



## 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.<sup>1-3</sup>
2. Depression and anxiety are present in approximately 45% and 25% in patients with chronic pain, respectively.<sup>4-9</sup> 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.<sup>4,10-12</sup>
  - 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.<sup>6,9,13</sup>
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.<sup>14,15</sup>
  - 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.<sup>15</sup>

#### **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.<sup>16</sup>
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.<sup>17,18</sup>
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.<sup>19,20</sup>

**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.<sup>21-23</sup> These medications can reduce the amounts of opioid required and are particularly effective for neuropathic pain, other centralized pain syndromes, and fibromyalgia.<sup>24-26</sup>
  - b. The analgesic effects of antidepressants generally occur at lower dosages and with a shorter time of onset than their antidepressant effects.<sup>24</sup>
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.<sup>24,27-30</sup>
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.<sup>24,26,31,32</sup>
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.<sup>17,18</sup>
  - 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.<sup>17,18,33</sup>
  - 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.<sup>17,33,34</sup>
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.<sup>35,36</sup>



- 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.<sup>35,36</sup>
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.<sup>24</sup>
7. Consider consultation or co-management with a specialist in behavioral/mental health when prescribing opioids to manage pain in patients treated with antidepressants.<sup>24</sup>

### 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](#))

### References

1. Henschke N, Kamper SJ, Maher CG. The epidemiology and economic consequences of pain. *Mayo Clin Proc* 2015;90:139-47. [PMID: 25572198](#)
2. Steel Z, Marnane C, Iranpour C, et al. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *Int J Epidemiol*. 2014;43(2):476-493. [PMID: 15939839](#)
3. Von Korff M, Crane P, Lane M, et al. Chronic spinal pain and physical-mental comorbidity in the United States: results from the national comorbidity survey replication. *Pain* 2005;113:331-9. [PMID: 15661441](#)
4. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med*. 2003;163(20):2433-45. [PMID: 24214740](#)
5. Cheatle MD, Gallagher RM. Chronic pain and comorbid mood and substance use disorders: a biopsychosocial treatment approach. *Curr Psychiatry Rep*. 2006;8(5):371-6. [PMID: 16968617](#)

6. Edlund MJ, Martin BC, Devries A, Fan MY, Braden JB, Sullivan MD. Trends in use of opioids for chronic noncancer pain among individuals with mental health and substance use disorders: the TROUP study. *Clin J Pain* 2010;26:1-8. [PMID: 20026946](#)
7. Knaster P, Karlsson H, Estlander AM, Kalso E. Psychiatric disorders as addressed with SCID on chronic pain patients: The anxiety disorders precede the onset of pain. *Gen Hosp Psychiatry* 2012;34:46-52. [PMID: 22001549](#)
8. Radat F, Margot-Duclot A, Attal N. Psychiatric co-morbidities in patients with chronic peripheral neuropathic pain: a multicentre cohort study. *Eur J Pain*. 2013;17(10):1547-57. [PMID: 23720357](#)
9. Sullivan MD, Edlund MJ, Steffick D, Unutzer J. Regular use of prescribed opioids: association with common psychiatric disorders. *Pain* 2005;119(1-3):95-103. [PMID: 16298066](#)
10. Grattan A, Sullivan MD, Saunders KW, Campbell CI, Von Korff MR. Depression and prescription opioid misuse among chronic opioid therapy recipients with no history of substance abuse. *Ann Fam Med*. 2012;10(4):304-11. [PMID: 22778118](#)
11. Gerrits MM, Vogelzangs N, van Oppen P, van Marwijk HW, van der Horst H, Penninx BW. Impact of pain on the course of depressive and anxiety disorders. *Pain*. 2012;153(2):429-36. [PMID: 20026946](#)
12. Kroenke K, Outcalt S, Krebs E, Bair MJ, Wu J, Chumbler N, et al. Association between anxiety, health-related quality of life and functional impairment in primary care patients with chronic pain. *Gen Hosp Psychiatry*. 2013;35(4):359-65. [PMID: 23639186](#)
13. Seal KH, Shi Y, Cohen G, Cohen BE, Maguen S, Krebs EE, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. *JAMA*. 2012;307(9):940-7. [PMID: 22396516](#)
14. Gerrits MM, van Oppen P, van Marwijk HW, Penninx BW, van der Horst HE. Pain and the onset of depressive and anxiety disorders. *Pain*. 2014;155(1):53-9. [PMID: 24012953](#)
15. Hooten WM. Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment. *Mayo Clin Proc*. 2016;91(7):955-70. [PMID: 27344405](#)
16. Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, Boer JAd, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. *Journal of Psychopharmacology*. 2014;28(5):403-39. [PMID: 20945576](#)
17. Somogyi AA, Barratt DT, Collier JK. Pharmacogenetics of opioids. *Clin Pharmacol Ther* 2007;81:429-444. [PMID: 21412369](#)
18. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2016). <http://medicine.iupui.edu/clinpharm/ddis/clinical-table/>
19. Mason MJ, Golladay G, Jiranek W, et al. Depression moderates the relationship between pain and the nonmedical use of opioid medication among adult outpatients. *J Addict Med* 2016;10:408-413. [PMID: 24648481](#)
20. Turner BJ, Liang Y. Drug Overdose in a Retrospective Cohort with Non-Cancer Pain Treated with Opioids, Antidepressants, and/or Sedative-Hypnotics: Interactions with Mental Health Disorders. *J Gen Intern Med*. 2015;30(8):1081-96. [PMID: 25650263](#)
21. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: Systematic review, meta-analysis and updated NeuPSig recommendations. *Lancet Neurol* 2015;14:162-173. [PMID: 27559846](#)
22. Jann M, Slade JH. Antidepressant agents for the treatment of chronic pain and depression. *Pharmacotherapy* 2007;27:1571-1587. [PMID: 17963465](#)
23. Verdu B, Decosterd I, Buclin T, Steifel F, Berney A. Antidepressants for the treatment of chronic pain. *Drugs* 2008;68:2611-32. [PMID: 19093703](#)

24. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. MMWR Recomm Rep. 2016;65(1):1-49. [PMID: 26987082](#)
25. Hauser W, Wolfe F, Tolle T, Uceyler N, Sommer C. The role of antidepressants in the management of fibromyalgia syndrome. A systematic review and meta-analysis. CNS Drugs 2012;26:297-307. [PMID: 17963465](#)
26. Washington State Agency Medical Directors' Group (WSAMDG). Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain: An Educational Aid to Improve Care and Safety With Opioid Treatment. Corvallis, WA: Washington Department of Health, 2015. [www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf](http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf)
27. Busse J, Craigie S, Juurlink D, et al. Guideline for opioid therapy and chronic noncancer pain: Appendix. CMAJ 2017. [PMID: 26461074](#)
28. U.S. Department of Veterans Affairs. VA/DoD clinical practice guideline for opioid therapy for chronic pain. Washington, DC: US Department of Veterans Affairs; 2017. <https://www.healthquality.va.gov/guidelines/pain/cot/>
29. Bohnert AS, Ilgen MA, Ignacio RV, McCarthy JF, Valenstein M, Blow FC. Risk of death from accidental overdose associated with psychiatric and substance use disorders. Am J Psychiatry. 2012;169(1):64-70. [PMID: 21955932](#)
30. Crump C, Sundquist K, Winkleby MA, Sundquist J. Mental disorders and risk of accidental death. Br J Psychiatry. 2013;203(3):297-302. [PMID: 23969485](#)
31. Dumas EO, Pollack GM. Opioid tolerance development: a pharmacokinetic/pharmacodynamic perspective. AAPS J. 2008;10:537-51. [PMID: 18989788](#)
32. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction 1999;94:961-72. [PMID: 10707430](#)
33. Brennan MJ. The clinical implications of cytochrome p450 interactions with opioids and strategies for pain management. J Pain Symptom Manage. 2012;44(6 Suppl):S15-22. [PMID: 23218232](#)
34. Smith HS. The metabolism of opioid agents and the clinical impact of their active metabolites. Clin J Pain 2011;27:824-838. [PMID: 21677572](#)
35. Gillman PK. CNS toxicity involving methylene blue: the exemplar for understanding and predicting drug interactions that precipitate serotonin toxicity. J Psychopharmacol. 2011 Mar;25(3):429-36. [PMID: 20142303](#)
36. Gillman PK. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. Br J Anaesth. 2005 Oct;95(4):434-41. Epub 2005 Jul 28. Review. [PMID: 16051647](#)