Regulatory Agencies (WHO, FDA) Offer Ill-Conceived Advice about Serotonin Toxicity (Serotonin Syndrome) with 5-HT3 antagonists: a Worldwide Problem

Abstract

Various regulatory agencies worldwide, including the WHO, the FDA, Health Canada, and most recently the TGA in Australia, have issued misleading 'warnings' informing doctors that ondansetron (and other 5-HT3 antagonists) may cause serotonin syndrome, otherwise known as **serotonin toxicity** (**ST**). It may be surprising to learn that there is no sound evidential basis for these warnings. The cases of ST described are unconvincing accounts, mostly from inexpert observers. Several such cases have been published in scientific journals, none of which are likely to be ST. The other logical deficiency is that, contrary to speculations in the WHO & FDA reports, the crucial requirement of a plausible explanatory causative mechanism is absent. Yet drug companies are being instructed/advised to include warnings about ST risk in their product information. This commentary aims to clarify and explain how this incorrect advice and undesirable state of affairs came to be. If these warnings are taken at face value, they will engender misunderstanding and unnecessary changes in treatment that may include negative consequences for patients. Experts are concerned that these regulatory agencies are not adequately assessing the scientific evidence and appear to have an insufficient grasp of clinical pharmacology and toxicology. Good science impels us to conclude there is no significant evidence of a risk of ST from ondansetron and related 5-HT3 antagonists, nor is there sound reason to theorise that such a risk even exists. These warnings are ill-informed, unjustified and harmful. It would be preferable that they were formally withdrawn.

Introduction and History

Poorly informed and uncritical comment concerning **serotonin toxicity** (**ST**) continues unabated since my critique about this was published some years ago [1]. The generally poor quality and low scientific value of case reports is widely recognised as a problem [2, 3]), many of the case reports concerning ST have been criticised and rebutted by experts (e.g. [4-15]), but they continue to be cited without these rebuttals being noted.

The warnings from the WHO/FDA etc. have no foundation except for these poor-quality case reports.

That constitutes poor scholarship and poor science. It is damaging to science that such poor scholarship is prevalent and that the (mis)citation of references sometimes reaches a degree that goes beyond carelessness and is closer to academic fraud — I know because **one of the published cases I authored was completely misrepresentated by the FDA**, that is detailed below.

This commentary has been precipitated by pronouncements of the regulatory agencies Health Canada [16] and the TGA in Australia [17] both promulgating warnings concerning the dangers of supposed ST occurring in association with the anti-nausea drugs ondansetron (and the family of other similar 'Trons'). These warnings follow on from the original one by the WHO in 2012 [18]. None of the subsequent reports add any substantive data, understanding, or interpretation of the original material presented by the WHO. Indeed, it would

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be fair to state they uncritically parrot what the WHO stated. This commentary will therefore mainly address the material presented in the original WHO advisory, which concluded:

> VigiBase case reports, together with published case reports, indicate that ondansetron may contribute to the development of the serotonin syndrome in susceptible patients concomitantly receiving other drugs affecting the serotonin system

This is not the first time inappropriate warnings have been issued and I have previously commented concerning problems with advice and warnings about the anti-migraine 'Tryptan' drugs [19] and also methylene blue [20-22] [a.k.a. methylthionimium]. Several Government-type agencies produced unclear or incorrect advice about both of these drugs. It would appear that lessons have not been learnt.

