

## EDUCATION MODULE

### PRESCRIBING OPIOIDS FOR PATIENTS TREATED WITH BENZODIAZEPINES\*

*This module provides information about concurrent use of opioids and benzodiazepines 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>1,2</sup>
2. Depression and anxiety are present in approximately 45% and 25% in patients with chronic pain, respectively.<sup>3-8</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>3,9-11</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>8,12,13</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>10,14</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>14</sup>

#### **Benzodiazepines and opioid overdose**

1. Concurrent use of opioids with other central nervous system (CNS) depressant drugs or substances may lead to profound sedation, respiratory depression, coma, and death.<sup>15-17</sup> (see also: FDA label)
2. CNS depressants that can potentiate opioid-induced respiratory depression and sedation include benzodiazepines, non-benzodiazepine sedatives/hypnotics (e.g., zolpidem, zaleplon, zopiclone, eszopiclone), barbiturates, muscle relaxants, alcohol, general anesthetics, and certain antipsychotics, antidepressants, and anticonvulsants (e.g., gabapentinoids).<sup>15-17</sup> (see also: FDA label)



- a. Concurrent use of a benzodiazepine and opioid has been identified in 31% to 61% of U.S. and Canadian prescription drug overdose deaths.<sup>18-21</sup>
- b. Benzodiazepine use in opioid analgesic-users increases the risk of fatal overdose by up to 10-fold compared to use of opioids alone, particularly at higher opioid dosages.<sup>18,22</sup>

### **Risk-mitigation interventions to consider when prescribing opioids in patients treated with benzodiazepines**

[Refer to the full prescribing information (FDA label) for important product-specific details]

1. The preferred therapies for anxiety disorders include psychotherapy (e.g., cognitive behavioral therapy), selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants, and non-benzodiazepine anxiolytics.<sup>23,24</sup>
  - a. Most patients with anxiety disorders should continue pharmacotherapy for at least 12 to 24 months.<sup>23-25</sup>
  - b. Benzodiazepines should be used on a short-term basis only.<sup>24</sup>
2. Avoid concurrent use of an opioid analgesic and benzodiazepine or other CNS-depressant unless alternative treatment options are inadequate or contraindicated.<sup>15,16</sup>
3. In patients who are concurrently taking a benzodiazepine and an opioid [for analgesia or as pharmacotherapy for opioid use disorder (OUD)], prescribe the lowest effective dosages and minimum durations of concomitant use. Taper the benzodiazepine (or other CNS depressant) to discontinuation if possible (see below).<sup>16,26</sup>
  - a. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid, and titrate based on clinical response.
  - b. If a benzodiazepine or other CNS depressant is initiated in a patient already taking an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid (except for epilepsy), and titrate based on clinical response.
4. For patients receiving OUD pharmacotherapy with methadone or buprenorphine, concurrent use of benzodiazepines or other CNS depressants (prescribed or illicit) increases the risk of serious adverse reactions including overdose and death. However, OUD pharmacotherapy should not be categorically denied to patients taking other CNS depressants. Prohibiting or creating barriers to OUD pharmacotherapy can pose an even greater risk of morbidity and mortality due to untreated OUD.<sup>27</sup>
  - a. Educate patients about the risks of concurrent use of benzodiazepines, sedatives, opioid analgesics, or alcohol, and that benzodiazepines are not the treatment of choice for anxiety or insomnia. Consider alternative medications and non-pharmacologic treatments to address anxiety or insomnia (see below).

- b. Conduct periodic urine drug testing to monitor therapeutic adherence by the presence of prescribed controlled medications and to detect undisclosed use of nonprescribed controlled medications or illicit drugs.<sup>16,17</sup>
  - c. Check the state prescription drug monitoring program (PDMP) data to confirm the history of controlled medications and to check for use of multiple prescribers or pharmacies, which raise concern for other SUD or diversion.
5. Closely monitor for respiratory depression and over-sedation in opioid-treated patients who are taking a benzodiazepine or other CNS-depressant.<sup>16,26</sup>
  - a. Advise patients to not drive or operate heavy machinery until the effects of concurrent use of the opioid and benzodiazepine or other CNS depressant have been determined.
  - b. Warn patients and caregivers about the risks of respiratory depression and over-sedation if opioids are taken with benzodiazepines, alcohol, or other CNS depressants (including illicit or recreational drugs).
6. Consider consulting or co-managing with, or referral to, a specialist in pain medicine, addiction medicine, or behavioral/mental health for those patients who are treated with concurrent opioids and benzodiazepines or other CNS depressants.<sup>16</sup>
7. Consider prescribing take-home naloxone to an opioid-treated patient who is taking a benzodiazepine to reverse life-threatening respiratory depression if an overdose occurs.<sup>16</sup>
8. 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>16</sup>

**Special considerations: Tapering benzodiazepines (or other CNS depressant medications that are used concomitantly with opioids)**

