MAOIs updated

Exordium

There have been a number of reviews about the pharmacology and clinical therapeutics of MAOIs in the last decade: yet most standard medical texts still have incorrect and misleading information and opinion. I have convened an international group of more than 200 eminent experts who are interested in furthering knowledge and increasing utilisation of MAOIs. There is extensive concern in that group about their under-usage, the lack of teaching about them, and the fact that in many countries their availability is lessening or has even ceased.

The group has published a position statement on the safety and under-usage of MAOIs which appears as an editorial in the journal CNS spectrums. It has been endorsed by more than 80 eminent specialists and researchers from all over Europe and North America [link]. One can only hope that the weight of opinion of many eminent people will have some influence — **but what is even more important is that everybody reading this spreads the word throughout their networks**.

Many in this field consider that under-usage of MAOIs is leading to a great deal of increased suffering and unnecessary deaths by suicide.

The relevant members of this class (irreversible, non-selective, MAOIs) are; **tranylcypromine, phenelzine, isocarboxazid, and selegiline**.

Selegiline, being selective for MAO-B, probably does not elevate dopamine as much as the other non-selective MAOIs, PET studies indicate it does not inhibit brain levels of MAO-A to a substantial extent at 'selective' dose levels [1, 2]. That fits with its seemingly lesser effectiveness, unless it is used at higher (oral) doses of 30-60 mg.

MAOIs have been out of patent for decades, and were, for a long time, inexpensive drugs. However, in the last decade the price of some of them, in various countries, has gone up by a hundred-fold or more, for no obvious or justifiable reason (tranylcypromine now costs GBP >300 for only 30 tabs, meaning that a typical one-month supply is approaching GBP 2,000). It has been suggested that price-gouging, corruption, and price-fixing may be the explanation, and in view of the recent Washington Post revelations in the USA about price-fixing of generic drugs, that is a plausible explanation. Some are fighting back, like Civica Rx. In the US Civica Rx has been formed, it is a substantively capitalised enterprise connected with many US hospitals which seeks to source or produce generic drugs on a not-for-profit basis. That indicates how bad a large number of American hospitals think the situation has become.

I would also note that individual patients can fight back too. UK customs seem to have no problem with people ordering drugs from abroad for personal medical use. I have a number of people who have contacted me via the website who did this without a problem.

One of the prime functions of my website is to provide information about MAOIs. I have published several scientific papers about these drugs [3-11] and I am widely regarded as an expert about them, and the interactions between psychotropic drugs generally.

This updated series of commentaries will provide the latest information concerning their pharmacology and therapeutic use. It will also suggest ways in which consumers of medical services can influence developments and improve

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the availability of drugs. Patient groups that are not connected to, or financed by, 'big pharma' have an important part to play, and it would be helpful if they were mobilised and coordinated.

History

We should note the early 1960s reviews about MAOIs by Atkinson, Atchley, Lesse, [12-15], and Cole [16], Cole's was updated in 2002 [17].

Other more 'recent' (it is a relative term) reviews are: [6, 7, 18-43]. The number of reviews certainly suggests an underlying ground-swell of interest.

Although these reviews are 'noteworthy' that does not infer I recommend or endorse them: only some are useful, and most of them are not without significant omissions and errors (many of these errors relate to ST and tyramine, my special areas of expertise). Indeed, the less than perfect knowledge about MAOIs was one of my motivating factors when I decided to form the international experts group.

Medical science publishing has become poorly governed and it is difficult for most readers to ascertain what is reliable and worth reading — therefore experts such as myself need to state plainly when the material they are referring to is not considered reliable, even if that does discombobulate a few people, however eminent or 'expert' they might be considered to be.

That reminds me of the quote from the Nobel prize-winning physicist, Neils Bohr:

> An expert is a man who has made all the mistakes it is possible to make, but only in a very narrow field

I used that quote when acting as an expert witness in a court case. I turned to the judge and said: 'and I, your honour, am definitely an expert'. It diffused a situation and made the judge laugh.

