MAOIs: Introductory Comments

Beware of false knowledge; it is more dangerous than ignorance

~ *George Bernard Shaw*

Introduction

MAOI antidepressant drugs are safe and effective, with levels of side-effects that generally compare favourably with other drugs, and for tranylcypromine (TCP, Parnate) are notably better than most for not causing sexual SEs or weight gain.

With an appropriate knowledge base, they are not difficult to use.

Seeing patients who we have treated achieved complete remission after years of illness, and after failed ECT, is one of the most rewarding feelings and achievements that we get as doctors and specialists. You will experience that feeling often once you have learned to treat people with MAOIs.

Many specialists are missing the opportunity to effectively treat large numbers of patients by not knowing about these drugs and how to use them. We are but a child of our time. We are moulded by the social and commercial milieu that forms our training experience. The profit-driven pharmaceutical company forces that powerfully shape that milieu are not always ones that have patient welfare as their priority.

There has been an MAOI-deficient environment for a long time — there is a lot of misinformation. Most classic text books and reviews have seriously mis-informed fact and comment.

I discovered that methylene blue (MB) was an MAOI, so read, as an example of this, my analysis of the methylene blue fiasco and learn how the FDA, EMA, and the UK MHRA made extensive errors and gave ill-informed advice to doctors.

The three decades of the Prozac era may now be receding, I recall the previous chapters in the story and see the perspective. That causes me to comment that many of the 'Prozac-era' drugs have caused more difficulties and problems than the MAOIs ever did. When reviewing the Prozac era, I am struck by the fact that such a large number of patients are treated so extensively with a group of drugs of such marginal efficacy: indeed, one is tempted to call it the 'anodyne era' (do less harm, but not much good either). SSRIs have done a lot of harm: particularly the most widely used for many years, fluoxetine (Prozac), which has a terrible record for causing pharmaco-kinetic drug interactions some of which are serious — I remember a lady who lost most of her fingers and toes because she was given ergotamine whilst on fluoxetine, as a result of its CYP3A4 inhibition [1-4].

The Prozac era, or the 'anodyne era' — do no harm, but little good either

We may note here that this supposed saying (*primum non nocere*), and the 'Hippocratic oath' itself, is a misinterpreted myth. First, it has little or nothing to do with Hippocrates — the predominant form of this aphorism is always rendered in Latin, but Hippocrates did not write in Latin; second, it never appeared in writing in the medical literature until the mid 20th century; third, it has no more legitimate ethical or philosophical parentage than any other facile aphorism [5]. As Brewin noted [6]:

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> As a guide to medical practice, it is laudable but obviously deficient. It emphasizes the negative and the prevention of harm — altogether a desirable behaviour and attitude, but inadequate as a guide to practice and general ethics.

The history and the biases

It is difficult to summarise the history of MAOI use in psychiatry without being critical of the level of pharmacological knowledge in the profession. One strong influence which compounds the misinformation/misperception problem about drugs in general, and out-of-patent drugs in particular, is the strong bias concerning promotion, advertising and teaching produced by the financial dominance of pharmaceutical companies. Their primary objective, which may override all other considerations, is to sell new generation expensive in-patent drugs, irrespective of whether they can actually present the 'evidence' to make them look better or not.

I am an internationally acknowledged expert on serotonin toxicity and have published extensively about drug toxicity and interactions involving most psychotropic drugs (1-9). ST is the only serious drug-drug interaction relevant with MAOIs. Let me just elaborate that statement briefly — the tyramine pressor response *may* be more common, but it is usually mild and even when it causes large elevations of blood pressure it very rarely results in subarachnoid haemorrhage: whereas serotonin toxicity is quite frequently serious and sometimes fatal.

Note that serotonin toxicity is only serious or fatal when associated with a combination of therapeutic doses of an MAOI combined with an SRI — it is not dangerous or fatal when associated with single drug ingestions or combinations **not** involving MAOIs — see the serotonin toxicity section for a deeper understanding of this issue.

