

Serotonin Syndrome with Triptans: Facts vs. Fear

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The serotonin syndrome (SS), also known as serotonin toxicity (ST), is an acute toxic reaction to substances that enhance serotonergic activity within the central nervous system. ST typically develops abruptly and progresses rapidly within six hours of exposure to numerous medications, either alone or in combination.

The clinical features of ST consist of a triad of altered mental status (confusion, agitation), neuromuscular hyperactivity (clonus, myoclonus, hyperreflexia, tremor, shivering, rigidity), and autonomic hyperactivity (tachypnea, tachycardia, fever, diaphoresis, mydriasis). Incomplete presentations are common. The diagnosis of ST rests upon application of either of two sets of diagnostic criteria in current usage: Sternbach and Hunter¹.

The severity of ST cases ranges from mild to fatal. Life-threatening ST cases are generally only associated with combined exposures to monoamine oxidase inhibitors (MAOIs) with selective or nonselective serotonin reuptake inhibitors (SRIs). Numerous other drugs have been implicated in provoking ST including tricyclic antidepressants, some opioids, amphetamines, MDMA (ecstasy), L-tryptophan, chorpheniramine, and lithium (in combination with venlafaxine).

In 2006, the FDA issued an alert concerning 27 cases of presumptive ST following exposure to SRIs combined with triptan medications. Subsequently, a total of 60 cases of presumptive “triptan-associated ST” have been assembled by the FDA from all sources including their Adverse Event Reporting System. Some of these 60 putative cases were reported following triptan monotherapy.⁴ On average, the FDA has received a total of 5 to 7 new cases of presumptive “triptan-associated ST” annually for the past several years.⁵

The FDA alert led to fundamental concerns about the safety of triptans given their widespread use for the acute treatment of migraine and the fact that migraine is highly co-morbid with key indications for SRIs (i.e. anxiety and depression). The seriousness of ST prompted an appraisal of the evidence that led to the alert. Several questions arise:

- **How prevalent is co-exposure of triptans with SRIs?** Recent annualized estimates of the number of Americans prescribed a triptan concomitantly with an SRI range from 1,319,763 (2007-2008) to 833,963 (2009)^{3,4}.
- **How prevalent are cases of ST induced in the setting of triptan use alone or in combination with SRIs?** Any prevalence estimate would depend upon knowledge of the percentage of all such cases that are reported to the FDA and whether the FDA cases were accurately diagnosed as ST. ST cases are certainly

under-diagnosed and under-reported to the FDA; 85% of clinicians are unaware of ST. On the other hand, the FDA alert might have led to more cases reported to the FDA.

Assuming approximately 1 million Americans are co-prescribed SRIs with triptans annually (based on data above), and that no more than 1% of the presumptive “triptan-associated ST” cases occurring annually in the US are actually reported to the FDA, the annual prevalence of presumptive “triptan-associated ST” appears to be no greater than 0.07% of those patients co-exposed to SRIs along with triptans, without even taking into consideration the much greater total number of Americans taking triptans annually³. By contrast, a published estimate of ST prevalence due to SRI treatment alone is 0.5 to 0.9 cases per 1,000 patient-months of SRI treatment.

- **How accurate were the diagnoses of ST among the FDA cited cases?** The FDA case reports available for review are rife with incomplete clinical information rendering most of the diagnoses uncertain². None of these FDA cases met Hunter criteria and only a third of these cases met Sternbach criteria. A number of cases were clearly misdiagnosed as ST based upon the available clinical information.
- **Are the molecular mechanisms underlying ST compatible with triptan induction of the syndrome?** Available data from animal models strongly implicate agonism of serotonin 5HT_{2A} receptors in the induction of ST, and drugs that antagonize these receptors (i.e. cyproheptadine) are mainstays of clinical therapy for ST. Triptans have no pharmacological activity at 5HT_{2A} receptors at clinically indicated dosages, but rather agonize 5HT_{1B}, 5HT_{1D}, and 5HT_{1F} receptors. Acute application of triptans in rats consistently leads to a reduction in brain serotonin synthesis, and does not demonstrate enhanced serotonin release in brain.

We concluded that “insufficient data are available to judge whether the addition of triptans to the use of SSRIs/SNRIs actually increases the risk of serotonin syndrome at all. Given the seriousness of this condition, caution is certainly warranted, but it would be unfortunate if disabled patients were denied the antidepressant, anxiolytic, or anti-migraine therapeutic benefits of these classes of medications based on a misinterpretation of a small number of case reports.”³

References:

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- 2) EVANS RW. The FDA alert on serotonin syndrome with combined use of SSRIs or SNRIs and triptans: An analysis of the 29 case reports. *Medscape.* (2007) 9:48.

3) SKLAR DA et al.: Concomitant Use of Triptan, and SSRI or SNRI After the US Food and Drug Administration Alert on Serotonin Syndrome. *Headache*. (2012) 52:198-203.

4) FINE A, BASTINGS E: Letter to the Editor. Triptans and Serotonin Syndrome. *Headache* (2012) *in press*.

5) TEPPER S et al.: Letter to the Editor. Triptans and Serotonin Syndrome. *Headache* (2012) *in press*.

Disclosures:

Since 2011, Robert Shapiro, MD, PhD has served on a scientific advisory board for MAP Pharma.