Therefore, I cannot omit special mention of the particularly poor review from 2007 by Krishnan (cited by some, x7 in PubMed, and x73 in Google Scholar) which was the review that appears to have qualified him for writing the American Psychiatric Association psychopharmacology textbook chapter on MAOIs (which I presume was ghost-written by the same people as 'his' review), about which I have made severe criticisms previously — such people are not worthy of respect. His 2007 review article is clearly ghost written and has serious errors. It is a classic example of the blind leading the blind, and of how careful one has to be when reading the literature, because much is poor quality, and 'written' by people who have no substantive claim to be experts [44]. I will say no more, except that if he continues writing more articles like this he will, eventually, become a 'Bohr' accredited expert.

Caveat lector.

An aside

I must slip in a quick story, necessarily abbreviated as it is, about the MAOI book chapter written by a famous London teaching hospital psychiatrist — it was poor. Later, when he was working at the same teaching-hospital as me, I became responsible, temporarily, for his patients, and cured one of them (who had already been in hospital for two months), in the 10 days he was away, with tranylcypromine. When he returned, he was delighted with the (obvious) improvement, but when he realised it was caused by tranylcypromine, he burst into an anxious sweat and ceased the treatment. The patient had no side-effects! The doctors who worked with him regularly told me, subsequently, that he never used MAOIs — but he wrote the book chapter about them! As Shaw said:

Those who can, do; those who can't, teach [45]

I remember one day in the coffee room we added a few more stages to Shaw's maxim, '… and those can't teach write books, and those who can't write books do drug-comparison trials…'

Although that was Coffee-room humour, there is an element of truth to it.

Now you know why I sometimes call psychiatrists timorous, and even pusillanimous [46].

Basic pharmacology

It is worth reminding our-selves of a few basics that are especially relevant when considering MAOIs. From my perspective these are as follows.

First, drugs that have specific effects on only one transmitter are generally less effective, as exemplified by SSRIs, and NRIs like reboxetine.

Second, drugs with a true dual effect, and that may **exclude** duloxetine and venlafaxine (which fall short as NRIs, see specific commentary is about this) but certainly does include clomipramine, are almost certainly more potent.

Third, drugs that effect all three systems, i.e. including the Cinderella transmitter, dopamine [47], are even better.

The non-selective irreversible MAOIs are the only drugs have that 'triple effect', and indeed appear to be generally the most powerful.

There have been mutterings about triple reuptake inhibitors, with various drugs in various stages of trials (e.g. Liafensine). Some have already 'failed'. In my view this is an absurd idea, since we simply do not know what relative potencies in the different pathways are optimal. The chance of synthesising such a drug with an ideal ratio of potencies would be impossibly difficult, if not plain impossible: a hiding to nothing. Furthermore, the optimal balance needed in different people and types of depression is sure to be different. Use the flexible regime with sertraline, nortriptyline and methylphenidate, or similar (I am not stating that definitely works, or is definitely better, merely that it is the logical way to go about experimenting).

> The idea of a single drug that is a triple reuptake inhibitor is absurd

One might also point out that the K_I potency that is associated with significant clinical activity for different drugs is largely unknown, that is why I have used serotonin toxicity data, in this paper [48], to elucidate that question as far as serotonin is concerned. That indicates a K_I potency in low single figures is necessary for significant clinical activity. That tells us that none of the TCAs are 'dual-action' except for clomipramine: and clomipramine has the best evidence for superior efficacy.

Non-MAOI dopaminergic drugs

What non-MAOI drugs are there that reliably elevate DA, that can be used either by themselves, or in combination? This is a relatively neglected area. One or two recent reviews advance the cause [49-51]. See also my specific commentaries on MAOI and stimulant drugs.