1. Benzodiazepine withdrawal entails more risk relative to opioid withdrawal, and tapering opioids can be associated with anxiety. In patients treated with both benzodiazepines and opioids who require tapering to reduce the risk of overdose, it may be safer and more practical to taper opioids first.<sup>16</sup>
2. Taper benzodiazepines slowly over several months to avoid serious complications including seizures, delirium, and emergent anxiety or insomnia.<sup>16,28</sup> (see also: Ashton Manual 2013, Deprescribing Guidelines and Algorithms)
  - a. Cognitive behavioral therapy increases the success rate of medication tapering and might be particularly helpful for patients struggling with a benzodiazepine taper.<sup>16,29</sup>
  - b. Consider consultation with, or referral to, a specialist in pain medicine, addiction medicine, or behavioral/mental health for those patients who experience serious challenges in tapering.<sup>16</sup>

- c. Adjust or pause (for 1 to 2 weeks) tapering as needed to manage withdrawal symptoms. Use non-opioid, non-benzodiazepine adjunctive agents, if necessary, such as antidepressants, beta-adrenergic antagonists, and non-benzodiazepine treatment options for insomnia (see below). If possible, taper the benzodiazepine to discontinuation.<sup>29</sup>

### Special considerations: Treatment of insomnia

1. Sleep disturbances occur in 50% to 80% of patients with chronic pain. The relationship is bidirectional: disturbed sleep can aggravate pain, and pain can interfere with sleep.<sup>30</sup>
2. Instruction in sleep hygiene practices followed by cognitive behavioral therapy are recommended as initial interventions for chronic insomnia.<sup>31,32,33</sup>
3. If pharmacologic treatment for insomnia is required, avoid benzodiazepines and hypnotic medications. Consider low-dose tricyclic antidepressants such as doxepin (3mg to 6mg) or trazodone, melatonin, ramelteon, suvorexant, or other non-controlled medications.<sup>17,32,33</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. [Ashton Manual: Protocol for the treatment of benzodiazepine withdrawal.](#) (Newcastle University, 2013) Available at: <https://www.benzo.org.uk/manual>
3. [Clinical Practice Guideline: Deprescribing benzodiazepine receptor agonists.](#) (Deprescribing.org)
4. [American Academy of Sleep Medicine](#)

### 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. 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](#)
3. 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](#)

4. 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](#)
5. Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M Risk factors for clinically recognised opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain* 2007;129:355-62. [PMID: 16968617](#)
6. 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](#)
7. 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](#)
8. 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](#)
9. 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](#)
10. 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](#)
11. 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](#)
12. 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](#)
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. Hooten WM. Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment. *Mayo Clin Proc.* 2016;91(7):955-70. [PMID: 27344405](#)
15. Busse J, Craigie S, Juurlink D, et al. Guideline for opioid therapy and chronic noncancer pain: Appendix. *CMAJ* 2017. [PMID: 26461074](#)
16. 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](#)
17. 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)
18. Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisl KM, Marshall S. Cohort Study of the Impact of High-Dose Opioid Analgesics on Overdose Mortality. *Pain Med.* 2016;17(1):85-98. [PMID:16968617](#)
19. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med* 2011;171:686–91. [PMMID: 21482846](#)
20. Jones CM, McAninch JK. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. *Am J Prev Med.* 2015;49(4): 493–501. [PMID: 26143953](#)

21. 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](#)
22. Larochelle MR, Liebschutz JM, Zhang F, Ross-Degnan D, Wharam JF. Opioid Prescribing After Nonfatal Overdose and Association With Repeated Overdose: A Cohort Study. *Ann Intern Med.* 2016;164(1):1-9. [PMID: 26720742](#)
23. Stein MB, Sareen J. CLINICAL PRACTICE. Generalized anxiety disorder. *N Engl J Med.* 2015;373(21):2059-2068. [PMID: 26580998](#)
24. 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. GAD- NICE 2004. [PMID: 20945576](#)
25. Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry.* 2014;14 Suppl 1:S1-244X-14-S1-S1. Epub 2014 Jul 2. [PMID: 25081580](#)
26. [FDA Drug Safety Communication.](#) FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: Careful medication management can reduce risks. 2016
27. [FDA Drug Safety Communication.](#) FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines. 2017
28. Lader M, Tylee A, Donoghue J. Withdrawing benzodiazepines in primary care. *CNS Drugs* 2009;23:19-34. [PMID: 19062773](#)
29. Belanger L, Belleville G, Morin G. Management of hypnotic discontinuation in chronic insomnia. *Sleep Med Clin* 2009;4:583-592. [PMID: 20607118](#)
30. Cheatle MD, Foster S, Pinkett A, Lesneski M, Qu D, Dhingra L. Assessing and Managing Sleep Disturbance in Patients with Chronic Pain. *Sleep Med Clin.* 2016;11(4):531-41. [PMID: 23218232](#)
31. Brasure M, Fuchs E, MacDonald R, et al. Psychological and behavioral interventions for managing insomnia disorder: An evidence report for clinical practice guideline by the American College of Physicians. *Ann Intern Med.* 2016; 165(2):113-124. [PMID: 27136619](#)
32. Qaseem A, Kansagara D Forceia MA, et al. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2016;165:125-33. [PMID: 27136449](#)
33. Sateia MJ, Buysse DJ, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med.* 2017 Feb 15;13(2):307-349. [PMID: 27998379](#)