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MAOI update: Clarifications concerning pharmacology and terminology

Abstract

This paper points out that precise use of terms in pharmacology and nosology is essential to understanding MAOI drugs and their potential uses and interactions. The approved indications for their use, according to bodies such as the FDA, have varied considerably over the decades without new data or scientific justification to underpin those changes. Much of the material about these drugs in standard texts is written by those with inadequate practical experience or knowledge of pharmacology, as exemplified by the American Psychiatric Association textbook on psychopharmacology, which has multiple significant errors. The main falsehoods and misconceptions are explained and clarified by an internationally recognised expert.

Introduction

The first objective of this commentary is to clarify misunderstandings about the range of clinical usefulness, and the pharmacology and side-effects, of these (MAOI) drugs, which are not clearly explicated in current sources, including FDA approved product information (PI). The lack of interest and acceptance surrounding these drugs has meant that many texts have become out of date or have been updated by authors not conversant with the advances that have occurred in the last few decades — much of the literature is stuck in the 1980s, like the literature on serotonin toxicity (ST), with which it is closely inter-twined.

I first wrote clarifying the misinformation surrounding interactions between MAOIs and narcotic analgesics more than a decade ago [1]. Recently, I have published a couple more papers discussing and updating some important aspects of MAOI pharmacology [2-6].

First things first

One fundamental consideration in understanding the actions and uses of MAOIs is to be continually aware of the imprecisions surrounding the words used, be they words from pharmacology (like TCAs), or nosology: many such words have

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meanings that are either poorly defined, or of unproven validity (like atypical depression).

The types of depression that MAOIs have been considered to be useful for, or have been 'officially' approved for, in the sources like the '**Physicians' desk reference' PDR**, reflect various non-scientific influences that have affected such matters over the last few decades. Similarly, guidelines are essentially derived from RCTs and generally include little information relating to experience derived from clinical practice. This biases information and opinion away from MAOIs.

Throughout discussions about these drugs the distinctions between pharmacology and science, as opposed to the economics, politics, biases of profit-driven marketing, and regulatory affairs and legal considerations, must be borne in mind. Unfortunately, insufficient understanding of these distinctions has had a major adverse effect on clinical practice (for instance, via the inclusion of PDR ADR information in electronic health computer systems: these introduce false and baseless warnings about adverse drug interactions).

> Electronic health computer systems introduce false and baseless warnings about adverse drug interactions

The Product information issued varies in different countries and has a slightly indirect relationship to the practical aspects of treating depressed patients and is not much informed by practical experience, since it is mostly determined before the drugs are widely used in the real world. It is not always adequately updated, or in keeping with up-to-date pharmacological knowledge. My experience of this is focused on the inter-related topics of MAOIs and serotonin toxicity, in which area the information is poor. It is a compilation of the information required by regulatory agencies, like the FDA and the EMA, for the approval of drugs, and therefore has content determined by those agencies, and the submitting drug company [7]. It is also 'shaped' by legal advice which can lead to unhelpful and incorrect content*. When it comes to advice and guidance about clinical pharmacology doctors will profit from consulting texts on clinical therapeutics and pharmacology, not the PDR.

A BMJ review by several eminent Australian toxicologists [8] strongly agrees with my views. I quote:

> Several systematic reviews clarify the extent to which severe serotonin toxicity may result from drug interactions. However, spurious associations and cautions have proliferated elsewhere in the medical literature, and product information is a major impediment to sensible decision support in this area.

> Product information is a major impediment to sensible decision support in this area

Indications

The history of the changes in the indications for MAOIs, that are in the PDR and similar sources, relating to approvals by the FDA, is lost in the mists of time. I consulted the eminent historian of science, Professor Edward Shorter, on this matter recently, and even he had lost track of what had happened. One might

* As I have commented before the 'PDR' is a masterly marketing exercise of turning a necessity into a virtue. This documentation is required by law to be provided to the FDA and the European Medicines Authority (EMA): somebody has parcelled it together as a book, computer program etc., and then sold it to doctors, hospitals etc. for a considerable price — chutzpa and sheer genius! But, from a clinical pharmacology and therapeutics point of view this is a disaster, because the legalistically framed and non-clinical information is incorporated into electronic health record systems, and suchlike software, thereby promulgating false warnings and misinformation which might serve medicolegal defensiveness but not treatment practicalities.

argue that hardly matters, but that is true only if one recognises the caveats stated above. Nevertheless, a couple of brief observations may illustrate the chaotic and arbitrary nature of events.

In the 1975 PDR, tranylcypromine was approved for 'severe endogenous depression' (i.e., melancholia). However, by the turn of the millennium this had somehow shifted to 'major depressive disorder' *without* melancholia.

A GSK PI for Parnate dated 2017, contradicted the FDA approval by stating that it is effective for psychotic depression (I agree with that); generally speaking the various versions I have seen from this millennium contain much information that is contrary to established data, and also information that is without significant scientific foundation — indeed, some of the misinformation is sufficiently serious that if a doctor gave such advice to a patient they would be making themselves liable to an indefensible malpractice action.

