Serotonin syndrome

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TO THE EDITOR: I enjoyed the article "Serotonin syndrome: Preventing, recognizing, and treating it."[1] I am a relatively new internal medicine physician, out of residency only 1 year, and sadly I felt that the psychiatric training I received was minimal at best. Therefore, I was very excited to read more about serotonin syndrome since such a large percentage of my patients are on selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors.

Could you speak to the time frame it takes for serotonin syndrome to develop? For instance, if someone is taking an SSRI and develops a terrible yeast infection, would 3 doses of fluconazole be enough to tip the scales? Or as-needed sumatriptan, with some ondansetron for migraine? The problem I have is that patients often require short doses of many medications that can interact, and I routinely sigh, briefly explain the possibility of serotonin syndrome, and then click through the flashing red warning signs on the electronic medical record and send patients out with their meds—though in honesty I do not know the likelihood of developing even mild symptoms of serotonin syndrome with short courses of interacting medications.

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IN REPLY: The questions posed by Dr. Rose reflect critical issues primary care physicians encounter when prescribing medications for patients who are taking serotonergic agents. "Switching strategies" have been described for starting or discontinuing serotonergic antidepressants.[1] Options range from conservative exchanges requiring 5 half-lives between discontinuation of 1 antidepressant and initiation of another vs a direct cross-taper exchange. Decisions regarding specific patients should take into account previous adverse effects from serotonergic medications and half-lives of discontinued antidepressants. To our knowledge, switching strategies have not been validated and are based on expert opinion. Scenarios are complicated further if patients have already been prescribed 2 or more antidepressants and 1 medication is exchanged or dose-adjusted while another is added. With this degree of complexity, we recommend referral to a psychiatrist.

Dr. Rose's questions on prescribing nonpsychiatric serotonergic drugs concurrently with antidepressants broaches a topic with even less evidence. Some data exist about nonpsychiatric serotonergic drugs given in combination with triptans. Soldin et al[2] reviewed the US Food and Drug Administration's Adverse Event Reporting System and discovered 38 cases of serotonin syndrome in patients using triptans. Eleven of these patients were using triptans without concomitant antidepressants. Though definitive evidence is lacking for safe prescribing practice with triptans, the authors noted that most cases of triptan-induced serotonin toxicity occur within hours of triptan ingestion.[2]

The evidence on the risk of serotonin syndrome with other medications is limited to case reports. In regard to linezolid, a review suggested that when linezolid was administered to a patient on long-term citalopram, a prolonged serotonin syndrome was precipitated, which is not an issue with other antidepressants.[3] The World Health Organization has issued warnings for serotonin toxicity with ondansetron and other 5-HT3 receptor antagonists based on case reports.[4,5] No data are available for the appropriate prescribing of 5-HT3 antagonists with antidepressants. A review of cases suggests a link between fluconazole and severe serotonin toxicity in patients taking citalopram; however, no prescribing guidelines have been established for fluconazole either.[6]

Dr. Rose asks important clinical questions, but evidence-based answers are not available. We can only recommend that patients be advised to report symptoms immediately after starting any medication associated with serotonin syndrome. For patients on multiple antidepressants, psychiatric assistance is advised. An observational cohort study of patients using antidepressants while exposed to other suspect drugs may better delineate effects of several pharmaceuticals on the serotonergic axis. Only then may safe prescribing practices be validated with evidence.

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