Serotonin: It's Possible to Have Too Much of a Good Thing

Stephen M. Stahl, M.D., Ph.D.

Issue: *Although serotonin can mediate numerous therapeutic actions, too much serotonin can cause dangerous toxicity.*

Serotonin has been at the heart of innovation in psychopharmacology for the past decade.[1,2] Serotonin selective reuptake inhibitors (SSRIs) in particular have led the way, but many other agents also act on serotonin, in one fashion or another.[2] These include other antidepressants, as well as novel atypical antipsychotics, various antiemetics, modern migraine therapies, and certain drugs of abuse. Also included is the appetite suppressant fenfluramine, both in its *d,l* form (Pondimin) and in its pure *d* form (Redux).[2]

Does Serotonin Use Demand Too High of a Price?

When the SSRIs are administered, they increase serotonin in every serotonin pathway and at every one of the dozen or more serotonin receptor subtypes. Although this is something akin to dunking the brain into a bucket of serotonin, the net consequence is not only antidepressant action, but also therapeutic effects in a number of other conditions, including obsessive-compulsive disorder, panic attacks, bulimia, and others.[3]

However, the price of doing business is often higher than desired. Increasing serotonin in places where it is not welcome can produce the side effects of anxiety, insomnia, sexual dysfunction, and gastrointestinal disturbances.[4] Most of these problems are more of a nuisance than a danger and commonly abate with time as tolerance to them develops. Furthermore, newer antidepressants such as nefazodone and mirtazapine enhance serotonin yet simultaneously block serotonin's actions at some of its undesired places, reducing the price of doing business in some cases.[4] Under other circumstances, however, the price escalates beyond what is reasonable.

Can You Have Too Much Serotonin?

If serotonin increases too much, it can be life-threatening and occasionally lethal. Serotonin toxicity manifests itself after certain drug combinations, especially when SSRIs are combined with monoamine oxidase inhibitors.[5] The consequential serotonin syndrome can mimic the

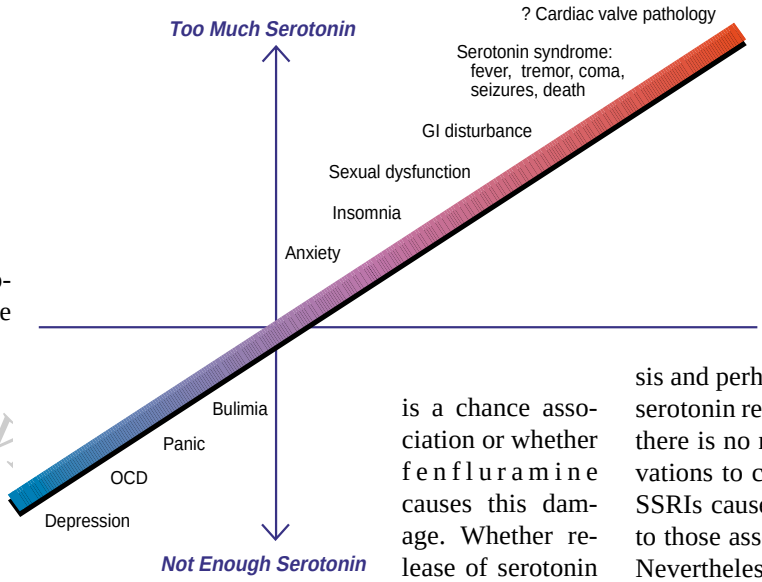
Take-Home Points

- Enhancing serotonin in key CNS pathways and at desired serotonin receptor subtypes hypothetically mediates therapeutic actions in depression, obsessive-compulsive disorder, panic disorder, and bulimia
- Toxic levels of serotonin can cause a life-threatening serotonin syndrome of fever, myoclonus, coma, seizures, cardiovascular collapse, and death
- Damage to cardiac valves in patients receiving Fen-phen led to withdrawal of the serotonin-releasing agent fenfluramine from the U.S. market and is provoking a search to determine whether serotonin is responsible

BRAINSTORMS is a monthly section of The Journal of Clinical Psychiatry *aimed at providing updates of novel concepts emerging from the neurosciences that have relevance to the practicing psychiatrist.*

From the Clinical Neuroscience Research Center in San Diego and the Department of Psychiatry at the University of California San Diego.

Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, 8899 University Center Lane, Suite 130, San Diego, CA 92122.



symptoms of neuroleptic malignant syndrome but does not have muscular breakdown. The serotonin syndrome is a combination of fever, myoclonus, coma, seizures, cardiovascular collapse, and death. Treatment is with cooling mattresses, serotonin-2 antagonists, dopamine agonists, and intensive care.[5]

Although the side effects of SSRIs alone are hypothetically due to serotonin as well, the term *serotonin syndrome* is reserved for the clinical consequences of dangerous serotonin toxicity. Such toxicity is fortunately rare, as the risk of certain serotonergic drug combinations is generally well known.

Does Too Much Serotonin Break Your Heart?

Both drugs and diseases can increase the release of circulating serotonin. For example, some malignant carcinoid tumors secrete serotonin and can cause waves of serotonin release into the systemic circulation, which in turn can make the patient flush.[6] Over time, these tumors are associated with cardiac valvular damage, especially on the right side of the heart, which presumably gets bombed with the serotonin before the serotonin moves to the lungs where metabolic enzymes chew it up.[6]

Recent reports indicate that similar cardiac valvular pathology is associated with fenfluramine administration.[7] It is not known whether this is a chance association or whether fenfluramine causes this damage. Whether release of serotonin onto these valves by fenfluramine is the mechanism of this damage is a possibility, but it is unproven.

Fenfluramine is associated with other toxicities, both cardiovascular and CNS; that is, there is an increased incidence of primary pulmonary hypertension not only in fenfluramine users, but also in those with obesity, i.e., those most likely to take fenfluramine in the first place.[8] Long-lasting depletion of serotonin from the brain due to destruction of serotonergic axon terminals is also observed in rats exposed to fenfluramine brain concentrations about 10 times higher than those in man.[9] Although there have been no reports of long-lasting or permanent serotonin depletion in brains of human fenfluramine users, or any proven changes in behavior, this possibility has always been a nagging concern for the long-term safety of fenfluramine use.

Since fenfluramine also causes long-term depletion of serotonin in circulating platelets, as do the SSRIs, there is some pharmacologic overlap between these two classes of drugs. Although fenfluramine and its active metabolite are predominantly serotonin releasers, they are also reuptake inhibitors like SSRIs, in addition to being inhibitors of serotonin synthesis and perhaps directly active at some serotonin receptor subtypes.[2–4,9] So far, there is no rationale or empiric observations to create any concern that the SSRIs cause cardiac problems similar to those associated with fenfluramine. Nevertheless, vigilance for the unexpected is the duty of prescribers.

In summary, there is good news and there is bad news about serotonin. The right amount in the right places is a powerful therapeutic tonic. But, too much in the wrong places can be hazardous to your health. ◆

REFERENCES

1. Sambunaris A, Keppel Hesselink J, Pinder R, et al. Development of new antidepressants. J Clin Psychiatry 1997;58(suppl 6):40–53
2. Stahl SM. Essential Psychopharmacology. New York, NY: Cambridge University Press; 1996
3. Stahl SM. Mechanism of action of serotonin selective reuptake inhibitors: serotonin receptors and pathways mediate therapeutic effects and side effects. J Affect Disord. In press
4. Stahl SM. Psychopharmacology of Antidepressants. London, England: Dunitz Press; 1997
5. Sternbach H. The serotonin syndrome. Am J Psychiatry 1991;148:705–713
6. Levine RJ. Serotonin and the carcinoid syndrome: histamine and mastocytosis. In: Bondy PK, Rosenberg LE, eds. Duncan's Diseases of Metabolism. Philadelphia, Pa: WB Saunders; 1974:1651–1684
7. Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997;337:581–588
8. Redux (*d*-fenfluramine). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 1997:2911–2914
9. Harvey JA, McMaster SE. Fenfluramine: cumulative neurotoxicity after chronic treatment with low dosages in the rat. Communications in Psychopharmacology 1977;1:3–17