There are many other sections on this website related to safe and effective use of drugs and my special expertise in serotonin toxicity enables me to talk particularly authoritatively concerning that aspect of MAOI interactions.

I have reviewed elsewhere the evidence relating to the declining use of MAOIs by doctors over the last three or four decades. Although there is little or no data relating to the younger generation of doctors, it is reasonable to assume that an even smaller proportion of the latest generation have adequate experience, or knowledge, of these drugs — I receive frequent comments via the website from trainees and younger doctors who state they have had little or no training or teaching about this. Indeed, what is even more disappointing is that they are frequently told these drugs are out of date, ineffective, dangerous and should not be used. That is poor teaching at a level which would have to be described as decidedly substandard. Anyone who encounters such lack of knowledge might like to refer the teacher to the story about the Dutch professor who became psychotically depressed and was cured by tranylcypromine (TCP, Parnate).

Those who wish to learn more about MAOIs will require a little intellectual courage and tenacity because what is written about these drugs is a good example of how easy it is for dogma to become established as fact, even when it is based on poor knowledge and evidence. Sadly, much of what has been written about MAOIs is simply third-rate scholarship, much of which is factually incorrect, as the latest edition of the APA textbook embarrassingly exemplifies.

> MAOIs are an example of how myth and dogma become established as fact, merely by unthinking repetition

I do not want to dwell on that aspect here, but it is important to be confident of the accuracy and objectivity of that statement. The brief example I will use is

that of the generally accepted proscription that one cannot combine TCAs and MAOIs. This is reproduced in most standard texts. How and why that is incorrect is dealt with in great detail in several of my papers about serotonin toxicity. Perhaps the best general overviews of that question are in my 'Biological Psychiatry' review (5) and the MB review (8). I am also preparing a brief commentary for the website specifically about that, simply because it is such a common misconception [link]. Doctors who prescribe such combinations are not infrequently subject to criticism and even censure for doing so. I have had numerous reports of pharmacists who have refused to fill scripts because of the misinformation (in computerised drug interaction databases) and misconceptions about this mythical interaction. I also gave a report to the Australian medical board. Their 'experts' incorrectly asserted that a doctor was negligent for giving a combination of TCP and amitriptyline. For those who put themselves forward as experts, judging their colleagues, that is ignorance, woeful ignorance.

So, if you are going to use MAOIs you need to acquire the knowledge, and have the intellectual fortitude, to challenge misconceptions and dogmas — much of that knowledge can be gained by reading my papers, and what is on this website. Those who are unable to marshal those qualities will have greater difficulty challenging commonly accepted, but erroneous, views and the various misleading clinical guidelines on treatment. Guidelines are admirable things for general purposes and for less experienced practitioners, but it is important to remember that all good guidelines are preceded by specifically stated caveats relating to the importance of individual cases and the use of clinical judgement by the treating doctor. They are only guides, not *ex cathedra* dictates. When doctors hurriedly check the guidelines to make sure they are not going to be criticised, the basic and essential EBM tenets are frequently overlooked or forgotten, these **require**:

> ...integrating ... the best available external clinical evidence from systematic research...[with] the proficiency and judgment that individual clinicians acquire through clinical experience and clinical practice... [without which] even excellent external evidence may be inapplicable to or inappropriate for an individual patient' [7].

All guidelines should emphasise the importance of individual treatment assessment, the patient's right to choose, and refuse, and the use of clinical judgement by each treating doctor — not slavish, thoughtless, adherence to guidelines

Those who opine that treatments should not be given because they do conform to the guidelines do not understand the responsibilities of the clinician and the priorities of good clinical medicine, and the rights of patients to choose which treatment they prefer — like trying TCP before being given ECT.

That idea conceptually meshes with the George Bernard Shaw quote:

> 'When a stupid man is doing some-thing he is ashamed of, he always declares that it is his duty.'

Or in our field of endeavour the individual would protest that they had 'followed the guidelines'.

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