Depression was diagnosed 6 years earlier in a 37-year-old woman; it has been successfully managed since then with fluoxetine and outpatient psychotherapy. Since her teenage years, the patient has also experienced sporadic (fewer than 3 or 4 per year) mild or occasionally severe headaches, which she has usually self-treated with over-the-counter (OTC) agents or "just slept off."

THE CASE:

Depression was diagnosed 6 years earlier in a 37-year-old woman; it has been successfully managed since then with fluoxetine and outpatient psychotherapy. Since her teenage years, the patient has also experienced sporadic (fewer than 3 or 4 per year) mild or occasionally severe headaches, which she has usually self-treated with over-the-counter (OTC) agents or "just slept off."

In the past 6 to 12 months her headache attacks have become more frequent (now about 2 per month), more severe, and unresponsive to OTC drugs. She has never exhibited signs or symptoms of organic disease. Two months ago, she consulted her primary care physician about the headaches; he diagnosed migraine and prescribed 4-mg sumatriptan subcutaneous injections. She reports that the triptan relieves her headaches so that she is able to return to work.

Last week, when she attempted to refill her sumatriptan prescription, the pharmacist told her that the combination of sumatriptan and fluoxetine was "potentially dangerous." At first he refused to fill the prescription; he finally dispensed the sumatriptan only after she agreed to speak with her physician.

The dialogue:

Primary care doctor: My patient was visibly upset by the pharmacist's comments, and she's now concerned about the safety of her regimen. Why would the pharmacist have made such disturbing comments, especially about a patient's ongoing, successful, well-tolerated therapy?

Headache specialist: I suspect that the basis for his remarks was a 2006 FDA advisory about the combined use of triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). 1 The advisory was based on 27 reports—collected over a span of 5 years—of serotonin syndrome associated with the combined use of triptans and SSRIs/SNRIs. These included 2 reports of life-threatening events and 13 reports of events that required hospitalization.

Primary care doctor: What sort of clinical perspective would be helpful in this situation?

Headache specialist: SSRIs are the most frequently prescribed class of medications in ambulatory clinics in the United States: these agents are prescribed more than 117 million times annually. 2 Among migraineurs, triptans are widely prescribed as well.

Primary care doctor: What are the most common presenting symptoms of serotonin syndrome?

Headache specialist: There are 3 categories of symptoms associated with serotonin syndrome 4:Cognitive and behavioral changes, which may include agitation, confusion, delirium, anxiety, and hallucinations. Autonomic dysfunction, which can present as diarrhea, hyperactive bowel sounds, diaphoresis, flushing, mydriasis, or tachycardia. Neuromuscular abnormalities, which may include hyperreflexia, myoclonus, restlessness, and tremors.

Primary care doctor: The list of symptoms is fairly extensive. Are there any diagnostic tests that can identify serotonin syndrome?

Headache specialist: Unfortunately, no laboratory values or other test results have been found to be diagnostic of serotonin syndrome. Nonetheless, we obviously must strive to identify the syndrome and initiate treatment before the patient's condition becomes serious. To try to facilitate prompt diagnosis, some clinicians have come up with diagnostic criteria, but there is no consensus on how
many symptoms must be present to make the diagnosis. One expert has stated that at least 3 of the following clinical features need to be present: agitation, mental status changes, diaphoresis, myoclonus, diarrhea, fever, hyperreflexia, tremor, or incoordination. 6 Other authorities have developed algorithms that require 1 (eg, spontaneous clonus) or 2 (eg, ocular clonus and either agitation or diaphoresis) symptoms to be present. 5 Regardless of the number of symptoms, the patient must currently be taking a serotonergic agent and other causes must have been ruled out before serotonin syndrome can be diagnosed.

**Primary care doctor:** So, what should I tell my patient about the risk of serotonin syndrome associated with triptan-SSRI therapy?

**Headache specialist:** Ideally, the risk would have been discussed at the time sumatriptan was prescribed for her—although I do not raise this issue with all my patients who are receiving triptans and SSRIs, and it is debatable whether such a discussion is necessary.

**Primary care doctor:** Besides patient education, what are your recommendations about the clinical implications of the recent FDA advisory?

**Headache specialist:** I firmly believe that patients should not be denied the combination of an SSRI and a triptan merely because of the recent advisory. The potential benefits of this combination therapy are considerable: they include effective management of debilitating migraine attacks and rapid return to normal function. This patient's case exemplifies the effectiveness of such therapy. The potential downside of combination therapy is a rare, often mild, and usually manageable event. This information has now been uploaded into many community pharmacy computer systems and can cause a warning to flash on the computer screen when prescriptions for both types of agents are presented simultaneously. Unfortunately, a pharmacist who sees this warning may convey the information to the patient without also providing a clinical perspective or his or her professional judgment.

From 2000 to 2001, more than 185,000 Americans took a triptan and an SSRI within the same 4-week period at least once. The annual incidence of serotonin syndrome in these patients was less than 0.03%, and the annual incidence of life-threatening cases was less than 0.002%. Thus, among patients who are receiving medications from these 2 classes, serotonin syndrome, although completely unpredictable, is extremely rare.

Mild cases of serotonin syndrome usually manifest as neuromuscular symptoms; more severe cases present with hyperthermia. The onset of symptoms is rapid, typically within 6 hours of consuming either a new serotonergic medication or a newly increased dose. In severe cases, metabolic acidosis, rhabdomyolysis, and subsequent acute renal failure may be seen in the late stages of the illness.

After you reassure your patient about the rarity of this drug interaction, point out that she has already used these drugs successfully without adverse consequences. Also point out that neither the FDA, nor the manufacturers, nor the medical literature advises not to give these drugs in combination.1,7 Moreover, to my knowledge, no other country’s regulatory agency has issued an advisory similar to the FDA's statement; this is significant, given the widespread use of SSRIs and triptans in many foreign countries.

Finally, I would educate her about the symptoms of serotonin syndrome and the need to seek help if and when these symptoms occur. Also let her know that although the risk of serotonin syndrome is remote, it is most likely to occur when the dose of either the SSRI or the triptan is increased or when a new serotonin-active medication is prescribed.

If your patient decides she wants a different therapy, simply comply with her request. Alternatives for treating depression that do not risk serotonin syndrome include nonserotonergic medications (eg, bupropion) and psychological counseling. Reasonable substitutes for triptans include both oral and injectable NSAIDs, acetaminophen, and droperidol—and possibly narcotics with careful monitoring. Nondrug options for the treatment of acute migraine, such as biofeedback and other relaxation techniques, can also be considered.

**References:**


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