



Risks of Co-prescribing Opioids and Benzodiazepines

According to the Centers for Disease Control and Prevention (CDC), overdose deaths involving prescription opioids increased nearly five-fold from 1999 to 2020, with 16% of opioid-related deaths in 2020 also involving benzodiazepines (BZDs).^{1,2} Many studies have highlighted the dangers of co-prescribing opioids and BZDs due to their additive adverse effects and potential to cause profound sedation, respiratory depression, coma and death. Opioids and BZDs now have FDA boxed warnings in their prescribing information highlighting the potential dangers of using them together.³ In 2022, the CDC released updated opioid practice guidelines which recommend avoiding concomitant BZD and opioid use.⁵

The CDC practice guidelines recommend the following:⁵

- Avoid co-prescribing opioids with BZDs. Check the Prescription Drug Monitoring Program before writing new prescriptions.
- Offer BZD alternatives to patients receiving opioids who require treatment for anxiety or insomnia (Table 1).
- Taper medications if risks of concomitant use outweigh benefits:
 - Reduce BZD dose gradually by 25% every 1 to 2 weeks.
 - Reduce opioid dose by 10% of starting dose monthly for treatment duration over 1 year.
 - Reduce opioid dose by 10% of starting dose weekly for treatment duration less than 1 year.
- Offer naloxone if concurrent opioid and BZD use is necessary.
- Monitor closely for signs of respiratory depression.

Table 1. Medi-Cal Rx and OneCare Formulary BZD Alternatives

Indication	Generic (Brand)	Dosing ⁶
Generalized Anxiety Disorder	bupirone (Buspar)	20–30 mg/day in two or three divided doses; max 60 mg/day
	duloxetine (Cymbalta)	Initial 30–60 mg once daily; max 120 mg/day
	escitalopram (Lexapro)	10–20 mg once daily; max 20 mg/day
	paroxetine (Paxil)*	20 mg once daily; max 20 mg/day
	sertraline (Zoloft) [†]	Initial 25 mg once daily for 1 week; max 200 mg/day
	venlafaxine ER capsules (Effexor XR)	Initial 37.5–75 mg once daily; max 225 mg/day
Insomnia	mirtazapine (Remeron) ^{†‡}	15 mg once daily; max 45 mg/day
	ramelteon (Rozerem)	8 mg once daily at bedtime; max 8 mg/day
	trazodone (Desyre) [†]	50–100 mg once daily at bedtime; max 100 mg/day

*High risk medication in older adults age 65 and above; [†]Off-label indication; [‡]For concomitant depression

References

1. Centers for Disease Control and Prevention. Drug Overdose. <https://www.cdc.gov/drugoverdose/deaths/prescription/overview.html>. Published 2022. Accessed on August 18, 2022.
2. National Institute on Drug Abuse (NIH). Benzodiazepines and Opioids. March 2018. <https://www.drugabuse.gov/drugs-abuse/opioids/benzodiazepines-opioids>. Accessed on August 18, 2022.
3. U.S. Food and Drug Administration. Drug Safety Communications: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. August 31, 2016. <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM518672.pdf>. Accessed on August 18, 2022.
4. Koch NV, Butterfield RJ III. An observational study of the factors associated with frequency of outpatient benzodiazepine prescribing to patients receiving chronic opioid analgesic therapy in primary care at a major academic center. *BMC Prim Care*. 2022;23(1):322. Published 2022 Dec 13. doi:10.1186/s12875-022-01936-z
5. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. *MMWR Recomm Rep* 2022;71(No. RR-3):1–95.
6. IBM Micromedex Solutions. Truven Health Analytics Inc. <http://micromedex.com>. Accessed March 23, 2023.