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Meta description (<300 char/~50 words)	An overview of the advantages and disadvantage of MAOI drugs, especially compared to modern alternatives, which are often less effective

Monoamine oxidase inhibitors: Perspectives and pros and cons

Introduction

Full details of the interactions between MAOI drugs and other drugs are dealt with separately, and in full detail, in the various other commentaries in this MAOI section. Below are some general comments about MAOIs in relation to the principles of drug interactions, and their safety relative to other drugs.

Some of their peripheral benefits, both established and supposed are covered.

The place of MAOIs in treatment

A brief survey about the place of MAOIs in modern practice provides perspective and reveals the disproportionate influence on doctors' prescribing practices of 'promotion' in its various and often deceitful guises. The pressure to influence doctors to prescribe new drugs has been driven by pharmaceutical companies and has been hugely successful. It is a triumph of commercialism, barely restrained by ethics or considerations of patient benefit. The commercialism and advertising that now dominate science, to such a disproportionate extent, are regarded by many as a great problem. Sponsored scientific articles (which includes most RCTs) have been dubbed 'McScience' and these publications are, regrettably, new reality, as the erstwhile Lancet editor warned us [1, 2]:

> Journals have devolved into information laundering operations for the pharmaceutical industry

Part of this process of promoting new more costly drugs is the necessary advertising manoeuvre of emphasising how they are better. In the current risk-averse climate, that often means supposedly safer. The other side of that coin inevitably means that previously existing drugs must have their disadvantages,

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even if these are imaginary, exaggerated and repetitively detailed by drug representatives who are selling new drugs to practising doctors.

> It takes years to establish the safety record of a drug, the statement that a new drug is safer is oxymoronic

This drug detailing and promotion process must, perforce, emphasise how they are safer and better than 'old and dangerous drugs' — no matter how false that narrative is.

Usage of MAOIs

The incredibly low rate of prescription of MAOIs is starkly incongruent with the fact that they are recommended and endorsed by many reviewers and in many recent guidelines about the treatment of depression [3-18].

Yet only a tiny fraction of specialists ever use MAOIs [11, 15, 19, 20], despite opinion and evidence of their superior effectiveness for various groups of patients [13, 17, 21-25].

My international expert group on MAOIs has published an editorial statement on this subject, co-signed by >80 experts, which we hope will influence increased usage [26], and is in the process (March 2022) of producing an international guideline for the use of MAOIs, to be published in a prominent journal.

MAOIs are not dangerous

It is common to hear and read of MAOIs being described as 'dangerous'. That is neither correct, nor logical, nor reasonable, especially when you compare them to the various long-term complications of SSRIs and side-effects that have only emerged since they have been in use for longer. These include the tendency to increase bleeding time and increase the morbidity from all sorts of blood loss events — see other commentaries for further information.

MAOIs are not more risky than being ill with unresolved, or incompletely treated depression, because, not only is the life-time risk of death by suicide around 10%, but also the **Standardised Mortality Ratio SMR** (which includes death from other causes than suicide) is as much as 10-30 times elevated [27-38].

> Standardised Mortality Ratio for depression is 10-30 times elevated

The view has been argued by the eminent medical historian, Edward Shorter, that the dangerousness idea was encouraged and spread by pharmaceutical companies extolling the virtues of newer drugs [39], and that necessarily involves exaggerating the disadvantages of previously existing drugs. I have no doubt that is correct. A white paper by White and Simpson for the ACNP (adopted as an official 'position statement' in 1981) used the word 'superstition' to describe the concern about the risks of MAOIs — and they have become safer since then, for various reasons.

Tranylcypromine has no clinically relevant pharmaco-kinetic interactions (in usual doses) and phenelzine has few, certainly few that are at all likely to be clinically significant [12], which makes them better, in this respect, than most of the SSRIs and some other newer drugs.

Many miscellaneous benefits

Therapeutic hypotensive effect of MAOIs

> **Myth**: MAOIs cause hypertension and should not be given to hypertensive patients.

MAOIs lower blood pressure. The notion that MAOIs raise blood pressure is a widespread misconception, and one of the commoner incorrect statements you will see. That is incontrovertibly incorrect: it is only the interaction with releasers like tyramine that produces hypertension.

In the 1960s MAOIs were used to treat hypertension, until better drugs were found [40-42], and indeed using MAOIs for those suffering both depression and hypertension works well.

> In the 1960s MAOIs were used to treat hypertension

The still repeated, but incorrect, prohibition about giving MAOIs to patients with pre-existing hypertension is thus another example of ignorance about pharmacology. Again, the basis on which this opinion has insinuated itself into the literature is impossible to pin down. It appeared and was unthinkingly repeated by the pharmacologically ~~ignorant~~ less informed, perhaps because it sounds sensible and responsible. The post-Parnate-withdrawal hysteria (1964) created fertile ground for such admonitions. Having been repeated often, it became 'received clinical wisdom', and even 'expert opinion'.

> Expert opinion can be a capricious beast, regard it with circumspection — including mine

Other therapeutic benefits or uses

Neuroprotective, anti-parkinsonian (better than rasagiline or selegiline), anti-migraine, anti-hypertensive, anti-epileptic, narcolepsy

> MAOIs have fewer problems from pharmaco-kinetic interactions than most of the SSRIs

Thus, TCP constitutes an excellent treatment for older patients with prodromal Parkinson's, accompanied by depression, who also have hypertension! And it may also have a neuroprotective effect and slow progress of Parkinson's and dementia.

