

Can Triptans and SSRIs Be Used Together?

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The FDA has issued a Public Health Advisory that warns of possible serotonin syndrome in patients receiving 5-hydroxytryptamine receptor agonists (triptans) together with either selective serotonin reuptake inhibitors (SSRIs) or selective serotonin-norepinephrine reuptake inhibitors (SNRIs).¹ The FDA Advisory was based on "important new safety information," but the nature of that information was not elucidated.

What Drugs Are Involved in the Advisory?

The triptans, SSRIs, and SNRIs included in the FDA Advisory are listed in the Table. We have added clomipramine and imipramine to the list of SNRIs, since both (especially clomipramine) inhibit serotonin uptake in therapeutic doses.

What Evidence Supports the Interaction?

A few cases of serotonin syndrome have been reported with combined use of triptans with SSRIs or SNRIs.²⁻⁴ Apparently the FDA has received information on additional patients who have developed serotonin syndrome with these combinations. Nonetheless, serotonin syndrome has not been observed in clinical and pharmacokinetic studies involving over 2000 patients receiving triptans and SSRIs.⁵⁻⁹ Moreover, triptans are regularly used with SSRIs or SNRIs; about 50,000 patients in the United States were taking triptans and SSRIs,

Table

Drugs Involved in the FDA Advisory		
Triptans	SSRIs	SNRIs
almotriptan (Axert)	citalopram (Celexa)	clomipramine (Anafranil)*
eletriptan (Relpax)	escitalopram (Lexapro)	duloxetine (Cymbalta)
frovatriptan (Frova)	fluoxetine (Prozac)	imipramine (Tofranil)*
naratriptan (Amerge)	fluvoxamine (Luvox)	venlafaxine (Effexor)
rizatriptan (Maxalt)	paroxetine (Paxil)	
sumatriptan (Imitrex)	sertraline (Zoloft)	
zolmitriptan (Zomig)		

*Clomipramine and imipramine were not listed in the FDA advisory as SNRIs.

based on an estimate published in 2003,⁵ and this may well be an underestimate. Thus, it appears that if these combinations cause serotonin syndrome, it must be in only a small percentage of people receiving the drugs.

What About Pharmacokinetic Interactions?

Fortunately, most SSRIs do not inhibit the cytochrome P-450 isozymes involved in the metabolism of triptans. Fluoxetine and paroxetine are potent inhibitors of CYP2D6, but this isozyme is not important for metabolism of triptans. One SSRI of concern is fluvoxamine, which is a potent inhibitor of CYP1A2. Since zolmitriptan and frovatriptan are metabolized by CYP1A2, it would be prudent to avoid these triptans in patients receiving fluvoxamine. Fluvoxamine is also a moderate inhibitor of CYP3A4, an isozyme involved in the metabolism of eletriptan. Nonetheless, clinical trials have found little evidence of an adverse interaction between CYP3A4 inhibitors (even potent ones) and eletriptan.⁷

What Explains the Reports of Serotonin Syndrome?

Some of the published case reports of serotonin syndrome with concurrent use of triptans and SSRIs or SNRIs were not presented in sufficient detail to: (1) ensure that the patient actually had serotonin

syndrome; (2) ensure that the symptoms were not caused by one of the drugs acting alone instead of due to a drug interaction; and (3) ensure that the reaction was not caused by some other drug given at about the same time (serotonin syndrome may occur when SSRIs are combined with various drugs). Nonetheless, one cannot rule out that the interaction does occur in some patients.

Are Some Patients at Greater Risk?

It is possible that only certain predisposed patients develop serotonin syndrome when SSRIs or SNRIs are used with triptans, and that explains the rarity of case reports. Unfortunately, risk factors have not yet been established, so it is not possible to identify ahead of time which patients should not receive these combinations.

Summary

Isolated case reports suggest that some patients may develop serotonin syndrome with combined use of triptans with SSRIs or SNRIs, but a majority of patients do not appear to be affected. **P**

For a list of references, send a stamped, self-addressed envelope to: References Department, Attn. A. Rybovic, Pharmacy Times, Ascend Media Healthcare, 103 College Road East, Princeton, NJ 08540; or send an e-mail request to: arybovic@ascendmedia.com