

Serotonin syndrome associated with triptan monotherapy. N Engl J Med 2008;358(20):2185-6. Soldin OP, Tonning JM. www.nejm.org may 15, 2008
A critique and rebuttal. Gillman, P K

As a widely published author and expert on serotonin toxicity I was dismayed to see Soldin's contribution on triptans (1), which has little scientific merit, in the NEJM: I am sure it was not peer reviewed. The NEJM editor has declined to reveal whether it was peer-reviewed, or if they asked whether it had been previously reviewed and rejected by another journal. Previous rejection is likely because one would hardly do all the work required with the primary intent of a publication like this, i.e. a vague letter with no proper data. Likewise, the authors to whom I also wrote, remain silent on the matter. It may surprise some readers to know that there is only slightly less evidence to implicate vitamin C as a cause of serotonin toxicity ST (aka SS). There is no *a priori* reason to theorise triptans might precipitate ST. The NEJM have declined to publish my comments on the grounds of space; they state they sent it to Soldin et al anyway (again, no response). Whatever Soldin's agenda is, scientific debate is not on it.

Soldin et al inappropriately announce the conclusion in the title: a presumption that is usually dis-allowed by editors, and explicitly forbidden in 'authors instructions' by many reputable journals. The impartiality and absence of presumption that must always be a part of good science requires that title should be framed in a way that does not presume the answer to the question being addressed by the paper: 'Serotonin syndrome associated with triptan monotherapy' (there is not even a question mark at the end). This implicitly states that 1) it is serotonin syndrome, and 2) it is associated with triptans. Note also the rubbery use of 'associated' which is going to be read as 'causes', especially because that is what the authors are implying in the text. Both these 'facts' are highly questionable; neither are the symptoms described likely to represent serotonin syndrome, nor can they be presumed to be related to triptans. The title should read, e.g. 'Possible serotonergic symptoms in patients on triptans: is there an association?'

Soldin continues with scientifically simplistic and unfounded generalisations, '... triptans may precipitate the serotonin syndrome, a potentially life threatening condition'. Again, that seems to be a statement of supposed fact and as such it is wrong: that proposition has not been established, even tentatively. Furthermore ST is a synaptic concentration-related

phenomenon, it is only fatal if serotonin levels reach 10-50 times baseline 'physiological' levels (2). Most drugs are not capable of raising serotonin that much: e.g. SSRIs do cause ST, but not fatal ST. It is therefore important for readers to remember that just because a drug can cause serotonergic side effects, or ST, does not automatically mean it can cause fatalities. Fatal and serious ST is mediated by 5-HT_{2A} receptors, not 1A (3, 4), and triptans simply do not have *any* affinity whatsoever for those receptors. Even if 1A receptors were proposed to be crucial triptans affinity for them is two orders of magnitude less than at 1B/D receptors (see PDSP Ki database). If triptans were active at central 5-HT_{1A} receptors they would cause hypothermia, not hyperthermia, as do all other 1A agonists. Triptans may have adverse/unintended CNS effects via the receptors for which it has the higher affinity (1B/D/F), e.g. somnolence (5).

Agonistic activity at the CNS 5-HT_{1A} receptor causes hypothermia, a fact well established and agreed by all major reviews on the subject for twenty years (4, 6-11). There has never been any report of hypothermia from triptans in either experimental animals or humans (NLM ("hypothermia"[MeSH Terms] OR "hypothermia"[All Fields]) AND triptan[All Fields] = 0 records). The above facts about ST and triptans being well established, any mechanism by which triptans could produce ST, or hyperthermia, is unfounded speculation: that therefore requires extra-ordinary and strong evidence to make the notion of triptans and ST plausible. Case reports are no more able to generate evidence of that calibre than a handgun is able to stop a chieftain tank.

The other aspect of this contribution that renders it scientifically valueless is the lack of any proper method in defining ST or establishing any causality. They state, apropos of ST criteria '*such strict criteria may lack appropriate sensitivity when applied to databases containing spontaneously reported adverse drug events from the public, such as the AERS*'. They do not appear to have any experience or understanding of the clinical toxidrome of ST, one hardly requires *sensitivity* to detect 'life-threatening' interactions. As far as lesser degrees of 'serotonergic' side effects are concerned we already have better quality data from the placebo-corrected data from trials which does appear to show the possible significance of somnolence as a CNS side effect (5). They quote Sclar (12) who estimated that over 2 years (2003/4) nearly 700,000 patients had taken the combination. That adds up to millions worldwide in the last ten or so years. There is not one single documented death from ST, indeed there is not even one instance of definite SS/ST. If triptans 'have the potential' to cause serotonin toxicity then that adds up to an awful lot of unrealized potential.

If they wish their cases to be taken seriously they must publish full clinical details to justify calling them ST: I am sure that they have previously attempted to do that, and peer review has worked, i.e. Soldin's publication had already been rejected by another journal. The authors' failure to respond to my inquiry about this with a denial bears only one interpretation in my book. Also, extensive experience of other similar situations involving false positive reports of ST, e.g. drugs like trazodone, nefazodone, amitriptyline, that have no serotonergic effects, have taught us that only the highest quality observations can constitute admissible evidence. That clearly does not include spontaneous reports from the public i.e. data from the AERS.

It is most discouraging to see such poor quality material and poor thinking in a journal such as the NEJM.

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