

DRUG INTERACTIONS NEWSLETTER

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Question: Part 1: How does the opioid analgesic tramadol (Ultram®; Ultram ER®, Ultracet®) increase the risk for developing serotonin syndrome in patients taking SSRI antidepressant medications?

Answer: This is part 1 of a 2 part series. Chronic pain syndromes are common in patients with depression and have been associated with an increase in morbidity and mortality.^{1,2} Clinicians are increasingly placed in scenarios in which they must simultaneously treat both of these conditions. Tramadol (Ultram®; Ultram ER®; Ultracet®) is a weak mu-opioid analgesic indicated for the treatment of moderate to moderately severe chronic pain and has also been recommended by some for pain patients with underlying depressive symptoms.³ Tramadol may be useful in patients with underlying depressive symptoms because it is also an inhibitor of the reuptake of the noradrenergic neurotransmitters norepinephrine and serotonin.³ Tramadol's effects on these neurotransmitters are dose dependent and have been shown to increase the risk of seizures and serotonin syndrome.^{3,4}

Serotonin syndrome is often described as changes in mental status (e.g., agitation), autonomic hyperactivity (e.g., diaphoresis, mydriasis, tachycardia, diarrhea) and neuromuscular abnormalities (e.g., clonus, hyperreflexia).^{4,5} In addition, it is important to recognize that this acute problem is not just an idiopathic drug reaction, but rather a predictable consequence of excess serotonin in the central nervous system (CNS), which produces a spectrum of clinical manifestations ranging from barely predictable to lethal.⁴ The risk of tramadol-induced serotonin syndrome increases with the use of higher doses of tramadol, tramadol's opioid effect, concomitant use of medications that inhibit the metabolism of tramadol and concomitant use of medications that increase serotonin levels in the CNS. The last three causes are the focus of the remainder of this issue.

As previously mentioned, patients with depression frequently experience chronic pain that warrants treatment. It is therefore, very feasible that these patients could receive tramadol for pain while also receiving a selective serotonin reuptake inhibitor (SSRI) for depression.^{1,2} The problem with the coadministration of these medications is two-fold. First, tramadol, as well as all of the SSRI antidepressant medications (fluoxetine, paroxetine, citalopram, etc), increase the concentration of serotonin in the synaptic cleft of two connecting serotonergic neurons found in the midline raphe nuclei within the brainstem. The neuronal pathways influenced by this include the rostral end of this system, which is known to regulate affective behavior, wakefulness, thermoregulation and food intake.⁴ In addition, the serotonergic neurons of the raphe in the lower pons and medulla are known to regulate nociception and motor tone.⁴ Lastly, serotonergic pathways in the peripheral nervous system can influence vascular tone and gastrointestinal motility.⁴ It is likely the influence of all of these neuronal pathways that result in many of the classic symptoms seen in serotonin syndrome. While there are 7 families of serotonin receptors (5-HT1 through 5-HT7), it appears that excessive binding of serotonin to 5-HT2A and possibly to 5-HT1A are the pathways most likely to result in the symptoms described above.⁶⁻⁹ This drug interaction is also supported by several case reports where an SSRI (citalopram (10 mg/day), fluoxetine (20-80 mg/day), paroxetine (10-20 mg/day) and sertraline (100 mg/day)) was given with tramadol 100-800 mg/day and the combination resulted in the patient developing serotonin syndrome.¹⁰⁻¹⁶