Ondansetron-like drugs antagonise (block, prevent) the action of serotonin at 5-HT3 receptors, which lessens nausea. They are widely used and must have been taken by millions of patients over the last 2 decades without reports indicating the likelihood of serotonin-mediated side-effects, never mind toxic effects. Toxic effects can only be caused by large elevations of serotonin. Hundreds of thousands of patients have taken these drugs in combination with SSRI type antidepressant drugs. This reaction of ST is not idiosyncratic, it is an entirely predictable and inevitable result of certain sorts of drug combinations (that substantially elevate serotonin). If ST is going to occur it will inevitably happen if the doses of the respective drugs reach effective concentrations. In this way it is totally different to something like NMS or an allergy to penicillin. Therefore if 5-HT3 receptor antagonists can precipitate ST and if hundreds of thousands of patients have taken such combinations, then one would confidently predict that many thousands of typical cases of ST would have occurred. Needless to say, it is blindingly obvious that has not happened (cf. the methylene blue story). Not one single convincing case of ST or ST-like signs, has been documented (see appendix).

I expect it has already occurred to readers that if ST is to do with having too much serotonin and these drugs block the effect of serotonin then how can they possibly lead to symptoms related to large excesses of serotonin? You might think that, and you would also be right to wonder what possible reasoning could convince us of the contrary: some extra-ordinary evidence would be required for this 'refreshingly original' view to become credible.

I am by no means the only expert who is concerned about this mis-information, other criticisms are available [23, 24] [and more since the original version of this country was written] and I shall be much surprised (and disappointed) if even more criticisms do not follow.

This is an excellent example for anyone who teaches anything to do with health sciences as an exercise for students in how to do good science and how to think critically and logically.

The Supposed 'Evidence'

It would be possible to write in great detail and at great length concerning this convoluted story. Fortunately, two simple points encapsulate the essence of what is required to make a decision about whether we think it is logical and sensible to postulate that ST might be caused by ondansetron-like drugs.

First, science requires at least a hint of a plausible mechanism that might produce the effect in question. The reason for this requirement is that the observation of a rarely occurring association between two things is not sufficient to conclude that one causes the other. To make an inference of a causal link requires a plausible explanatory mechanism. This is an essential requirement with ST

because we know the mechanisms that are capable of raising serotonin and the drugs that affect those mechanisms: ST does not 'just happen'. If it were proposed that vitamin C caused ST we could dismiss that idea immediately and confidently because enough is known about vitamin C to state that it cannot affect serotonin levels. It would be time-wasting to even consider the question, unless those making the claim were able to adduce new evidence and explanation as to how vitamin C affected serotonin levels.

Theory and practice do not always coincide and therefore, second, one requires a reasonable quality of evidence that the effect in question (i.e. cases of ST from ondansetron) have definitely occurred (was that shadow in the night, a ghost, or is there another explanation?). In this situation what that means is that cases that are reliably established to be ST have followed rapidly after the administration of the drug in question in a timeframe that reflects its known pharmaco-kinetics. If the drug takes effect in five minutes, and the reaction starts the next day, then there is not a convincing connection between the two.

Speaking as an expert on this subject and having read the available details of the cases in question, it is possible to state definitely and confidently that none of them are likely to represent ST (see appendix 1 for more detail). It is possible to go a step further than that and say that they do not represent ST.

The exemplar of how such an investigation should proceed is illustrated by the methylene blue story, see Gillman [21], other aspects of which are contained in a commentary here.

Speculations on an Implausible Mechanism

What about the necessary plausible mechanism by which this putative effect might be mediated? The answer to that is simple, there is no plausible mechanism.

That should be the end of the story. The fact that it is not is because the above-mentioned agencies have issued official 'warnings' which most doctors are unable to understand.

The proposed mechanism for this putative effect is the notion that increased levels of free serotonin are generated by 'displacement' of serotonin that is 'free' because it is unable to bind to 5-HT3 receptors which are already blocked (i.e. 'occupied') by ondansetron. At least, that is what I think, they think, they mean. But the text below indicates a lack of clarity and precision in the formulation of this idea, which was mooted in the penultimate paragraph (left-hand column at the bottom of page 20) of the WHO document [18], which says:

> A mechanism for a suggested increased vulnerability to serotonin syndrome when concomitantly using 5-HT3 antagonists and other serotonergic drugs might be that blocking of the 5-HT3 receptor subtype, and at the same time increasing the levels of serotonin, results in excessive serotonin to other serotonin receptor subtypes, including 5-HT1A and 5-HT2A [25, 26].

