nervous system reaction called serotonin syndrome, in which high levels of the chemical serotonin build up in the brain and cause toxicity (see List of Serotonergic Medicines).
- Taking opioids may lead to a rare, but serious condition in which the adrenal glands do not produce adequate amounts of the hormone cortisol. Cortisol helps the body respond to stress.
- Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility.

Opioids are a class of powerful narcotic pain medicines that are used to treat moderate to severe pain that may not respond well to other pain medicines (see List of Opioids). They can help manage pain when other treatments and medicines are not able to provide enough pain relief, but they also have serious risks including misuse and abuse, addiction, overdose, and death.

Recommendations and information for patients and health care professionals

Serotonin syndrome:
Patients taking an opioid along with a serotonergic medicine (see List of Serotonergic Medicines) should seek medical attention immediately if they develop symptoms such as agitation; hallucinations; rapid heart rate; fever; excessive sweating; shivering or shaking; muscle twitching or stiffness; trouble with coordination; and/or nausea, vomiting, or diarrhea. Symptoms generally start within several hours to a few days of taking an opioid with another medicine that increases the effects of serotonin in the brain, but symptoms may occur later, particularly after a dose increase.

Health care professionals should discontinue opioid treatment and/or use of the other medicine if serotonin syndrome is suspected.

Cases of serotonin syndrome in the FDA Adverse Event Reporting System (FAERS) database were reported more frequently with the opioids fentanyl and methadone used at the recommended doses. Therefore, we are requiring a new statement in the *Warnings and Precautions* section to be added to these drug labels. Some opioids, including tramadol, tapentadol, and meperidine, already have warnings about serotonin syndrome. Cases were also reported with other opioids, so the labels of all these drugs will be updated to include information about serotonin syndrome in the *Drug Interactions* and *Adverse Reactions* sections.

Adrenal insufficiency:
Patients should seek medical attention if they experience symptoms of adrenal insufficiency such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure. **Health care professionals** should perform diagnostic testing if adrenal insufficiency is suspected. If diagnosed, treat with corticosteroids and wean the patient off of the opioid, if appropriate. If the opioid can be discontinued, follow-up assessment of adrenal function should be performed to determine if treatment with corticosteroids can be discontinued.

We are requiring a new statement about adrenal insufficiency to be added to the *Warnings and Precautions* section of all opioid labels.

Decreased sex hormone levels:
Patients should inform their health care professionals if they experience symptoms of low libido, impotence, erectile dysfunction, lack of menstruation, or infertility.
Health care professionals should conduct laboratory evaluation in patients presenting with such signs or symptoms.

We reviewed published studies that assessed levels of sex hormones in patients taking opioids chronically;[1-21] however, all had limitations that make it difficult to determine whether the symptoms were caused by the opioids or other factors. The labels of some opioids already describe this possible risk, and we are now adding consistent information to the *Adverse Reactions* section of all opioid labels.

We urge patients and health care professionals to report side effects involving opioids or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

List of Opioids

Generic Name	Found in Brand Name(s)
alfentanil	Alfenta
buprenorphine	Belbuca, Bunavail, Buprenex, Butrans, Suboxone, Zubsolv
butorphanol	No brand name currently marketed
codeine	Fioricet w/ codeine, Fiorinal w/ codeine, Tylenol w/ codeine
dihydrocodeine	Synalgos-DC
fentanyl	Abstral, Actiq, Duragesic, Fentora, Ionsys, Lazanda, Sublimaze, Subsys
hydrocodone	Anexsia, Hysingla ER, Lortab, Norco, Reprexain, Vicodin, Vicoprofen, Zohydro ER
hydromorphone	Dilaudid, Dilaudid-HP, Exalgo
meperidine	Demerol
methadone	Dolophine, Methadose
morphine	Astramorph PF, Duramorph PF, Embeda, Infumorph, Kadian, Morphabond, MS Contin
oxycodone	Oxaydo, Oxycet, Oxycontin, Percocet, Percodan, Roxicet, Roxicodone, Xartemis XR
oxymorphone	Opana, Opana ER
pentazocine	Talwin
remifentanil	Ultiva
sufentanil	Sufenta
tapentadol	Nucynta, Nucynta ER
tramadol	Conzip, Ultracet, Ultram, Ultram ER