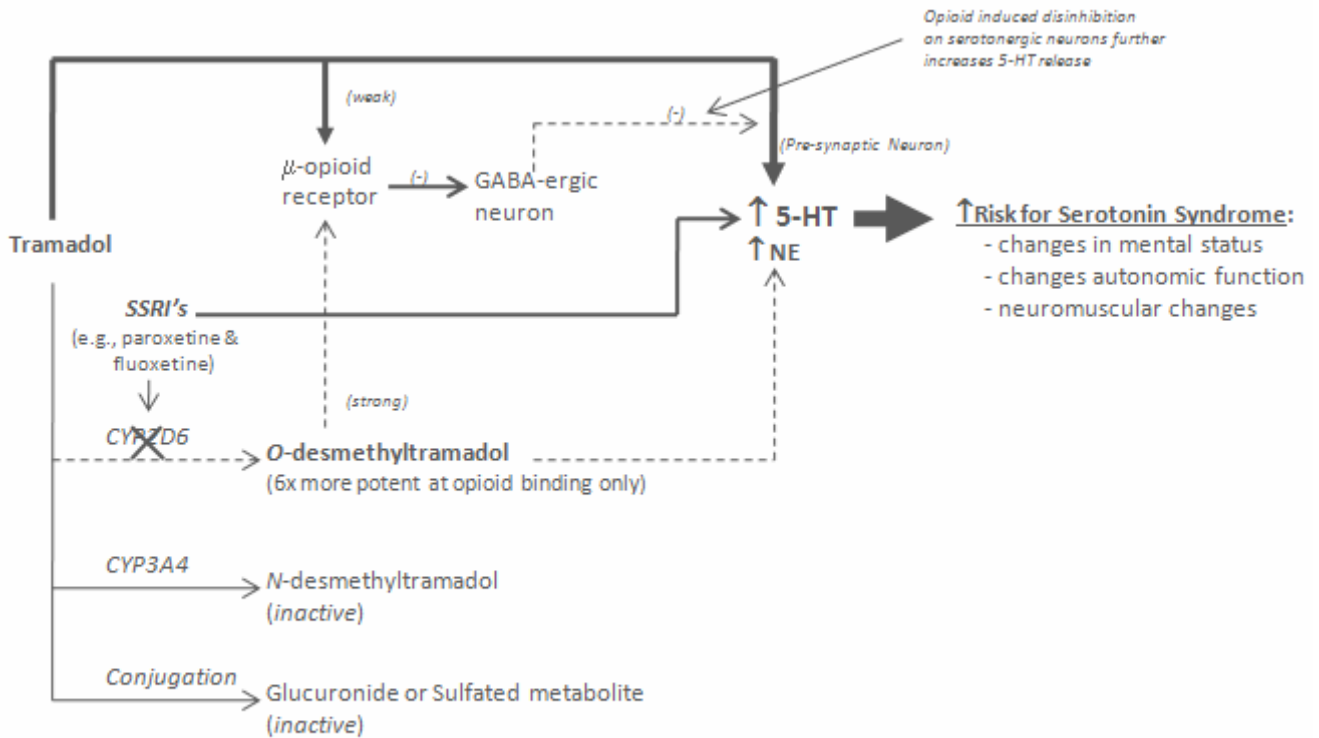


Figure 1. Mechanism of tramadol and SSRI induced serotonin syndrome.
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The second factor that may influence the development of serotonin syndrome is the plasma concentration of tramadol. Tramadol is normally metabolized by CYP2D6 and CYP3A4 enzymes to active and inactive metabolites.³ Therefore, inhibitors of either enzyme will potentiate the effects of tramadol causing an increase in the amount of norepinephrine and serotonin found in the synaptic cleft. Several of the SSRIs (fluoxetine and paroxetine in particular) are potent inhibitors of CYP2D6 and are likely to cause increases in tramadol concentrations.^{3,17,18} As mentioned earlier, the risk of developing serotonin syndrome while taking tramadol alone is notable and increases with higher doses of the drug; this risk is compounded by coadministration of SSRI's (specifically fluoxetine and paroxetine).^{3,17,18} As such, the manufacturer of tramadol provides a bolded warning regarding this drug interaction.³

The third influencing factor is ability of opioid medications to increase serotonin release. This is not a direct effect of opioids but rather an indirect effect. Opioids can also inhibit GABA-ergic neurons that are known to decrease serotonin release.^{19,20} Therefore, opioids cause a disinhibition that results in an increase in serotonin release.^{19,20} Given the above information, how common is serotonin syndrome in clinical practice with the coadministration of these two classes of medications? This will be answered in part 2 of this series.

