

Can combining triptans with SSRIs or SNRIs cause serotonin syndrome?

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In 2006, the FDA issued a warning of the risk of potentially fatal serotonin syndrome when 5-hydroxytryptamine receptor agonist antimigraine medications (triptans) and selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRI) are coprescribed.¹ As a result, most drug interaction programs trigger a serotonin syndrome warning when triptans are prescribed with an SSRI or SNRI.² However, many patients with depression or anxiety also suffer from migraines and require treatment with both triptans and an SSRI or SNRI.^{3,4} Kalaydjian et al⁴ found the incidence of major depression and generalized anxiety disorder were approximately 3 times greater in patients with migraines than in those without migraines. Should we avoid coprescribing triptans and SSRIs or SNRIs?

What is serotonin syndrome?

Serotonin syndrome is an adverse drug reaction that results from excessive serotonin stimulation. There are 2 sets of validated diagnostic criteria: the Sternbach Criteria and the Hunter Serotonin Toxicity Criteria; the latter is considered more stringent.^{3,5-7} Symptoms of serotonin syndrome include mental status changes, autonomic hyperactivity, and neuromuscular changes such as muscle rigidity.⁵⁻⁷ Typical manifestations of serotonin syndrome on physical exam include spontaneous and/or inducible clonus, agitation, diaphoresis, tremor, hyperreflexia, hypertonia, and temperature >38°C.⁶ In severe cases, serotonin syndrome can lead to seizures, coma, and death. Management includes supportive treatment, discontinuing the offending agents, controlling agitation

with medications such as benzodiazepines, and possibly administering cyproheptadine, a 5HT_{2A} antagonist.⁸ Most cases resolve within 24 hours of discontinuing the offending agents or appropriate treatment.⁵

What did the FDA say?

The 2006 FDA warning initially was based on 27 reports of serotonin syndrome in patients receiving triptans and SSRIs or SNRIs; this was later expanded to include 29 patients.^{1,9} No patients died but 13 required hospitalization and 2 had life-threatening symptoms. However, most cases lacked data necessary to diagnose serotonin syndrome.⁹ Further, reviews of the available clinical information have suggested that in some cases, clinicians did not rule out other disorders as required by diagnostic criteria, while others were viral in nature or resolved despite ongoing treatment with the presumed offending agents.⁹⁻¹¹

Some clinicians met the FDA's assessment with skepticism. Only 10 of the 29 cases met the Sternbach criteria of serotonin syndrome and none met the more rigorous Hunter criteria. Additionally, the theoretical basis has been questioned.⁹⁻¹¹ Available evidence indicates that serotonin syndrome requires activation of 5HT_{2A} receptors and a possible limited role of 5HT_{1A}.⁹⁻¹² However, triptans are agonists at the 5HT_{1B/1D/1F} receptor subtypes, with weak affinity for 5HT_{1A} receptors and no activity at the 5HT₂ receptors.^{13,14} Additionally, triptan medications are used as needed, not as standing treatments, with parameters limiting the maximum dose, dosing interval, and frequency of use. In clinical practice, it appears that these dosing guidelines are being followed: Tepper et al¹⁵ found the typical

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Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Most cases of serotonin syndrome linked to use of triptans plus an SSRI or SNRI lacked complete diagnostic data

Related Resource

• Sclar DA, Robison LM, Castillo LV, et al. Concomitant use of triptan, and SSRI or SNRI after the US Food and Drug Administration alert on serotonin syndrome. *Headache*. 2012. www.headachejournal.org/SpringboardWebApp/userfiles/headache/file/sclar.pdf.

Drug Brand Name

Cyproheptadine • Perinctin

female patient experiences 1 to 2 migraines per month; on average, patients use 1.2 to 1.8 triptan tablets per month.

Our opinion

We believe it is reasonable to coprescribe SSRIs or SNRIs with triptans because:

- data indicate that many patients are treated with a combination of triptans and SSRIs or SNRIs but the number of reported cases of serotonin syndrome is extremely limited
- the nature of serotonin syndrome cases reported in the literature is questionable
- the interaction is biologically implausible
- triptans remain in the body for a limited time
- triptans are used infrequently.⁵⁻¹¹

This view is supported by the most recent American Headache Society position paper,¹¹ which states that inadequate data are available to assess the risk but current evidence does not support limiting use of triptans with SSRIs and SNRIs.

How we deal with the warning in clinical practice. In practice we are alerted to this interaction by notification in our e-prescribing systems, by pharmacists calling with concerns about dispensing an SSRI or SNRI for a patient already receiving a triptan, and during patient visits that involve prescribing an SSRI or SNRI.

Although it is relatively easy to override a drug interaction warning in our e-prescribing system, we discuss the issue with pharmacists and patients. We provide information about the signs and symptoms of serotonin syndrome and its potential dangerousness. We note that serotonin syndrome is a theo-

retical concern, but highly unlikely with this combination of medications because of their pharmacologic properties. We explain the parameters of triptan use, recommend that our patients use triptans for migraines when needed, and reassure patients we are available to answer questions. When a patient uses triptans more than twice monthly, we consider discussing this usage with the patient and the treating physician.

References

1. U.S. Food and Drug Administration. Public health advisory—combined use of 5-hydroxytryptamine receptor agonists (triptans), selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs) may result in life-threatening serotonin syndrome. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/PublicHealthAdvisories/ucm124349.htm>. Published July 19, 2006. Accessed September 18, 2012.
2. Kogut SJ. Do triptan antimigraine medications interact with SSRI/SNRI antidepressants? What does your decision support system say? *J Manag Care Pharm*. 2011;17(7):547-551.
3. Tepper SJ. Serotonin syndrome: SSRIs, SNRIs, triptans, and current clinical practice. *Headache*. 2012;52(2):195-197.
4. Kalaydjian A, Merikangas K. Physical and mental comorbidity of headache in a nationally representative sample of US adults. *Psychosom Med*. 2008;70(7):773-780.
5. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med*. 2005;352(11):1112-1120.
6. Sternbach H. The serotonin syndrome. *Am J Psychiatry*. 1991;148(6):705-713.
7. Dunkley EJ, Isbister GK, Sibbritt D, et al. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM*. 2003;96(9):635-642.
8. Ables AZ, Nagubilli R. Prevention, recognition, and management of serotonin syndrome. *Am Fam Physician*. 2010;81(9):1139-1142.
9. Evans RW. The FDA alert on serotonin syndrome with combined use of SSRIs or SNRIs and triptans: an analysis of the 29 case reports. *MedGenMed*. 2007;9(3):48.
10. Gillman PK. Triptans, serotonin agonists, and serotonin syndrome (serotonin toxicity): a review. *Headache*. 2010;50(2):264-272.
11. Evans RW, Tepper SJ, Shapiro RE, et al. The FDA alert on serotonin syndrome with use of triptans combined with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors: American Headache Society position paper. *Headache*. 2010;50(6):1089-1099.
12. Ahn AH, Basbaum AI. Where do triptans act in the treatment of migraine? *Pain*. 2005;115(1-2):1-4.
13. Pediatric & Neonatal Lexi-Drugs. Hudson, OH: Lexi-Comp, Inc.; 2011.
14. Sclar DA, Robison LM, Castillo LV, et al. Concomitant use of triptan, and SSRI or SNRI after the US Food and Drug Administration alert on serotonin syndrome. *Headache*. 2012;52(2):198-203.
15. Tepper S, Allen C, Sanders D, et al. Coprescription of triptans with potentially interacting medications: a cohort study involving 240,268 patients. *Headache*. 2003;43(1):44-48.

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