In summary, there is clearly persuasive evidence that various dopaminergic drugs ('stimulant' is a term that should be retired) can be used with care to effectively and safely augment MAOI response. And, in the spirit of respecting clinical experience, and elevating it to its appropriate place in forming opinion, one should note that a number of members of my International MAOI expert group

would confidently endorse the potentially life-saving effectiveness of such intervention in patients with severe depression.

Methylphenidate

One long-used and often forgotten drug is the **dopamine reuptake inhibitor** methylphenidate: there is persuasive evidence, from a respected research group, that it can be specifically effective in melancholic depression [52, 53].

> Methylphenidate: Human cloned receptor affinities, DAT 40 nM, NAT 350, SERT 10,000 (i.e. inactive)

There is more information about this in specific commentaries on MAOI and stimulant drugs.

Many interesting, but unaddressed, research questions remain to be answered.

This discussion brings us to the important question of **'neuroscience-based nomenclature'** [54-59]. In other words, talking about drugs according to their pharmacological action, not according to the arbitrary names attached to them, often by the marketing arm of the pharmaceutical company, not pharmacologists.

> Tricyclic antidepressants are not a pharmacologically homogenous group, neither are the 'stimulant' drugs

Thus, discussions of drugs that might be added to MAOIs, on the general presumption that they are 'stimulant' amphetamine-like releasers and dopaminergic and addictive, and dangerous are misleading.

Interactions and toxicity

Another slight digression is in order: my observations from a consideration of these kinds of serious drug interactions, and particularly my studies in serotonin toxicity, is that one can make a generalisation — it is this: interactions between MAOIs and releasers generally produce more profound perturbations of neurotransmission and greater toxicity than do interactions between MAOIs and reuptake inhibitors. This appears to be the case across the three neurotransmitter pathways, serotonin, noradrenaline, and dopamine. Presumably this tells us something about the production and regulation of neurotransmitters in these different pathways, and the system's sensitivity to the perturbations thereof, but I have never seen any discussion of this most interesting question. It also suggests that if a dopaminergic agent is required, as an addition to an MAOI, then methylphenidate is theoretically the drug of choice. Modafinil is discussed elsewhere (in the commentaries on MRIs and stimulants), but may be regarded as a dopaminergic drug with useful alerting properties that is safe in combination with MAOIs.

Dopamine: The Cinderella effect

Once upon a time a little orphan molecule called Dopar was adopted by a wicked uncle called Big P. Harmer*: he was fat and greedy, and his wife was a selfish and dishonest; they had two children of their own, Serotee and Nora (who were mean and lazy and did hardly any work round the house and rarely helped other people). They mollycoddled and spoilt their own children and spent a lot of money on them and sent them to lots of beauty pageants, especially Serotee, who was pretty and fashionable. Poor little Dopar was confined to the house doing menial jobs and was neglected and forgotten: until one day …

* Several people have told me they did not realise that 'Big P. Harmer' is a homophone for big Pharma!

I have written elsewhere about this puzzling neglect of dopamine in neuropharmacology research. My earliest recollection of relevant discussion about the role of dopamine in depression is the dimensional interpretation advanced by Van Praag [60, 61].

In animals, even low doses of DA antagonists impair reward-related behaviours [62, 63]. Therefore, one might suspect that small changes in dopamine transmission are clinically relevant. Reducing dopamine is bad for depression, increasing it is good. For further details on this question see the above referenced commentary 'Bupropion: still hazy …'.

There is much evidence that low dopamine activity is an important part of severe depression: one would have to regard the current fashion of using antipsychotic drugs, which lower dopamine levels, as being inadvisable, from a theoretical viewpoint.

> Using antipsychotics, which lower dopamine levels, is inadvisable: some might say contrary to knowledge and logic

It is the dumbest thing psychiatrists have done in a long time, and the one based on the lowest-grade, and the most biased, evidence. Clearly, this new generation of antipsychotic drugs is one of the biggest money-earners for big Pharma (we are talking about hundreds of billions of dollars), in a time when new drugs are thin on the ground: I don't think you have to look far to see where the drive behind this, and misdirection about it, is coming from.