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Take Home Points:

- Since chronic pain syndromes and depression simultaneously occur in many patients, it is likely that tramadol and an SSRI will be used together. However, concomitant use of these drugs is known to increase the risk for seizures and serotonin syndrome.
- Tramadol is a mu-opioid receptor agonist as well as an inhibitor of the reuptake of norepinephrine and serotonin in the central nervous system (CNS).
- SSRIs contribute to this interaction by increasing serotonin levels in the CNS and may also inhibit the metabolism of tramadol via CYP2D6, thereby increasing the concentration of tramadol.
- The coadministration of tramadol and SSRI antidepressants should be prescribed with caution, if at all.

Considerations for Clinicians Based on Setting:

Outpatient Setting:

Since the clinical presentation of serotonin syndrome can be variable, it would be important to monitor for changes in mental status (agitation), autonomic hyperactivity (diaphoresis, mydriasis, tachycardia, diarrhea) and neuromuscular abnormalities (clonus, hyperreflexia) if tramadol and an SSRI are being used together. This would be most relevant after the addition of either medication to a regimen containing the other. Thus, a thorough medication evaluation should be done to identify patients at increased risk for this adverse event.

Inpatient Setting:

Same as in the outpatient setting; however, if the patient is admitted to the hospital for treatment and evaluation of seizures, new onset changes in mental status, GI complaints, tachycardia, and/or clonus, it would be important to review the patient's medication profile for recent changes to rule out the above drug interaction.

Important Counseling Bullet Point(s):

- It would be important to inform the patient to notify their primary care physician about their current medications in order to avoid the introduction of a new medication that could put them at risk for the above complications. If the potential benefits outweigh the known risks and the combination of tramadol and an SSRI is prescribed, the patient should be counseled to inform you or their primary care physician about any changes in mental status (such as agitation), autonomic hyperactivity (diaphoresis, mydriasis, tachycardia, diarrhea) and neuromuscular abnormalities (clonus, hyperreflexia).

Medical/Legal Consideration(s):

- There were no legal cases identified in the 2008 edition of LexisNexis' Drugs in Litigation regarding drug interactions between tramadol and SSRI's²¹, and Pharmacology Weekly's legal counsel has not identified any such cases to date. Nevertheless, it would be prudent to consider avoiding the coadministration of tramadol and SSRI as recommended by the manufacturer. In addition, it is worth noting that there was a case in 2007 against a physician and pharmacy, where a patient was prescribed methadone, after already taking tramadol, and the patient died several days later. *Warren v. Walgreens*, No. CV2003-0587 (Coconino County, Ariz. Oct. 11, 2007). The pharmacy also allegedly changed the methadone dosage from five to ten milligrams, without the physician's knowledge. The physician settled for an undisclosed amount, and the jury returned a verdict that the pharmacy was 97% liable, the physician was 2% liable, and the patient was 1% liable, with \$6 million in damages to be paid by the pharmacy to the patient's children and parents.

Test Questions for CE:

Tramadol (Ultram®; Ultram ER®; Ultracet®) is best described as what type of medication?

- a. Antidepressant only
- b. Opioid analgesic only
- c. Opioid analgesic with some antidepressant properties
- d. Muscle relaxant

The coadministration of tramadol and an SSRI puts the patient at risk for which of the following conditions?

- a. Serotonin syndrome
- b. Migraine
- c. Amnesia
- d. Dementia

What liver enzyme is, in part, responsible for the metabolism of tramadol and also inhibited by paroxetine and fluoxetine?

- a. CYP1A2
- b. CYP2C9
- c. CYP2D6
- d. CYP3A4

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