

The Holy Trinity

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The medical “holy trinity” is a combination of an opioid, a benzodiazepine, and carisoprodol, most commonly prescribed as alprazolam (Xanax), carisoprodol (Soma), and either hydrocodone or oxycodone. As will be discussed in this article, this combination of medications has a high risk of overdose as well as an extremely high risk of abuse or addiction. Because of the risks associated with this medication combo, many pharmacies in California are required to contact the prescribing physician for a justification as to why all three medications are needed.

As we are in the middle of the opioid epidemic, most of us are very aware of the hazards of opioids – and have begun to change our practice to prescribing fewer opioids. However, there are some significant issues with the other medications in the trinity that are worth discussing.

Carisoprodol (Soma)

Carisoprodol (Soma) is prescribed as muscle relaxant, but it's not really a muscle relaxant. Soma is metabolized to meprobamate, an anxiolytic, known for its addictive potential – which is currently used very infrequently due to issues with addiction. Meprobamate was first synthesized in 1950 and marketed as Miltown. It was a medication that was originally thought to be a minor tranquilizer that was addiction free and overdose free. It turned out to be neither.

Soma is rapidly absorbed in the GI tract, and quickly crosses the blood brain barrier. The half-life of carisoprodol is only 100 minutes, but the half-life of meprobamate is 6 to 17 hours – so unfortunately the effects of this highly addictive metabolite of carisoprodol stay in the system for a long time.

Due to major issues with adverse effects and addiction, Sweden has taken Soma off the market in 2007, and Norway took it off the market in 2008. The European Medicines Agency recommended suspension of all medications that contain meprobamate "due to serious side effects..," and "concluded that the benefits of meprobamate do not outweigh its risks." The European Union advises against the use of Soma for chronic back pain. In Canada, Soma is a schedule I prescription drug. However, in the United States, Soma is only a Schedule IV medication at this time meaning it is minimally regulated but will at least show up on CURES reports.

One major issue with carisoprodol is the well described effect of enhancing the euphoric effects of other medications and drugs, including opioids, benzodiazepines, cocaine, and ethanol. Up to 10% of patients have reported that they take carisoprodol to augment the effect of another drug. Also, when studied, a large percentage of patients taking soma take more than prescribed and request early refills given its significant euphoric effects.

Although Soma is cheap, there are other muscle relaxant options that are better. Try Cyclobenzaprine (Flexeril) or Methocarbamol (Robaxin).

Alprazolam (Xanax)

Alprazolam is a benzodiazepine that is commonly prescribed for anxiety, and is the most commonly prescribed benzodiazepine – with over 50,000 prescriptions yearly written in the US. However, of all of the benzodiazepines, it crosses the blood brain barrier the fastest – giving it the most euphoric effect of all of the benzos. As such, it has the greatest potential for addiction and misuse. However, the clinical effects of the drug only last on average 5 hours, resulting in patients taking additional doses over a short time period – which can lead to addiction and dependence. Tolerance and dependence can develop in as little as 10 days.

Alprazolam and other benzodiazepines are most often prescribed for anxiety. However, there is evidence that long-term use increases baseline anxiety levels over time, exacerbating conditions such as panic disorder. There is also evidence demonstrating an association between long-term use of alprazolam and iatrogenic depressive disorder. Selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRIs), which do not have tolerance and abuse potential, remain first line therapy for anxiety disorders. The American Psychiatric Association Guidelines recommend benzodiazepines such as Xanax for short-term use only.

Opioids and benzodiazepines together

The combination of an opioid and benzodiazepine has become recognized as a very high risk combination, due to the additive sedative effects of both drugs. Use of the two medications together now carries a black box warning from the FDA, and the 2016 CDC guidelines on the treatment of chronic pain specifically recommended against using the medications together.

As far as specific risks of the combination go, using an opioid with a benzodiazepine increases the risk of death from overdose by ten fold as compared to opioids alone. Additionally, the use of an opioid with a benzodiazepine significantly increases the risk of a life-threatening illness or injury as compared to the use of benzodiazepine alone.

When a prescribing physician reviews a medication list and sees this combination, they should alert the patient and warn the patient not to take the two types of medication at the same time. For patients chronically on this combination, one potential approach is to wean the patient off of one of the two drug classes as this will dramatically improve patient safety. Many clinics have policies where patients cannot have prescriptions for both classes of medications due to the increased risk.

Tramadol

One last medication is worth discussing here...Tramadol. Have your patients asked you for a non-narcotic medication like tramadol (Ultram)? Are you prescribing Tramadol thinking that's it is a non-narcotic and non-addicting? Tramadol 50 mg actually has 1.5 times more opiate equivalents than hydrocodone 5 mg. Tramadol is, despite how it is often portrayed, an opioid, and has just as high a risk of abuse or misuse as other opioids. Furthermore, tramadol is actually higher risk than other opioids as it has interactions with multiple medications and can be associated with both serotonin syndrome and seizures.

For more information about safe prescribing, go to: <http://www.chomp.org/prescribe-safe/>

There is also a specific reference for physicians at: <http://www.chomp.org/prescribe-safe/prescribe-safe-clinical/>

Thank you for taking the time to review this information and consider the impact your prescribing has on the health and safety of our community.

Respectfully,



Adapted with gratitude from *SanDiegoSafePrescribing* information by Dr. Roneet Lev

References for scientific studies available on request. Contact prescribesafe@chomp.org