Letter to the Editor

Comment on Tapentadol and Serotonin Syndrome

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TO THE EDITOR:

Walczyk et al described a “probable” case of serotonin syndrome (SS), which they attributed to tapentadol overdose.¹ However, they bolster their conclusion with a misread of the literature and a faulty use of the Naranjo score.

First, the patient clearly had an opioid toxidrome (unconsciousness, mydriasis, respiratory depression, and brisk response to naloxone). The clinical description after the naloxone administration lacks a compelling description of SS, and the patient does not meet the Hunter criteria (named for a location and not a person).² The tachycardia, hypertension, and agitation are not specific for SS. Opioid withdrawal is a more likely cause of his symptoms after naloxone reversal. The authors do not describe the tremor or hyperreflexia after mentioning them only once. The patient did not receive treatment tailored to SS, but instead he received aggressive sedation with 8 mg of lorazepam, 10 mg of haloperidol, and 50 mg of diphenhydramine.

Second, assuming that he was experiencing SS, the co-ingestion of amitriptyline and duloxetine would have been sufficient to explain SS. It is impossible to conclude that tapentadol was the principal cause of SS, if it actually occurred.

Third, the authors misrepresent the prior case cited to support SS caused by tapentadol. Franco et al described the postmortem findings of a 40-year-old man found dead 3 days after anyone last saw him alive.³ There were no observations to support SS. He had an apparent overdose of tapentadol 75 mg (21 tablets missing), escitalopram 20 mg (10 tablets missing), and amitriptyline 100 mg (4 tablets missing). His heart blood tapentadol concentration was 6,600 ng/mL (>20 times the upper limit of the therapeutic range [5–300 ng/mL]).

Perhaps the only convincing published case of SS with tapentadol was a MedWatch case that involved venlafaxine.⁴ From this case, it is impossible to assign greater blame to tapentadol than to venlafaxine.

Finally, the Naranjo score is not designed for proving a toxic effect.⁵ Naranjo and colleagues devised the checklist to reduce interobserver variability among pharmacists assessing suspected adverse drug reactions.⁶ However, Naranjo et al specifically excluded intentional or accidental poisoning and drug abuse.^{5,6} Even if it were useful in understanding the present case, the authors have calculated this incorrectly. We find that the maximum score is 1 (Table 1), which falls at the bottom the “possible” range.

In summary, there is insufficient evidence to assert that SS occurred in this case and to blame tapentadol primarily for any observed symptoms.

REFERENCES

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Table 1. Reported and corrected Naranjo scores for tapentadol as suspected cause of serotonin syndrome

	Yes	No	Don't know	Reported score	Corrected score	Reason for disagreement
Are there previous <i>conclusive</i> reports of this reaction?	+1	0	0	+1	0	No conclusive report of SS solely caused by tapentadol.
Did ADE appear after suspected drug?	+2	-1	0	+2	+2	
Did the ADE improve when the drug was discontinued or <i>specific</i> antagonist was administered?	+1	0	0	+1	0	Discontinuation was not the primary treatment. No specific antagonist given.
Did the ADE reappear when the drug was readministered?	+2	-1	0	-1	0	No re-challenge with tapentadol.
Are there alternative causes (other than the drug) that could, on their own, have caused the ADE?	-1	+2	0	+2	-1	Duloxetine, amitriptyline could cause SS. Drug withdrawal or anticholinergic delirium.
Did the ADE appear when a placebo was given?	-1	+1	0	0	0	
Was the drug detected in the blood or other fluids in concentrations known to be toxic?	+1	0	0	0	0	
Was the ADE more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	+1	0	No trial of dose titration to observe effects.
Did the patients have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0	0	
Was the adverse event confirmed by any objective evidence?	+1	0	0	+1	0	SS not objectively confirmed.
Total				7	1	

Note: ADR = adverse drug reaction; SS = serotonin syndrome.