

## LETTERS TO THE EDITOR

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### The Spectrum Concept of Serotonin Toxicity

Important and recent advances illustrate that an adequate understanding of the complex topic of serotonin toxicity ST (serotonin syndrome [SS]) requires more space than a brief review such as that of Ener et al. [1] provides. It illustrates the difficulties authors have in reviewing the extensive and complex literature comprehensively, or even adequately. I suggest the referees of that paper might have provided the authors with more guidance on references. As an author of two recent review papers on ST [2,3], I suggest practicing clinicians will find the information, references, concepts, and comments below of additional assistance in managing patients with pain without entertaining ill-informed or excessive concerns about serotonergic interactions, most of which are of a nonserious nature.

Ener et al. briefly alluded to the concept of a spectrum of symptoms progressing from side effects to serotonin toxicity. This is a concept that both Professor Whyte, and colleagues, and I have developed and marshalled the evidence for over the last 5 years [2–12]. However, this field has been progressing swiftly, and important work and references might not have been known to Ener et al. at the time their paper was submitted (this date is not stated in the journal). References that support and elaborate on this important concept are therefore cited herein.

Whyte and Gillman have developed the concept of ST as a spectrum of serotonin-related side effects [2] progressing to toxicity [6]. The term SS is being used loosely to cover this broad spectrum of serotonin-mediated phenomena. That is confusing and diverts attention from the fact that it is not really a syndrome but a form of poisoning or toxicity. The features of ST have now been clearly defined as a triad of neuroexcitatory features [6]: 1) Neuromuscular hyperactivity—tremor, clonus, myoclonus, hyperreflexia, and (in the advanced stage) hypertonia/pyramidal rigidity; 2) Altered mental status—agitation, excitement, and (in the advanced stage) confusion; and 3) Autonomic hyperactivity—diaphoresis, fever, mydriasis, tachycardia, and tachypnea.

The relative risk of serotonin toxicity with different drugs and drug combinations is evaluated in

my reviews [2], and two very recent papers from Professor Whyte's group add substance to that estimate of risk [4–6]. It is a complex subject, and my regularly updated web-based paper [11] may be a useful resource for doctors and has tables particularizing the relative risks with relevant combinations of drugs.

Doctors such as those who read *Pain Medicine* will appreciate the importance of understanding the spectrum concept as illustrated by the high risk of monoamine oxidase inhibitor (MAOI)/serotonin reuptake inhibitor (SRI) combinations, especially because no other combination produces serious toxicity. The drugs that have such properties in humans at relevant doses are tabulated at <http://www.psychotropic.com/SerotoninToxicity.doc> (Ener et al.'s table has many significant inaccuracies).

In brief, drugs whose relevant properties may not be readily recognized are: the MAOIs furazolidone, procarbazine, linezolid, and moclobemide and the SRIs duloxetine, sibutramine, clomipramine, imipramine (but not other tricyclic antidepressants), tramadol, pethidine, dextromethorphan, dextropropoxyphene, pentazocine (but not other narcotic analgesics), chlorpheniramine, and brompheniramine.

#### References

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