

Tramadol and Serotonin Syndrome

John R. Horn, PharmD, FCCP, and Philip D. Hansten, PharmD

Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, including references if any, visit www.hanstenandhorn.com.

Reports continue to appear describing serotonin syndrome following combined use of tramadol (Ultram) with selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs). Because serotonin syndrome can be serious and is often difficult to detect, it is important for health professionals to be alert for this reaction. A recent study from Australia found that many patients are exposed to drug interactions that can result in serotonin syndrome.

What Is Serotonin Syndrome?

Serotonin syndrome is due to excessive serotonin effects in the central nervous system and usually results from concurrent administration of 2 or more serotonergic drugs. Serotonin syndrome also can occur with excessive doses of a single serotonergic drug.

Available evidence suggests that higher plasma concentrations of tramadol and/or SSRIs increase the risk of serotonin syndrome.

What Are the Symptoms of Serotonin Syndrome?

Some of the symptoms, such as confusion, agitation, and fever, are relatively nonspecific and can be caused by many disorders other than serotonin

syndrome. Other symptoms are more specific, however, and thus are more useful in the early detection of serotonin syndrome. These include myoclonus (muscle jerking), muscle rigidity, and tremor. Serotonin syndrome also can cause sweating, incoordination, seizures, and coma. Severe cases of serotonin syndrome can be fatal.

What About Tramadol?

Many case reports exist of patients taking SSRIs or SNRIs who developed serotonin syndrome while taking concurrent tramadol. Reported cases involved combining tramadol with citalopram, fluoxetine, paroxetine, nefazodone, sertraline, and venlafaxine. Some evidence suggests that mirtazapine also may interact with tramadol, but confirmation is needed.

Are There Risk Factors for This Interaction?

Available evidence suggests that higher plasma concentrations of tramadol and/or SSRIs increase the risk of serotonin syndrome. Some patients have tolerated the combinations, only to develop serotonin syndrome when the dose of one or both drugs is increased. Also, tramadol is metabolized by CYP2D6, and some of SSRIs are moderate-to-potent inhibitors of CYP2D6 (eg, fluoxetine, paroxetine, duloxetine). Finally, genetic deficiencies in the CYP450 isozymes that metabolize tramadol or SSRIs may increase the risk of serotonin syndrome by increasing plasma concentrations. One patient who developed serotonin syndrome following tramadol and citalopram had decreased activity of the isozymes involved in the metabolism of both tramadol (CYP2D6) and citalopram (CYP2C19).

Is Tramadol the Only Opioid Analgesic That Interacts?

Meperidine has long been known to have serotonergic effects and has produced severe serotonin syndrome when combined with drugs such as nonselective monoamine oxidase inhibitors (eg, tranylcypromine). Cases of serotonin syndrome have been reported when meperidine was combined with SSRIs.

Fentanyl also has serotonergic effects and, like meperidine, has been associated with serotonin syndrome when combined with SSRIs.

Fentanyl also has serotonergic effects and, like meperidine, has been associated with serotonin syndrome when combined with SSRIs. Morphine does not appear to have serotonergic effects and may be safer when combined with serotonergic drugs.

Conclusion

Concurrent administration of tramadol (and probably meperidine or fentanyl) with SSRIs or SNRIs appears to increase the risk of serotonin syndrome. In people who may require larger doses of tramadol, it would be prudent to avoid the combinations. If the combination is used, patients should be advised to watch for the telltale signs of serotonin syndrome, such as muscle jerking, muscle rigidity, and tremors, especially if accompanied by other symptoms, such as sweating, fever, and agitation. They should be advised to contact their prescriber should evidence of serotonin syndrome appear. ■