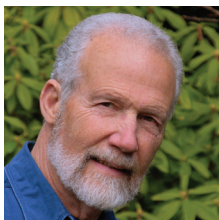


Triptans and SSRIs

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IN 2006, the FDA issued a warning of possible serotonin syndrome in patients receiving triptans together with either selective serotonin/norepinephrine reuptake inhibitors (SNRIs) or selective serotonin reuptake inhibitors (SSRIs).¹ Despite periodic reports providing evidence that the combination is not dangerous, the warning persists in the triptan labeling. Given that about one-fourth of patients on triptans receive SNRIs or SSRIs, it probably contributes substantially to “alert fatigue” for pharmacists. New evidence has appeared regarding the clinical importance of this interaction.

REASON FOR THE WARNING

Isolated cases of serotonin syndrome have been reported in patients using triptans and SNRIs or SSRIs,²⁻⁴ and the FDA apparently has received additional reports. It was not clear, however, that all the patients actually had serotonin syndrome, and it is possible that the reactions were caused by the SNRI or SSRI alone or by some other serotonergic drug given concurrently with it. The evidence in support of serotonin syndrome from triptans plus SNRIs or SSRIs, therefore, is meager.

NEW EVIDENCE

A 14-year electronic health records study looked at data from 19,017 patients who had concurrently received a triptan and an SNRI or SSRI.⁵ Just 2 patients were classified as having definite serotonin syndrome. These data are consistent with previous clinical and pharmacokinetic studies that failed to observe serotonin syndrome in more than 2000 patients receiving triptans and SSRIs.⁶⁻¹⁰ Although we cannot rule out the possibility that isolated patients on the combination may develop serotonin syndrome, the risk appears to be extraordinarily low. Indeed, the risk may be similar to the extremely small risk of serotonin syndrome from the use of SSRIs alone.⁵

MECHANISMS

In addition, from a theoretical standpoint, triptans should not interact with SNRIs or SSRIs to produce serotonin syndrome. The condition is thought to be mediated by 5HT_{2A} receptors and possibly 5HT_{1A}, yet the affinity of triptans is primarily for 5HT_{1B}

and 5HT_{1D} receptors. Pharmacokinetic interactions are possible because frovatriptan and zolmitriptan are metabolized by CYP1A2, and fluvoxamine is a potent inhibitor of CYP1A2. Although this would not result in serotonin toxicity, it would be prudent to avoid these triptans in patients receiving fluvoxamine.

RECOMMENDATIONS

Given the compelling evidence for an extremely low risk of serotonin syndrome in patients using triptans with SNRIs or SSRIs, it does not appear clinically necessary to warn prescribers about these interactions. Nonetheless, as long as the warnings remain on the triptan labels, it presents a dilemma for pharmacists. If, for example, the patient on a triptan and SSRI took some third drug with serotonergic effects, such as tramadol, the interaction between the SSRI and the tramadol might produce actual serotonin syndrome, and the triptan-SSRI combination might be falsely blamed for the adverse effect. An alternative to ignoring the interaction might be to advise the patient that the interaction is mentioned on the label but not generally considered to be clinically important. The patient also could be advised to be alert for symptoms of serotonin syndrome, especially the characteristic neuromuscular effects such as myoclonus, rigidity, and tremors. That would be useful even for patients on SNRIs or SSRIs because the syndrome occasionally occurs with the addition of other serotonergic agents.

CONCLUSION

Although isolated cases of serotonin syndrome have been reported with combined use of triptans with SNRIs or SSRIs, it is not clear that these cases represent an actual drug interaction.

Epidemiologic and pharmacokinetic studies suggest that the risk of serotonin syndrome from combining triptans with SNRIs or SSRIs is extraordinarily low and may be no higher than the use of SNRIs or SSRIs alone.

Given that the triptan labels warn of possible serotonin syndrome if SNRIs or SSRIs are used concurrently, there may be medicolegal considerations if the patient develops serotonin syndrome for whatever reason. Warning the patient about the signs and symptoms of serotonin syndrome is useful. ♦

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