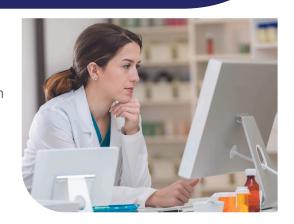
## Opioid Interactions: Potentiator Drugs That Increase the Risk of Overdose

**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.

Wellcare By Health Net (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.	
Barbiturates	phenobarbital		
Z-drugs/BZD-like hypnotics	zolpidem, zaleplon, eszopiclone	**The combination of opioid + benzodiazepine + carisoprodol ("Holy Trinity") carries a very high overdose risk.	
Gabapentinoids	gabapentin, pregabalin		
Muscle relaxants	tizanidine, cyclobenzaprine, baclofen, carisoprodol**		
Antipsychotics	quetiapine, olanzapine	Additive sedation and hypotension; some (especially with methadone) increase QT-prolongation risk.	
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.

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