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 errors 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 the MAOI antidepressants, which are not clearly explicated in current sources, including FDA-approved product information (PI) sheets. The lack of interest and acceptance surrounding these drugs has meant that many texts have become out of date or have been updated by authors not conversant with the advances that have occurred in the last few decades — much of the literature is stuck in the 1980s,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 intertwined.

I first wrote clarifying the misinformation surrounding interactions between MAOIs and narcotic analgesics two decades ago [1]. Recently, I have published a couple more papers discussing and updating some important aspects of MAOI pharmacology [2-12].

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 meanings that are either poorly defined, or of unproven validity (like treatment resistant depression[1] and 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. Also, 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 (see section on bias in science in the main menu).

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

[1] I suggest that all TRD means is 'we haven't used the right treatment yet' depression. It is an inherently faulty definition because it is context dependent.

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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 information on adverse drug reactions (which is frequently erroneous) in electronic health computer systems, which as a result introduce false and baseless warnings.

> Adverse drug reaction information in electronic health computer systems, derived from sources like the PDR, often has false and baseless warnings

The product information issued via such systems varies in different countries and has an 'indirect' relationship to the practical aspects of treating depressed patients; it is not much informed by practical experience, since it was mostly determined before the drugs were widely used in the real world. PDR information is not adequately in keeping with up-to-date pharmacological knowledge, as is claimed by Preskorn[2] in a review of PDR practices [14].

My experience of this is focused on the inter-related topics of MAOIs and serotonin toxicity, in which area the PDR information is abysmal — in fact, some of it is so poor that if a doctor gave that advice, they would be in danger of an accusation of malpractice. It is a compilation of the information required of pharmaceutical companies 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 pharmaceutical company [14]. It is also 'shaped' by legal advice which can lead to unhelpful and incorrect[3] 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.

> Some PDR information is so poor that doctors giving such advice might be accused of malpractice

A BMJ review by several eminent Australian toxicologists [15] 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.**

Indications

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

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[2] He states 'Safety and tolerability issues are addressed in the sections titled contraindications, warning and pre-cautions, adverse reactions, drug interactions, and use in special populations. The package insert is revised as new information becomes available.' That may once have been the stated intent, but it is clearly not happening even with potentially fatal interactions [13].

[3] As I have commented before, the 'PDR' is a masterful 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 parceled 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.

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 sheet 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.

> At different times TCP has been officially approved for: severe endogenous depression [melancholia], major depressive disorder *without* melancholia, and psychotic depression

Therefore, the statement in the review by Preskorn & McMahon in '*The package insert: who writes it and why*' [14]:

> 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

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

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

MAOIs are only effective for atypical depression, however that is defined. (This is false: they are effective in ***all*** types of biological depression, especially severe melancholic depression.)

The low-tyramine diet is difficult. (False — it never was difficult, but is now even easier, because foods have less tyramine than in the past.)

They cannot be combined safely with 'tricyclic antidepressants'. (False, with the important exceptions of clomipramine and imipramine, which are sufficiently potent SRIs that dangerous ST can manifest when combined with MAOIs.)

Serotonin toxicity is possible with a wide range of drugs. (False, only with potent SRIs or potent serotonin releasers.)

There are many problematic drug interactions. (False, they have less P450 interactions than many new drugs)

It is difficult to swap to and from other drugs. (False: one can safely co-administer MAOIs with any *therapeutic psychotropic* drug, except one that has significant potency either as an SRI or as a potent serotonin releaser.)

That MAOIs 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 alpha-1 agonists (false, but a dose reduction may be appropriate).

They cause elevated blood pressure (BP) and should not be used in patients suffering from hypertension. (False, they lower BP and improve hypertension.).

They are very dangerous in overdose (false, since improved ICU treatment in the 1990s the death rate has dropped from 30 per hundred thousand to zero)

Fatality in overdose

The fatality rate from MAOI overdose dropped near the end of the last millennium when it was realised that intubation and paralysis, if the temperature was elevated beyond 39°, was the definitive course of action. As this practice was adopted between 1985 and 1991 the fatality rate per hundred thousand scripts dropped from 30 to 0 [16]. This low fatality rate is reflected

in the statistics from the American *Annual Report of the National Poison Data System [13],* covering recent decades. Although blood pressure disturbances can occur following overdose, they are not seriously problematic and do not lead to death.

In my review in the 'Journal of Neural Transmission' [4] I elaborated on item 3 concerning TCAs[4] 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. Furthermore, patients on the combination experience less side-effects, not more [20-23].

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 MAOIs 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 MAO-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 my above point, that-FDA approved PIs contain basic pharmacological errors, and 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.

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[4] Yet again I draw attention to the notion of neuroscience-based nomenclature for drugs; see the references below: [17-19].
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.

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