Rasagiline and serotonin toxicity

by Dr Ken Gillman | Last updated Oct 21, 2021 | Published on Nov 13, 2011 | Serotonin Toxicity, Anti-Depressants

Comment concerning "Rasagiline-induced serotonin syndrome. Mov Disord, 2011. 26 766-767. Fernades et al"

This poor report by Fernades et al. about supposed ST with rasagiline [1] contains errors and misrepresentations of cited papers: that is a serious deficiency in scientific writing. Case reports constitute low grade evidence at best, but when, as in this instance, they are superficially researched and refereed, they are prone to spread misinformation and promote misconceptions.

I should state my opinion at the outset, that it is most improbable this case represents either side effects of rasagiline from serotonin-mediated mechanisms, or ST (aka serotonin syndrome). This is for the very simple reasons that there are: 1) no specific ST signs and 2) rasagiline is incapable of substantially elevating serotonin. Having stated, that I will comment on some aspects of the paper that have inadequate foundation.

Their list of drugs that are implicated in ST ("dopamine agonists, tricyclic antidepressants, and selective serotonin reuptake inhibitors" is largely incorrect (e.g. see [2-4]). Their citation supporting this claim contains no data whatsoever concerning those drugs and ST (neither does any other citation they provide, except for SSRIs). It is most unfortunate that they mis-cite these seminal references, from professors Whyte, Isbister and associates, which they utilize without evincing an understanding of their contents. They use the older non-specific and unvalidated Sternbach "diagnostic suggestions" while ignoring the more specific scientifically validated diagnostic criteria algorithm (Hunter Serotonin Toxicity Criteria HTSC) that are in the paper they cited [3]. By those more precise and discriminating criteria this case would definitely not be rated as ST. They describe her presentation after the increase in dose to 4 mg daily as "confusion agitation and loss of consciousness". These non-specific features do not conform to any usual presentation of ST, nor to the formal HSTC diagnostic criteria above: early appearance of tremor, hyperreflexia, and clonus would be expected.

In their second paragraph, they state that rasagiline increases dopamine (correct) and then, via an unreferenced and unelaborated logical *non sequitur* … "Thus, theoretically, rasagiline can cause serotonin syndrome". Drugs like rasagiline, that elevate dopamine, by definition, cannot cause ST. The toxidrome is called ST precisely because it is defined as being mediated by excess serotonin: it is hard to comprehend how anyone who understands pharmacology and toxidromes could make such a claim, without any supporting references (which, I assure readers, do not exist). For instance, tranylcypromine has much more potent MAO-A antagonism but does not cause ST in usual or high-therapeutic doses [4].

They describe a "pyrexia of 37.7°C", without specifying how often, where, or how, it was measured. That is both imprecise and incorrect terminology (because ST is a hyperthermic toxidrome, not an acute phase response, i.e. pyrexia): the generally accepted definition of hyperthermia is at the very least 38.5°C, and pyrexia 38.0°C sustained for 1 hour, or a single reading of 38.3°C.

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Space restraints [for permitted length of letters the journal] debar more detailed comments. I suggest readers consult the references provided for more accurate information.

The editors declined to accept this submission for publication. Their reply stated

> "I regret to inform you that the Editors of the journal have decided to reject your manuscript entitled, "Comment Concerning Supposed Rasagiline-Induced Serotonin Syndrome" without further review. If you are willing to resubmit a letter without without gratuitous comments, we would be willing to consider for publication
>
> Thank you for the opportunity to consider your submission.
>
> Sincerely, Professor José A. Obeso"

When asked to specify what they meant by "without **gratuitous*** comments" they declined to enter into any further correspondence. It seems that they are happy to publish bad science, but not criticism of it.

I relate this to give readers some understanding of the childishness of some editors. Being retired, it is not a problem to me, but bear in mind that for the average academic the two full working days that a submission like this would consume is a substantial effort of extra work over and above what a typical academic might be doing, which is probably 60 hours a week. Few people are going to have the determination and energy to pursue something like this.

The fact that the editor and referees of Fernandez's paper have reviewed it with such little care that they have not even noticed that the first reference contains no data whatsoever supporting the opening statement of paper is all anyone needs to know. To quote a reference that is completely out of context, and not a genuine mistake, is extremely poor academic behaviour. Doing that sort of thing repeatedly is tantamount to academic malpractice. We can be sure it is not a mistake because no other reference in the paper has data that would support that statement either.

It is certainly my view that to call robust criticism of such lax practices "gratuitous comment" is a travesty of the scientific process. It is using a false façade of being affronted to cover up laziness and incompetence. Taking-offence as a form of evasion and cover of a weak intellectual argument is a pathetic and despicable form of intellectual failing. It has become the default third millennium approach to shutting down any argument that is considered unwanted, both in science and in society at large.

Sadly, none of the above is exceptional or surprising and I have seen much similarly poor writing and refereeing even in journals which are supposed to be top class. It is unfortunately true that the commercial and competitive nature of academic science has now distorted much of the publication process to a stage where it has lost scientific value. Worse than that, it is misleading because the literature clogs up with erroneous papers like this one, which cause real chaos and misunderstanding in clinical medicine.

I referee quite a few papers, obviously mostly in the field of serotonin toxicity. Of the last 30 that I have refereed, 28 of them have been exceedingly poor, like this one, from almost every conceivable point of view. It is unfortunate that quite a few journals, indeed the majority of the ones I have dealt with in the last decade or more, do not provide the referees with the comments of the other referees (editors usually use 2 or 3 referees to comment on a paper). That is an important learning and auditing process as was recognized in the Parliamentary enquiry about medical publishing. On the occasions I have seen the other referee's comments in my field they have too often been of modest perspicacity.

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* Definition unwarranted, lacking good reason

References

1. Fernandes, C., P. Reddy, and B. Kessel, *Rasagiline-induced serotonin syndrome.* Mov Disord, 2011. **26**(4): p. 766-767.

2. Gillman, P.K., *A review of serotonin toxicity data: implications for the mechanisms of antidepressant drug action.* Biological Psychiatry, 2006. **59**(11): p. 1046-51.

3. Isbister, G.K., N.A. Buckley, and I.M. Whyte, *Serotonin toxicity: a practical approach to diagnosis and treatment.* Medical Journal of Australia, 2007. **187**(6): p. 361-5.

4. Gillman, P.K., *CNS toxicity involving methylene blue: the exemplar for understanding and predicting drug interactions that precipitate serotonin toxicity.* Journal of Psychopharmacology, 2011. **25**(3): p. 429-3.