Therefore the statement in the review by Preskorn & McMahon in '*The package insert: who writes it and why* [7]: '

> Hence, the package insert is one of the most evidence-based pieces of literature that can be cited about a specific drug in terms of its uses and risks

That is incorrect concerning MAOIs, and for statements about ST relating to many antidepressants and other drugs.

https://psychotropical.info/gsk-product-information-parnate/

Major misconceptions

In the editorial I wrote for Stephen Stahl's CNS Spectrums Journal in 2017 [3] I highlighted some of the major misconceptions.

Here is an expanded list of such falsehoods and misconceptions

- They are only effective for atypical depression, however that is defined (false, they are effective in ***all*** types of biological depression, especially severe melancholic depression)
- The low-tyramine diet is difficult (it never was difficult, but is now easier still, because foods now have less tyramine than in the past)
- They cannot be combined safely with 'tricyclic antidepressants' (false, with the exception of clomipramine and imipramine)
- Serotonin toxicity is possible with a wide range of drugs (false, only with potent SRIs)
- There are many problematic drug interactions
- It is difficult to swap to and from other drugs (false, one can safely co-administer them with any *therapeutic psychotropic* drug except one that has significant potency as an SRI)
- That they need to be ceased before anesthesia (false) & that opioid analgesia cannot be used (false, except for opiates that are SRIs, such as tramadol and meperidine (pethidine)
- One cannot give epinephrine, or alpha1 agonists (false, but a dose reduction may be appropriate)
- They *cause* elevated BP and should not be used in patients suffering from hypertension (false, they lower BP and improve hypertension)

In my review in the 'Journal of Neural Transmission' [4] I elaborated on item 3 concerning TCAs* by pointing out that there is good reason to be confident (from a huge amount of clinical experience in using such combinations over many years, and from basic pharmacology) that not only are the combinations safe, but it is almost certain that some of them usefully attenuate the tyramine pressor response, in proportion to their potency as NRIs.

It should also be noted that many texts, including the FDA approved PIs, omit mention of the fact that non-selective MAOIs increase dopamine. They mention the other neurotransmitters, but dopamine does not feature. This is an odd and significant omission since they are more or less the only group of drugs that do substantially increase dopamine transmission. It is also obviously inconsistent with the fact that rasagiline (and selegiline), irreversible inhibitors of MA0-B, are FDA approved specifically for the treatment of Parkinson's disease, because they increase dopamine. It is another clear demonstration that the left hand does not know what the right hand is doing.

It is bizarre, and proves the above point, that FDA approved PIs, fail to state that non-selective MAOIs increase dopamine

I conclude by observing that failure to understand the pharmaco-dynamics (and also the pharmaco-kinetics) of drug interactions is widespread: it underlies most of the misunderstandings and mistakes averred to above. This is an important gap in the education of doctors which must be addressed by improvements in both undergraduate and postgraduate medical education.

References

1. Gillman, P.K., *Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity.* British Journal of Anaesthesia, 2005. **95**(4): p. 434-441.

2. Gillman, P.K., *Advances pertaining to the pharmacology and interactions of irreversible nonselective monoamine oxidase inhibitors.* Journal of Clinical Psychopharmacology, 2011. **31**(1): p. 66-74.

3. Gillman, P.K., "*Much ado about nothing*": *monoamine oxidase inhibitors, drug interactions, and dietary tyramine.* CNS Spectr, 2017: p. 1-3.

4. Gillman, P.K., *A reassesment of the safety profile of monoamine oxidase inhibitors: elucidating tired old tyramine myths.* J Neural Transm (Vienna), 2018. **125**(11): p. 1707-1717.

5. Finberg, J. and P. Gillman, *Pharmacology of MAO-B inhibitors and the cheese reaction*, in *International Review of Neurobiology*, M. Youdim and P. Riederer, Editors. 2011, Elsevier Inc. Academic Press.: Burlington. p. 169-190.

6. Gillman, P.K., et al., *Revitalizing monoamine oxidase inhibitors: A call for action.* CNS spectrums, 2019.

*Yet again I draw attention to the notion of **neuroscience-based nomenclature** for drugs [9-11]: I remind readers that the term 'TCA' is unhelpful and outdated. The individual drugs in this 'category/class' **must** be considered according to their pharmacological profile, not their structure. Thus, the only two that are significant SRIs, and therefore contraindicated with MAOIs, are clomipramine and imipramine. The others are safe; but not ***all*** are sufficiently potent as NRIs to attenuate the pressor response.

7. McMahon, D. and S.H. Preskorn, *The package insert: who writes it and why, what are its implications, and how well does medical school explain it?* J Psychiatr Pract, 2014. **20**(4): p. 284-90.

8. Buckley, N.A., A.H. Dawson, and G.K. Isbister, *Serotonin syndrome.* BMJ, 2014. **348**: p. 10.1136/bmj.g1626.

9. Zohar, J., et al., *A review of the current nomenclature for psychotropic agents and an introduction to the Neuroscience-based Nomenclature.* Eur Neuropsychopharmacol, 2015. **25**(12): p. 2318-25.

10. Gorwood, P., et al., *Editorial: Neuroscience-based Nomenclature (NbN) replaces the current label of psychotropic medications in European Psychiatry.* Eur Psychiatry, 2017. **40**: p. 123.

11. Nutt, D.J. and P. Blier, *Neuroscience-based Nomenclature (NbN) for Journal of Psychopharmacology.* J Psychopharmacol, 2016. **30**(5): p. 413-5.