Lesser-Known Opioid Adverse Effects

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Question

What are the lesser-known adverse effects that the FDA recently added to opioid drug labeling?

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Opioids are commonly used to treat acute and chronic pain despite meager evidence supporting the effectiveness of long-term opioid therapy for relieving chronic pain or improving function.[1] The frequent prescribing of opioids for nonacute use has prompted concern about the increased risk for serious harm, including overdose, abuse, and addiction; and, in response, the Centers for Disease Control and Prevention (CDC) released the CDC Guideline for Prescribing Opioids for Chronic Pain.[2]

Some of the commonly associated adverse effects of opioids include central nervous system depression, hypotension, respiratory depression, constipation, nausea, and itching. The US Food and Drug Administration (FDA) recently mandated opioid labeling changes to highlight several of the less-recognized effects, including serotonin syndrome, adrenal gland suppression, and decreased sex hormone levels.[3]

Serotonin syndrome. Serotonin syndrome is a result of excess serotonin in the synapses. The mechanism by which opioids cause serotonin syndrome is thought to be weak inhibition of serotonin reuptake and/or inhibition of inhibitory gamma-aminobutyric acid-releasing (GABAergic) neurons. These effects result in retention of serotonin in the synapses and/or a downstream release of more serotonin by the serotonergic neurons.[4] Synthetic piperidine opioids (fentanyl, methadone, meperidine, propoxyphene, dextromethorphan, and tramadol) are proserotonergic as reuptake inhibitors. Phenanthrene morphine analogs (oxycodone, hydromorphone, oxymorphone, and buprenorphine) are not reuptake inhibitors but appear to work through some other unknown mechanism to increase serotonin.[4]

Overdoses of serotonergic drugs or drug interactions can increase serotonin levels and cause serotonin syndrome (Table). Fentanyl has been associated with serotonin syndrome most frequently, followed by oxycodone and methadone.[3,5]

Table. Serotonergic Drugs

Class	Examples
Selective serotonin reuptake inhibitors (SSRIs)	Paroxetine, fluvoxamine, fluoxetine, sertraline, citalopram, escitalopram
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine, desvenlafaxine, duloxetine, milnacipran
Tricyclic antidepressants (TCAs)	Amitriptyline, desipramine, clomipramine, imipramine, nortriptyline, protriptyline, doxepin, trimipramine
Monoamine oxidase inhibitors (MAOIs)	Isocarboxazid, phenelzine, selegiline, tranylcypromine
Other psychiatric medicines	Amoxapine, maprotiline, nefazodone, trazodone, buspirone, vilazodone, mirtazapine, lithium

Migraine medicines	Almotriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan
Antiemetics	Ondansetron, granisetron, dolasetron, palonosetron
Other	Dextromethorphan, linezolid, cyclobenzaprine, methylene blue, St. John's wort, tryptophan

Data from US Food and Drug Administration.[3]

The hallmark symptoms of serotonin syndrome are altered mental status, autonomic hyperactivity, and neuromuscular excitability,[6] which may manifest as anxiety, agitation, confusion, hypomania, visual hallucinations, restlessness, disorientation, coma, hypertension/hypotension, tachycardia, tachypnea, diarrhea, mydriasis, diaphoresis, hyperthermia, muscle rigidity, tremors, nystagmus, myoclonus, ocular clonus, hyperreflexia, ataxia, and trismus.[4]

While the symptoms of serotonin syndrome are reversible with prompt recognition and treatment, the diagnosis of serotonin syndrome in the context of opioid use may be difficult, as some symptoms of opioid toxicity and withdrawal are similar to symptoms of serotonin excess.[4] In the setting of long-term care facilities where comorbid pain and depression with concomitant opioid and serotonergic antidepressant treatment are not uncommon, clinical awareness of serotonin syndrome should be increased to initiate early treatment.[7]

Estimates of the incidence of opioid-associated serotonin syndrome are based on case reports to the FDA Adverse Event Reporting System (FAERS) database and scant retrospective analyses.

Adrenal insufficiency. Both endogenous and exogenous opioids appear to bind to opioid receptors in the hypothalamus.[8] By extension, opioid medications also may affect hormone levels. Multiple case studies of chronic opioid use describe symptoms of adrenal insufficiency and suppressed cortisol levels, which is the clearest indicator of adrenal suppression.[8-12] The removal and re-exposure to opioids results in an improvement with subsequent relapse in cortisol levels and symptoms. Hypercalcemia resulting from opioid-induced adrenal insufficiency has been reported.[10]

Symptoms of adrenal insufficiency include nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, and low blood pressure.[3]

In the FAERS database, the FDA identified 37 cases of adrenal insufficiency related to opioids; fentanyl, oxycodone, buprenorphine or buprenorphine/naloxone, hydromorphone, and tramadol were the common offenders. Most cases developed after at least 1 month of use. Several patients improved with corticosteroid treatment and modification or discontinuation of the opioid therapy.[3]

Evidence from small studies of heroin addicts and chronic pain patients suggests that adrenal hormonal effects are more pronounced with intravenous or intrathecal opioid therapy.[8]

Decreased sex hormones. Opioids inhibit the gonadotropin-releasing hormone in the hypothalamus, resulting in the decreased release of pituitary hormones, such as luteinizing hormone and follicle-stimulating hormone, which results in reduced production of sex hormone levels (eg, testosterone, estrogen).[8]

Symptoms of decreased sex hormone levels include low libido, impotence, erectile dysfunction, lack of menstruation, and infertility.

Hypogonadism appears to be a class effect of opioids, with no one drug implicated as a more common culprit. Knowledge of opioid-induced hypogonadism is largely from descriptive prevalence studies and case reports.[3,13,14] As such, a definitive link between opiates and decreased sex hormone levels is difficult to establish, but the number of descriptive cases led the FDA to require information regarding these symptoms in the Adverse Reactions section of opioid drug monographs.[3] Limited evidence suggests that patients receiving long-acting opioids have a higher prevalence of hypogonadism, but this observation may be flawed in light of the fact that dosage is typically lower with short-acting opioids.[14]

Updated Labeling

The FDA updated the labeling for all medications in the opioid drug class to include a statement about the risk for

serotonin syndrome in the Drug Interactions and Adverse Reactions sections, adrenal insufficiency in the Warnings and Precautions section, and decreased sex hormone levels in the Adverse Reactions section.

The strength of evidence is greater for serotonin syndrome than for the hormonal disturbances, but both warrant concern and extra scrutiny. In the case of hormonal imbalances, laboratory monitoring of hormone levels and corticosteroid replacement should be considered.[3] Further study is needed to define the scope and prevalence of these lesser-known adverse effects.

Healthcare providers should be vigilant for serotonin syndrome and hormonal disturbances in patients receiving opioids.

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