

Opioid Interactions: Potentiator Drugs That Increase the Risk of Overdose

KNOW WHICH MEDICATIONS MAY INTENSIFY OPIOID EFFECTS

Certain medications can magnify the effects of opioids, increasing the risk of overdose, respiratory depression and death. Awareness of these potentiator drug classes is essential for safer prescribing.

Health Net* is committed to supporting providers in preventing opioid misuse and improving patient safety. When combined with opioids, some medications may enhance their effects—leading to serious health consequences.

The table below highlights key potentiators. While not comprehensive, it highlights major drug classes and considerations for clinical review when coprescribing.



Opioid potentiators: Key drug classes and considerations

Drug class	Medication	Significant considerations
Central nervous system (CNS) depressants		
Benzodiazepines (BZDs)	alprazolam, clonazepam, diazepam, lorazepam	Both opioids and BZDs sedate users, suppress breathing and impair cognitive function.
Antihistamines	promethazine	Increased risk for respiratory depression, falls and injuries, coma, and death when combined with opioids. **The combination of opioid + benzodiazepine + carisoprodol ("Holy Trinity") carries a very high overdose risk.
Barbiturates	phenobarbital	
Z-drugs/BZD-like hypnotics	zolpidem, zaleplon, eszopiclone	
Gabapentinoids	gabapentin, pregabalin	
Muscle relaxants	tizanidine, cyclobenzaprine, baclofen, carisoprodol**	Additive sedation and hypotension; some (especially with methadone) increase QT-prolongation risk.
Antipsychotics	quetiapine, olanzapine	
Antidepressants (sedating/serotonergic)	amitriptyline, mirtazapine, trazodone	Additive sedation and orthostatic hypotension; certain combinations (e.g., with tramadol, methadone, meperidine) may precipitate serotonin syndrome.

(continued)

Drug class	Medication	Significant considerations
Pharmacokinetic enhancers		
Antibiotics	clarithromycin	CYP450 inhibition leads to increase in serum opioid concentration. Ultimately results in strong CNS depression.
Antifungals	itraconazole, ketoconazole, posaconazole	
HIV drugs	ritonavir, atazanavir, indinavir, cobicistat	
Other potentiators		
Cannabinoids	THC, cannabidiol (CBD)	Additive sedation, and cognitive impairment; CBD can inhibit CYP3A4/CYP2C19 which can lead to variable increase in opioid levels.
Stimulants	dextroamphetamine, methylphenidate	Extremely high abuse potential. Used in combination to combat fatigue and sedation caused by high daily doses of opioids or to increase the analgesic effect.

The chart above was adapted from the Centers for Medicare & Medicaid Services guidance.

Key takeaways for providers

- Review all current medications before initiating or renewing opioid therapy.
- Avoid coprescribing potentiators when possible or use the lowest effective doses for the shortest duration.
- Counsel patients on overdose risks and safe medication use.
- Consider prescribing naloxone for patients at increased risk.