List of Serotonergic Medicines

Generic Name	Found in Brand Name(s)
Selective Serotonin Reuptake Inhibitors (SSRIs)	
paroxetine	Paxil, Paxil CR, Pexeva, Brisdelle
fluvoxamine	Luvox, Luvox CR
fluoxetine	Prozac, Prozac Weekly, Sarafem, Selfemra, Symbyax
sertraline	Zoloft
citalopram	Celexa
escitalopram	Lexapro
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	
venlafaxine	Effexor XR
desvenlafaxine	Pristiq, Khedezla
duloxetine	Cymbalta
milnacipran	Savella
Tricyclic Antidepressants (TCAs)	
amitriptyline	No brand name currently marketed
desipramine	Norpramin
clomipramine	Anafranil
imipramine	Tofranil, Tofranil PM
nortriptyline	Pamelor, Aventyl
protriptyline	Vivactil
doxepin	Zonalon, Silenor
trimipramine	Surmontil
Monoamine Oxidase Inhibitors (MAOIs)	
isocarboxazid	Marplan
phenelzine	Nardil
selegiline	Emsam, Eldepryl, Zelapar
tranylcypromine	Parnate
Other Psychiatric Medicines	
amoxapine	No brand name currently marketed
maprotiline	No brand name currently marketed
nefazodone	No brand name currently marketed
trazodone	Oleptro
buspirone	No brand name currently marketed
vilazodone	Viibryd
mirtazapine	Remeron, Remeron Soltab
lithium	Lithobid
Migraine Medicines	
almotriptan	Axert
frovatriptan	Frova
naratriptan	Amerge

rizatriptan	Maxalt, Maxalt-MLT
sumatriptan	Imitrex, Imitrex Statdose, Alsuma, Sumavel Dosepro, Zecuity, Treximet
zolmitriptan	Zomig, Zomig-ZMT
Antiemetics	
ondansetron	Zofran, Zofran ODT, Zuplenz
granisetron	Kytril, Sancuso
dolasetron	Anzemet
palonosetron	Aloxi
Other Serotonergic Medicines	
dextromethorphan	Bromfed-DM, Delsym, Mucinex DM, Nuedexta
linezolid	Zyvox
cyclobenzaprine	Amrix
methylene blue	
St. John's wort	
tryptophan	

Facts about Opioids

- Opioids are powerful prescription medicines that can help manage pain when other treatments and medicines are not able to provide enough pain relief (see List of Opioid Medicines). However, opioids also carry serious risks, including of misuse and abuse, addiction, overdose, and death.
- Prescription opioids are divided into two main categories – immediate-release (IR) products, usually intended for use every 4 to 6 hours; and extended release/long acting (ER/LA) products, intended to be taken once or twice a day, depending on the individual product and patient.
- Certain opioids, such as methadone and buprenorphine, can also be prescribed as a form of treatment for opioid addiction.
- Opioids are available in many different formulations, including tablets, capsules, lozenges, sublingual tablets, transdermal patches, nasal sprays, and injections.
- Common side effects of opioids include drowsiness, dizziness, nausea, vomiting, constipation, physical dependence, and slowed or difficult breathing.
- The risk of opioid addiction, abuse or misuse is increased in patients with a personal or family history of substance abuse, or mental illness.
- It is important to lock up opioids and to dispose of them properly to keep them from falling into the wrong hands.

Additional Information for Patients

- FDA is warning about several safety issues with the class of powerful narcotic opioid pain medicines:

    - Opioids can interact with certain medicines that increase the effects of serotonin, which is a chemical in the brain. The interacting medicines include antidepressants and migraine medicines, and the interaction causes a serious central nervous system reaction called serotonin syndrome (see List of Serotonergic Medicines).
    - Taking opioids may lead to a rare, but serious condition called adrenal insufficiency in which the adrenal glands do not produce adequate amounts of the steroid hormone, cortisol, particularly during stressful conditions.
    - Long-term use of opioids may be associated with decreased sex hormone levels.
- Inform your health care professional about all the drugs you are taking, including prescription and over-the-counter medicines. It is helpful to keep a list of all your current medicines in your wallet or another location where it can be easily retrieved. You can fill out and print a copy of My Medicine Record.
- If you are taking an opioid pain reliever and don't know if you are also receiving serotonergic medicines or other medicines that interact with opioids, contact your health care professional.
- Opioids are powerful narcotic pain medicines that can help manage pain when other treatments and medicines are not able to provide enough pain relief. However, even when used properly, opioids also carry serious risks, and they can be misused and abused, causing addiction, overdose, and death.
- Seek medical attention immediately if you develop any symptoms of serotonin syndrome such as:
    - Agitation
    - Hallucinations
    - Rapid heart rate
    - Fever
    - Excessive sweating
    - Shivering or shaking
    - Muscle twitching or stiffness
    - Trouble with coordination
    - Nausea, vomiting, or diarrhea
- Also seek medical attention if you experience symptoms of adrenal insufficiency such as:
    - Nausea or vomiting
    - Loss of appetite
    - Fatigue
    - Weakness
    - Dizziness
    - Low blood pressure.
- Inform your health care professional if you experience signs or symptoms of decreased sex hormone levels such as low libido, impotence, erectile dysfunction, lack of menstruation, or infertility.