In support of this implausible speculation — and it is no more than pure speculation — the WHO & FDA documents quote both Turkel [25] and Altman [26]. Neither the Turkel nor Altman are researchers or experts in this field, their publications contain no original research data, nor any other referenced data (see below): they are merely musings that offer no science whatsoever to back up the WHO 'claim'.

The original WHO claims represent nothing more than the unfounded musings of amateurs

I mentioned above that the mis-citation of references can go beyond carelessness and become academic fraud. The references cited in science writing are supposed to substantiate the facts and arguments being put forward. If a paper is cited which does not say what the authors claim or insinuate it says, or it is simply irrelevant in that particular context, then it is mis-cited. That may represent occasional carelessness, but it is a serious academic failing which can rapidly shade into deceit and fraud. This is a serious issue that academics have difficulty facing up to.

This quote is what Turkel et al. (2001) state (no mis-citation is involved):

> Multiple serotonin receptors may be involved in producing the symptoms of the syndrome. The serotonin syndrome implies both central and peripheral serotonin dysfunction. Perhaps blocking one type of serotonin receptor and functionally increasing systemic and CNS levels of serotonin simultaneously, hence presenting excessive serotonin to other receptors, increases the risk for serotonin syndrome …

They offer no supporting evidence (and particularly, they offer no citation to substantiate this novel and imaginative idea), nor discussion about this speculation. In 2010 Altman et al. [26] cited Turkel, *en passant*, without adding anything. Therefore, to cite Altman, as if in support, is carelessly misleading since it gives a spurious impression that there is greater support for the idea than exists.

The FDA discussion states (it parrots the WHO, p. 12 under 'Discussion') '*In order for Altman's hypothesis to be true* …'. There are two reasons why this statement represents the sort of sloppy thinking that characterises both these documents. First, it was not Altman's idea, it was propounded by Turkel. Secondly, it is wrong to describe it as a hypothesis, it was vacuous speculation. To be fair to Turkel it was introduced as speculation ('***Perhaps*** *blocking one type of serotonin receptor* …'). Indeed, any good referee should have dis-allowed such speculation, unless it was substantiated by cogent reasoning and reliable references, which it most certainly was not.

It is onerous and tedious to have to dissect something as pedantically as this, but it is necessary to illustrate the point that much of what becomes accepted as part of the scientific literature about ST is poor science peppered with mis-reading and mis-interpretation of references.

Finally, a basic knowledge of neuro-anatomy and neuro-pharmacology gives us sound reasons for supposing that such a mechanism could not possibly exist or be relevant. Serotonin release from the pre-synaptic nerve diffuses across the tiny gap separating it from the receptors and only a small proportion of the released serotonin binds (i.e. locks onto) receptors. It diffuses rapidly into the local extra-cellular fluid and much of it is taken back up into the pre-synaptic nerve for re-use. The amount that binds to the receptor is a small proportion of the total amount present. That fact alone would indicate that the amount taken out of this pool by binding to a particular type of receptor would have a negligible effect on that pool. The notion is made even less plausible because the different types of receptors are not physically juxtaposed, they are separated by much greater distances than the synaptic gap. Because diffusion involves an inverse square law the rate of decrease in concentration of the neurotransmitter drops rapidly with increasing distance from the release site. I hope this conveys convincingly what an absurdly simplistic and untenable notion this is.

An analogy may help to convey the picture. Imagine being at the back of a press gallery with a myriad of reporters thrusting their microphones in front the speaker. Do you suppose that the sound waves absorbed by these microphones would make you significantly less able hear the speaker? No. Nor, if they were suddenly turned off would the speaker sound louder.

