

Opioids – Drug Safety Update

- On March 22, 2016, the [FDA announced](#) required class-wide safety labeling changes for immediate-release (IR) opioids and [announced additional safety label changes](#) about several issues with the entire class of [opioids](#) [extended-release/long-acting (ER/LA) and IR opioids].
- Opioids are pain-reducing medications that have benefits as well as potentially serious risks. These medications can help manage pain when prescribed for the right condition and when used properly. When misused or abused, they can cause serious harm, including addiction, overdose and death.
- Changes to the IR opioid drug labels will require:
 - A new *Boxed Warning* regarding the serious risks of misuse, abuse, addiction, overdose, and death.
 - The boxed warning will also include a precaution regarding chronic maternal use of opioids during pregnancy, which can result in neonatal withdrawal syndrome (NOWS). NOWS may be life threatening if not recognized and treated using protocols developed by neonatology experts.
 - An updated indication stating that IR opioids should be reserved for pain severe enough to require opioid treatment and for which alternative treatment options (e.g., non-opioid analgesics or opioid combination products) are inadequate or not tolerated.
 - Updated dosing information to provide clearer instructions regarding patient monitoring and drug administration, including initial dosage, dosage changes during therapy and a warning not to abruptly stop treatment in a physically dependent patient.
- The [FDA required](#) similar updates to the ER/LA opioid drug labels in 2013.
- Additionally, the FDA announced safety issues associated with all opioids, including serotonin syndrome, adrenal insufficiency, and androgen deficiency.
- *Serotonin Syndrome:*
 - Opioids can interact with antidepressants and migraine medicines to cause serotonin syndrome, in which high levels of serotonin build up in the brain and cause toxicity.
 - Serotonin syndrome symptoms may include agitation, hallucinations, rapid heart rate, and fever; excessive sweating; shivering or shaking; muscle twitching or stiffness; trouble with coordination; and/or nausea, vomiting, or diarrhea. Symptoms may start within a few hours to a few days, or after a dose increase.
 - Patients should seek immediate medical attention if they experience serotonin syndrome symptoms, and healthcare providers are advised to discontinue opioid treatment and/or use of the other medicine if serotonin syndrome is suspected.
 - Cases of serotonin syndrome were reported more frequently with [fentanyl](#) and [methadone](#), thus this information will be added to the *Warnings and Precautions* section of these drug labels. Because cases were also reported with other opioids, the *Adverse Reactions* and *Drug Interactions* sections of all opioid drug labels will be updated to include this information.

- *Adrenal Insufficiency:*
 - A new statement about adrenal insufficiency will be added to the *Warnings and Precautions* section of all opioid labels.
 - Taking opioids may lead to a rare, but serious condition in which the adrenal glands do not produce adequate amounts of the hormone cortisol.
 - Adrenal insufficiency symptoms are nonspecific and may include nausea, vomiting, fatigue, loss of appetite, weakness, dizziness, or low blood pressure. Healthcare providers should conduct diagnostic testing if adrenal insufficiency is suspected and treat appropriately.
 - Available information does not identify any particular opioid as more likely to be associated with adrenal insufficiency.

- *Androgen deficiency:*
 - Long-term use of opioids may be associated with decreased sex hormone levels, leading to symptoms such as low libido, impotence, erectile dysfunction, lack of menstruation, or infertility.
 - Patients should inform their healthcare provider if they experience such signs and symptoms of decreased sex hormone levels. Healthcare providers should evaluate and treat accordingly.
 - According to the FDA’s review of the published literature, studies assessing levels of sex hormones and chronic opioid use had limitations that made it difficult to determine the source of the symptoms.
 - Consistent information regarding androgen deficiency will be added to the *Adverse Reactions* section of all opioid labels, as some opioid labels already describe this possible risk.

- The FDA is also reviewing information about potentially serious outcomes related to interactions between benzodiazepines and opioids. Once the review is completed, the FDA will take necessary actions to ensure prescribers and the public are informed of the risks involved with the use of these medications.

- Last month, Dr. Robert Califf, the FDA’s Deputy Commissioner for Medical Products and Tobacco, [called for a review](#) of the FDA’s opioid policies and an action plan to reassess its approach to opioid medications. Additional information can be found [here](#).

- In addition, the [Centers for Disease Control and Prevention recently announced](#) the release of guidelines for prescribing opioids for chronic pain. Additional information can be found [here](#).



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