



EDUCATION MODULE

PRESCRIBING OPIOIDS FOR PATIENTS TREATED WITH ANTIDEPRESSANTS*

*This module provides information about concurrent use of opioids and antidepressants as a risk factor for opioid overdose and specific risk-reduction guidance. It **supplements** but does not replace the general best practices for opioid prescribing presented in the “**Considerations for Safe and Responsible Opioid Prescribing**” module.*

Background

1. Chronic pain and mental health disorders are common in the general population and often co-occur.¹⁻³
2. Depression and anxiety are present in approximately 45% and 25% in patients with chronic pain, respectively.⁴⁻⁹ Patients with co-occurring chronic pain and mental health disorders:
 - a. Have a greater intensity and longer duration of pain, poorer clinical outcomes, and increased health care utilization than those without mental health disorders.^{4,10-12}
 - b. Are more likely to be treated with opioid analgesics, and are more likely to receive higher potency opioids, higher dosages, and/or for longer duration (>90 days) than those without mental health disorders.^{6,9,13}
3. Epidemiological and neuroimaging evidence supports a bidirectional relationship between chronic pain conditions and mental health disorders that may be mediated in part by shared and mutually reinforcing neurobiological mechanisms.^{14,15}
 - a. Behavioral treatments and certain drug classes, including serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and selected anticonvulsants are efficacious for chronic pain conditions and mental health disorders; these treatments should be considered first-line psychotherapeutic interventions in patients with co-occurring conditions.¹⁵

Antidepressants and opioid overdose

1. Certain antidepressants (e.g., mirtazapine, paroxetine, and tricyclics such as amitriptyline, imipramine, and doxepin) are more sedating than other antidepressants, and can increase the risk of respiratory depression and/or over-sedation when used with opioids.¹⁶
2. Pharmacokinetic interactions between certain antidepressants and opioids can result in increased opioid plasma levels due to impaired opioid metabolism or elimination (see recommendations below) and increase the risk of opioid toxicity.^{17,18}
3. The risk of drug overdose in opioid-treated patients with non-cancer pain who are taking concurrent antidepressants, benzodiazepines, and/or sedatives/hypnotics (e.g., zolpidem, zaleplon, zopiclone, eszopiclone) involves complex interactions among concurrent mental health disorders and psychotherapeutic medications. **The underlying indication for use of an antidepressant may influence the patient’s risk for opioid overdose.** For example, in an opioid-treated patient with chronic pain,



stable, well-managed depression (or lower severity of depression) using an antidepressant may substantially reduce the risk of opioid overdose.^{19,20}

Risk-mitigation interventions to consider when prescribing opioids in patients treated with antidepressants
[Refer to the full prescribing information (FDA label) for important product-specific details]

1. In patients with chronic pain and depression, antidepressant treatment for depression can also improve pain symptoms.
 - a. Consider using tricyclic or serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants first-line for their analgesic and antidepressant effects unless these medications otherwise contraindicated.²¹⁻²³ These medications can reduce the amounts of opioid required and are particularly effective for neuropathic pain, other centralized pain syndromes, and fibromyalgia.²⁴⁻²⁶
 - b. The analgesic effects of antidepressants generally occur at lower dosages and with a shorter time of onset than their antidepressant effects.²⁴
2. Individuals with an active, unstable mental health disorder or uncontrolled suicide risk are at heightened risk for drug overdose. Stabilize such patients in consultation or co-management with, or by referral to, a behavioral health/mental health specialist before treating chronic non-cancer pain with opioids.^{24,27-30}
3. Closely monitor patients treated with concurrent opioids and antidepressants for respiratory depression, and over-sedation, suicidality, and opioid use disorder particularly during initiation and after dosage escalations.
 - a. The risk for overdose is greatest increased during the first 3 to 7 days after starting an opioid or increasing its dosage; this occurs because tolerance to the opioid's respiratory depressant effects is slower to develop and less complete than tolerance to its analgesic and or euphoric effects.^{24,26,31,32}
4. Use caution with certain opioid-antidepressant combinations.
 - a. In patients treated with codeine, oxycodone, and methadone, avoid bupropion (moderate CYP2D6 inhibitor), paroxetine, and fluoxetine (strong CYP2D6 inhibitors) and nefazodone (strong CYP3A4 inhibitor), due to reduced opioid metabolism.^{17,18}
 - b. Avoid bupropion (moderate CYP2D6 inhibitor), paroxetine, and fluoxetine (strong CYP450 2D6 inhibitors) with codeine, oxycodone, and methadone due to reduced opioid metabolism. Opioid plasma levels may increase and lead to respiratory depression and over-sedation.^{17,18,33}
 - c. Morphine, hydromorphone, tapentadol, levorphanol, or oxycodone are preferred opioids for use with bupropion, paroxetine, or fluoxetine because the metabolism of these opioids involves glucuronidation and largely bypasses phase I CYP450 enzymes.^{17,33,34}
5. Serotonin toxicity ("serotonin syndrome") is possible (albeit rare) and has been reported when serotonin-elevating antidepressants (e.g., SSRIs, SNRIs, clomipramine and imipramine) are combined with certain opioids, namely tramadol, fentanyl, or meperidine.^{35,36}



- a. The manifestations of serotonin syndrome fall along a spectrum of severity and can include abdominal pain, diarrhea, flushing, sweating, hyperthermia, lethargy, mental status changes, tremor, myoclonus, rhabdomyolysis, renal failure, cardiovascular shock, and may result in death.^{35,36}
6. Consider prescribing take-home naloxone for an opioid treated patient who is taking an antidepressant to reverse life-threatening respiratory depression if an overdose occurs. Educate the patient, family/household members, and caregivers about signs and symptoms of opioid overdose and train them to properly use naloxone if an opioid-related overdose is suspected.²⁴
7. Consider consultation or co-management with a specialist in behavioral/mental health when prescribing opioids to manage pain in patients treated with antidepressants.²⁴

Additional Resources

**The information presented in this module highlights some fundamental concepts of opioid prescribing for adult outpatients. It excludes certain populations (pediatrics, pregnancy, patients with active cancer or receiving palliative or end-of-life care) and settings (perioperative, emergency, in-patient). The information provided is intended to support safe and effective opioid therapy and minimize serious adverse outcomes, particularly overdose. It is not intended to be exhaustive nor substitute for consulting a medication's full prescribing information for complete details and warnings. Links and references to selected, more comprehensive clinical and prescribing resources are provided to facilitate safe and effective opioid prescribing.*

1. FDA-approved drug label information: [FDA Online Label Repository](#) or [Daily Med](#) (NIH/National Library of Medicine)
2. [Depression in Adults: Clinical Guidelines](#). (National Institute for Health and Care Excellence)
3. [Depression: Practice Guidelines](#) 2010 (American Psychiatric Association)
4. [Flockhart Table of Drug-Drug Interactions: Cytochrome P450 Drug Interactions](#) (2016)
5. Serotonin toxicity ([PsychoTropical Research](#))

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