Opinion and Conclusion

Science does not, and must never, allow speculation to be mis-represented as fact. To do that is to confuse science with rumour. The basic physical facts and laws applicable in this context make it implausible that the mechanism proposed by the WHO, subsequently uncritically repeated by others, could produce even a small alteration of serotonin, and certainly not the great increase that would be required to precipitate toxicity (i.e. a 10-50 fold increase [27]).

Then we have the other major stumbling block — the evidence this reaction ever happens is poor — pathetically poor. A comparison with the events leading to the discovery of the MAOI properties of methylene blue (and its involvement in ST) provides an illuminating contrast which contains valuable lessons [1, 28, 29].

The MB story illustrates good scientific method — the story of ondansetron illustrates something more akin to rumour-mongering. If only I had time to tell you about the fairies that my next-door neighbour (or was it his wife?) told me are at the bottom of their garden …

This leaves us with an important and worrying question hanging in the air. How can it be that these agencies repeatedly get things seriously and badly wrong? A lot of heads have got together in a lot of meetings to come up with this nonsense. Remember that this is not the first time this has happened, similar criticisms were made concerning previous pronouncements about ST and triptans and about ST and methylene blue [19, 20, 29-38].

There must be readers who, like me, are smiling to themselves and remembering the old joke about a camel being a horse designed by a committee. In this case they have taken it a step further and come up with a unicorn!

Good science impels us to conclude that there is no evidence of risk of ST from ondansetron and related 5-HT3 antagonists, nor is there sound reason to theorise that there might even be a risk.

The warnings are ill-informed, unjustified and harmful. It would be preferable that they were formally withdrawn.

Appendix 1

Specific Notes Concerning the FDA warning

Note that the PDF of the document [39] is obtainable by following the link given in my references below, but the FDA site is confusing and the document is not properly titled. It is not recommended as useful reading for the average doctor, nor for anyone else for that matter. It contains a lot of errors. It would be unnecessarily tedious to document them in detail. The most relevant point is to look at what they call their 'Best Representative Case'. I therefore quote it in full below, with their reviewer's comment.

Best Representative Case

Case 7055030 (69 y/o Female, 2009): This is a case from Great Britain of a 69 years-old female who suffered SS after receiving ondansetron hydrochloride for PONV related to knee replacement surgery. She also received oxycontin after the surgery. She did not receive general anesthesia; only a regional block was used for the knee arthroplasty. Her chronic medications were phenelzine sulphate, orlistat, ramipril, amiloride HCL and diazepam. Within hours of ondansetron exposure, the patient exhibited drowsiness, confusion, agitation, hallucination, hypertension (BP 160-180 mmHg systolic) and fever (T 38C). A diagnosis of SS was made and both ondansetron and oxycontin were discontinued. Aside from supportive care, she required chlorpromazine to manage her agitation. She returned to baseline on the fifth day post-operation with no reported sequelae.

Reviewer Comment: This is a probable case representing the *potential risk* [sic-tautology] of developing SS when a 5-HT3 receptor antagonist is given to a patient who chronically takes a serotonergic agent; in this case, phenelzine, a monoamine oxidase inhibitor (MAOI). The patient did not receive any other drug known to precipitate SS. The presentation of the symptoms within hours of ondansetron exposure supports a temporal relationship between the drug and **event*.**

If this is their best case, then it would be better if they kept their opinions to themselves and took a long holiday

These symptoms (drowsiness, confusion, agitation, hallucination), are not characteristic of ST. The specific symptoms of confusion and agitation, especially an elderly the patient, most certainly do not justify a diagnosis of ST, especially when the keys signs of hyper-reflexia and clonus are notably absent. As is common in these kinds of reports there are insufficient details to rule crucial things either in or out of consideration [2]. For instance, one temperature reading of 38 c does not meet the usually used definition of fever, and ST does not cause fever, it causes hyperpyrexia. That is not the same thing. However, it is interesting to note that the patient was given chlorpromazine which would be expected to produce rapid improvement if it was ST. It is specifically stated that this was not the case and that it took at least four days the patient to settle down. If it was ST precipitated by ondansetron it would have abated as that drug wore off, i.e. in hours not days.