- Talk to your health care professional if you have any questions or concerns about opioids or other medicines you are taking.
- Read the patient information leaflet or Medication Guide that comes with your filled prescription(s).
- Report side effects from opioids or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- FDA is warning about several safety issues with the class of opioid pain medicines. These include serotonin syndrome, adrenal insufficiency, and androgen deficiency.

Serotonin syndrome

- Serotonin syndrome can occur during concomitant use of opioids with serotonergic drugs. This may occur within the recommended dosage range.
- If concomitant use of an opioid with a serotonergic drug is warranted, carefully observe the patient, particularly during treatment initiation and dose increases.
- Symptoms of serotonin syndrome may include mental status changes such as agitation, hallucinations, or coma; autonomic instability such as tachycardia, labile blood pressure, or hyperthermia; and neurologic abnormalities such as hyperreflexia, incoordination, or rigidity.
- The onset of symptoms generally occurs within several hours to a few days of concomitant use but may occur later, particularly after dose increases.
- Discontinue opioid treatment and/or use of the concomitant serotonergic drug if serotonin syndrome is suspected.
- Counsel patients about the symptoms of serotonin syndrome and advise them to seek medical attention immediately if symptoms develop.
- Instruct patients to inform their health care professionals if they are taking or plan to take serotonergic drugs.

Adrenal insufficiency

- Cases of adrenal insufficiency have been reported with opioid use.
- Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure.
- If adrenal insufficiency is suspected, confirm with diagnostic testing as soon as possible. The patient should be treated with physiologic replacement doses of corticosteroids and weaned off of the opioid to allow adrenal function to recover.
- If the opioid can be discontinued, follow-up assessment of adrenal function should be performed to determine if treatment with corticosteroids can be discontinued.
- Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency.
- The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Androgen deficiency

- Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility.
- The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled in studies conducted to date.
- Patients presenting with symptoms or signs of androgen deficiency should undergo laboratory evaluation.

General information

- Encourage patients to read the information leaflets or Medication Guides that come with their filled prescription(s).
- Report adverse events involving opioids or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

FDA investigated several safety issues associated with the class of opioid pain medicines:

- Serotonin syndrome
- Adrenal insufficiency
- Androgen deficiency

Serotonin syndrome

A search of the FDA Adverse Event Reporting System (FAERS) database for the period January 1, 1969, to June 12, 2013, identified 43 cases of serotonin syndrome in which opioids were used concomitantly with other serotonergic drugs. The review excluded meperidine, tramadol, and tapentadol, which were already labeled for the risk of serotonin syndrome at the time of the review. The most commonly reported opioids associated with serotonin syndrome were fentanyl (n=28), oxycodone (n=7), and methadone (n=5). Other reported opioids included hydromorphone, morphine, alfentanil/remifentanil/sufentanil, hydrocodone, naltrexone, and pentazocine. Although there were no reports of serotonin syndrome with an opioid used alone, five cases reported that serotonin syndrome occurred with the use of two or more opioids concurrently. All of these five cases reported use of fentanyl along with at least one other opioid [oxycodone (n=4), morphine (n=1), hydromorphone (n=1), and hydrocodone (n=1)].

Adrenal insufficiency

A search of FAERS for the period January 1, 1969, to February 5, 2014, identified 37 cases of adrenal insufficiency reported with the use of opioids. Twenty-seven cases reported opioid monotherapy, and 10 reported use of more than one opioid at the same time. The most commonly reported opioids associated with adrenal insufficiency were fentanyl (n=10) and oxycodone (n=10), followed by buprenorphine or

buprenorphine/naloxone (n=7), hydromorphone (n=6), and tramadol (n=4). When reported, the time to onset of adrenal insufficiency after the start of opioid therapy ranged from within 1 day to more than 1 year; however, many of the cases reported adrenal insufficiency after at least 1 month of use. Many of the patients were hospitalized. Of the 37 cases, 21 described that the patients received corticosteroid treatment. Sixteen cases reported discontinuing or reducing the dose of the opioid. Of the 16, nine of these patients improved, three had ongoing symptoms, and four did not report an outcome. Some patients experienced a relief in symptoms when they were switched from one opioid to another.

Androgen deficiency

We reviewed the medical literature to evaluate the association between opioids and androgen deficiency. [1-21] A range of studies in a variety of settings demonstrated decreased gonadal hormones in men and women taking long-term opioids. However, most of the studies were descriptive prevalence studies that did not include baseline values for the hormone levels, and there was a lack of comparability between the opioid-treated groups and control groups regarding medical, physical, lifestyle, and psychological factors that may influence gonadal hormone levels. Due to limitations of the studies, it is unclear whether the low gonadal hormone levels and associated symptoms and signs in men and women could be attributed to long-term opioid use or to other factors such as the patient's underlying medical condition warranting opioid treatment; physical, mental, or life stressors; weight changes; or concomitant medication or supplement use.

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