One can only speculate about the reasons for this neglect of dopamine in research — incidentally, I do not think it is to do with the contents of the above paragraph, because I do not think they are that smart. It may be that concern relating to addiction has played a part in regulatory agencies discouraging research and approval of drugs elevating dopamine, a bit like cannabis and LSD. There was a report a while ago about a dopamine reuptake inhibitor that was discouraged because of concerns it might have the 'side-effect' of excessive libido, with the potential consequences that might entail. Such concerns are not unfounded, and one is reminded of the increasing problems being recognised with the direct dopamine agonists (like pramipexole), centring around gambling and inappropriate excess sexual activities. These have been reviewed recently in an article with the revealing title '*Don't ask, don't tell*' [64]. The slow emergence of recognition of such side effects reflects the general tendency of doctors to shy away from asking difficult questions, like questions relating to suicide and sexual activity. There may be a tendency for neurologists (who are the biggest users of such drugs) to be less 'people-orientated' (a polite way of saying 'below average social skills') and more inclined towards the perfectionist, or even obsessional, end of the personality spectrum. This exacerbates the difficulties of collecting deeply personal information. I speak from experience: in the early stage of my career, I worked in the sex therapy clinic, my co-therapist was the professor's wife, and I gained experience in helping doctors-in-training interview patients about sexual matters.

Methylphenidate and methodology

The papers cited above by Professor Parker are not controlled trials. In my view that does not make them any less valuable. Readers may be aware that I have argued repeatedly that the supposed superiority of randomised controlled trials is seriously over-rated — I have written extensively about that elsewhere. In this context I would mention that Sir Austin Bradford Hill, a statistician, and a fellow who might have got a Nobel prize for his work on smoking and cancer said:

> Randomization and blinding [and statistical analysis] of studies is only necessary when treatment effects are small

His report on occupational diseases of workers in the cotton mills contained multiple tables of data, but not one single statistical test! He stated explicitly that the differences were obvious, and statistics were unnecessary.

> You do not need an RCT to tell you that parachutes work [65].

Doctors and researchers have become hypnotised by statistics and P-values to the point of losing their ability to think scientifically. If the chronic P-value fiasco of the last 30 years does not convince you of the value of Bayesian reasoning, then nothing will.

It is important for younger researchers and doctors to appreciate that experienced people regard careful systematic observations of clinical experience as being of equal value to RCTs, even more valuable, especially for severe cases that are inadequately represented in clinical trials. Clinical trial methodologies, geared towards obtaining FDA approval for drugs, are ill-suited to answering the more sophisticated questions relevant to serious research*. I expect that is why Professor Parker did not trouble to do a double-blind trial.

In conclusion

MAOIs appear to be the most powerful antidepressants we have for serious cases of depression, especially melancholic depression; including when ECT has failed.

They are safe with, and compatible with, methylphenidate, and some other simulant drugs.

These sever types of depression appear to have even more involvement of dopaminergic pathways that less severe illnesses, and therefore require drugs that boost all three neurotransmitters, but especially dopamine, without which full remission is unlikely.

The long-running neglect of dopamine's role is reflected in the irony that the only reuptake inhibitor that acts specifically on dopamine (methylphenidate) is not classified as an antidepressant; it deserves to be used more often in severe and melancholic depression.

Much of the above discussion emphasises the usefulness of neuroscience-based nomenclature which should have been instituted long ago (see my 2006 TCA review, Table 6)).

The scene is thus set for understanding how and why MAOIs are important despite being unappreciated for so long, longer than Cinderella.

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* In a separate commentary I explain in detail how RCTs are unable to address the key question of mechanisms and causality. That is what science is about, without causality science is nothing.

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