It is absurd to suggest that this represents ST — this is risibly poor stuff

As suggested above, if this represents their best case then it is futile to read any more. Their report is bereft of substantive scientific value.

Nevertheless, I must note another example they use as a 'good case':

Case 7370213 (69 y/o Female, 2010): A 69-year-old female from the Netherlands died as a result of SS after receiving Kytril (granisetron), Sufenta (sufentanil citrate), Methylene Blue (methylthioninium chloride), and Droperidol. The SS developed after she underwent surgery for an unreported indication, but was initially diagnosed as malignant neuroleptic syndrome. The diagnosis of SS was made after the patient's death and only after reviewing the medical literature. She was taking Effexor (venlafaxine) XR 75 mg BID chronically for the previous 11 months.

Reviewer Comment: This is a probable case of serotonin syndrome related to use of multiple serotonergic drugs: granisetron, sufentanil, methylene blue, and venlafaxine.

I was one of the authors of this peer-reviewed published report [40], I do know a little bit about it!

It is indeed highly probable that this case was ST, but there was no reason to suppose it had anything whatsoever to do with granisetron, **we did not even mention it as a possibility**. It was a classic case of an MAOI/SRI interaction (i.e. methylene blue and venlafaxine), which is the main cause of fatal ST reactions. I trust that the FDA reviewer will now note this is a published peer-reviewed case and that the authors (and by implication the referees) did not consider granisetron was a contributing cause of this patient's fatal ST reaction.

* *Think about that last sentence, it is nonsense and meaningless — that such vacuous statement can occur in official FDA document is astonishing

The FDA comment is a dishonest mis-representation of our report

Appendix 2

Quote from Australian TGA [17]

Information for health professionals

Health professionals are advised to be alert to this issue.

The TGA is working with the sponsors of the different 5-HT3 receptor antagonists to update their Product Information (PI) regarding the risk of serotonin syndrome. Some sponsors already include this information in their PI.

The updated PI contains a new precaution and information on drug interactions advising that serotonin syndrome has been described following the use of 5-HT3 receptor antagonists when used concomitantly with other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs).

If concomitant treatment with a 5-HT3 receptor antagonist and other serotonergic drugs is clinically warranted, **it is advised that the patient and caregivers are advised of this issue and that appropriate observation is undertaken.**

'It is advised that the patient and caregivers are advised of this issue and that *appropriate observation is undertaken*.'

It is hard to calculate how many thousands of medical and nursing hours of patient interaction will be purposelessly expended, at great cost, in the pursuit of this pointless objective.

It is an absurd and ridiculous suggestion

NB "… *appropriate observation is undertaken*": I wonder exactly what they think 'appropriate observation' is, when they are not clear about the symptoms of ST themselves? And, if they are going to say that it is not their role to say what appropriate observation should be, then I would suggest there are also disqualifying themselves from the capacity to make an informed judgement about the diagnosis! They cannot have it both ways. It illustrates the superfluity of sloppy, illogical, and unscientific thinking that is going on.

There is little useful purpose in highlighting and dissecting every mistaken statement made by the TGA, therefore, I shall merely note one more instance which exemplifies my point. They state: 'Serotonin syndrome *has been seen in patients* using 5-HT3 receptor antagonists at the same time as other serotonergic medicines'. Not true, to say '*has been seen in patients'* is treating speculation as if it were an established fact. It would be more objective and accurate to restate this as:

'an infinitesimally small proportion of the enormous number of patients who have been treated with such combinations have shown symptoms which bear some slight resemblance to those seen in ST. However, no typical cases have been documented and there is no mechanism to explain why such drugs would increase serotonin or precipitate ST.'

The statement that ST 'has been seen' is a careless misrepresentation of the facts. Or maybe fairies are real.

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