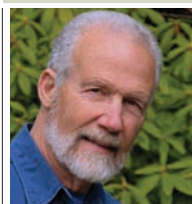# Serotonin Syndrome: Myths and Misconceptions

John R. Horn, PharmD, FCCP, and Philip D. Hansten, PharmD

John R. Horn, PharmD, FCCP

Philip D. Hansten, PharmD

Serotonin syndrome (SS) was one of the first serious drug interactions ever described, with the first cases reported more than 50 years ago. SS is caused largely by drug–drug interactions, although occasional cases have been reported following the use of single serotonergic drugs. Unfortunately, there is still some confusion and controversy about SS.

Misdiagnosis in Case Reports

A large number of cases of SS have been reported in the literature and to the FDA over the past few decades. Unfortunately, many of these cases probably do not represent actual SS. More than 20 years ago, psychiatrist Harvey Sternbach proposed a set of diagnostic features of SS known as Sternbach's criteria. While useful and sometimes still used today, these criteria included some relatively nonspecific symptoms, such as agitation, confusion, diarrhea, fever, and sweating. This resulted in misdiagno-

> Combining 2 serotonergic drugs does not necessarily increase the risk for serotonin syndrome.

sis of SS in many patients and sometimes, paradoxically, failure to identify mild forms of the disorder. There is now general agreement that the Hunter criteria—which focus more on the neuromuscular findings of clonus, muscle rigidity, tremor, and hyperreflexia—are more reliable for diagnosing SS.[1-3]

Errors Regarding Which Drugs Can Cause SS

Two primary misunderstandings are responsible for the erroneous listing of various drugs as causes of SS. First, drugs capable of exerting serotonergic effects differ widely in their likelihood of causing SS. Just combining 2 serotonergic drugs does not necessarily increase the risk for SS. There are many different serotonin receptors, and only some of them appear to be involved in the etiology of SS. Second, very few drugs (mainly the monoamine oxidase inhibitors) are capable of producing severe SS, while a much greater number of drugs can cause mild to moderate SS.[2]

A good example of the confusion regarding the risk of SS with particular drug combinations is the concurrent use of triptans with selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs). In July 2006, the FDA issued a warning, based on 29 cases reported to the FDA, that the combined use of triptans and SSRIs could result in life-threatening SS. In the November 2006 issue of this column, we pointed out that the evidence actually suggested that the combinations

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were probably safe in the vast majority of patients.

Even more important, neurologist Randolph Evans obtained the details of the cases from the FDA and determined that none of the 29 cases met the Hunter criteria for SS.[4] The issue continues to stimulate discussion, and it came up at the 2013 International Headache Congress, where Dr. Paul Rizzoli presented epidemiologic evidence suggesting that there is "… no reason to believe these medications interact in such a way that would produce SS."[5]

Yet even today, severe warnings about the concurrent use of triptans and SSRIs or SNRIs still appear in many computerized drug interaction systems, and the product information still warns about the possibility of life-threatening SS if triptans are combined with SSRIs or SNRIs.

Summary

SS is a drug-induced phenomenon and usually results from the combined effects of 2 or more drugs. The diagnosis is now made primarily on the basis of adverse neuromuscular effects as found in the Hunter criteria. Many published purported cases of SS do not represent actual SS, and this has resulted in much misinformation in computerized drug interaction detection systems. ∎

Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, including references, if any, visit www.hanstenandhorn.com.