MAOIs: Interactions and other quirks

> Science must begin with myths, then progress to the criticism of myths
>
> ~Karl Popper

Myth: MAOIs have many problematic interactions with other drugs

Interactions

The potentially risky interactions with MAOIs are pharmaco-dynamic:

- Serotonin syndrome, only caused by SRIs + MAOIs
- And the other, blood pressure elevation, less risky, caused by tyramine in food, or by the releasers like ephedrine

SRIs are easy to identify and avoid. Releasers are rarely used therapeutically and rarely cause reactions sufficiently severe to be high-risk — nevertheless it is important to avoid them, because:

1) they are not necessary treatments for any significant or severe illness
2) although the risk is low, the seriousness of the outcome is, however rarely, potentially serious (subarachnoid haemorrhage).

Doctors have been beguiled that MAOIs are difficult to manage? I hardly think so.

> The requirement, a simple requirement, is to learn which drugs are SRIs and which are releasers — then it is plain sailing

Standard texts and contradictions

It is helpful to understand why my commentaries, and my review papers, contradict what is said in standard textbooks and other similar sources (e.g. Physicians' Desk Reference, British National Formulary, Australian Medicines Handbook etc.). First, many of them are simply wrong. Second, such publications cover a wide field as concisely as possible. They therefore abbreviate and generalise to an extent that does not allow detailed evaluations. For example, such sources usually lump tricyclic antidepressants together as being contraindicated with MAOIs. Such texts have insufficient space to discuss the more precise considerations detailed in review papers. The view that the average doctor cannot understand such subtleties may also be a factor.

MAOI interactions are now clearly **understood***, **they are reliably predictable**, and they are straightforward to avoid — readers may note that I have published widely concerning both pharmaco-kinetic and pharmaco-dynamic interactions, and the cytochrome P-450 characteristics, of anti-depressant drugs.

Consult those papers if you wish to attain greater understanding of this subject. They provide the back-ground knowledge for understanding these interactions. See particularly my review, '*CNS toxicity involving methylene blue: the exemplar for understanding and predicting drug interactions that precipitate serotonin toxicity*' [43], which is my most recent summary of what needs to be understood to be confident about avoiding ST.

For other aspects of interactions, or rather, lack of them, see also: [12, 46-52]. There is an updated summary about the lack of interactions between MAOIs and TCAs here.

'Spontaneous' hypertensive episodes

One occasionally sees patients who do get brief (symptomatic) episodes of hypertension (but not hypertensive emergencies) lasting a couple of hours, most often following the second dose of the daily regime of MAOI. I estimate about 5% of MAOI takers. This seems to occur more often with TCP than with phenelzine or isocarboxazid. There are only a few reports in the literature [53-56].

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* As a matter of historical record and to recall the admonitions about learning from history — both the 1964 JAMA editorial [44], which used the word 'hysterical' (with which I agree) and Blackwell [45] opined that the American reaction of taking Parnate off the market (for six months in 1964 — the British did not follow suite), was way 'over the top'. Blackwell correctly pointed out that the 'cheese' reaction should have been anticipated from pre-existing research (cf. Marley); and I have said the same about the imipramine/MAOI interaction (i.e. ST), it took another 30 years before that began to be properly understood. Psychiatrists have a poor record as students of pharmacology. It was ever thus — something about which they should be ashamed. It is poor knowledge, combined with a therapeutically pusillanimous attitude, that is largely responsible for the enduring negative and timorous approach to MAOI use (it is 'too difficult' for most of them).

Modestly priced automatic BP machines are available, that patients can use at home, it is becoming evident that modest degrees of post-dose BP elevation may be more common than was previously realised

In my experience this usually gets less over a few weeks. If such elevations are problematically high, symptomatic, or enduring they will be controlled by giving propranolol with the MAOI dose (see detailed separate commentary), that also helps reduce exercise-induced postural hypotension by antagonising the noradrenaline beta-receptor-mediated vaso-dilation (in muscle vasculature).

However, there may also be another (presumably small) group of patients in whom such BP elevations are related to occult phaeochromocytoma, and I have encountered such a case. One or two cases have been reported in the literature [57, 58]. If such elevations are occurring outside of the 1–4 hr. post-dose 'window' then it is suggested that investigations for occult phaeochromocytoma, such as a high-resolution scan of the adrenals, should be undertaken to try to rule out a small adrenal tumour. MAOIs will magnify the pressor effect of even a small tumour.

Stopping and swapping, easier than supposed

On ceasing SRI-type antidepressants to start MAOIs, washout intervals varying between one and five weeks may be required. No washout is needed for non-SRI-type drugs. The rule of thumb is to allow 5 half-lives to elapse*, which is about one week for many of these drugs). This subject is dealt with in detail in other commentaries.

Swapping from one MAOI to another MAOI

The requirement or desire to swap from one MAOI to another MAOI is something that will be an uncommon occurrence. Furthermore, it will be an urgent need even more rarely. This subject is dealt with in detail in other commentaries.

Hypertension and the indirect relationship to subarachnoid haemorrhage

See my detailed and updated commentary on this subject.

Deaths from tyramine/MAOI induced hypertension are *extremely* rare. Indeed, there have been no deaths from MAOI induced hypertension reported in the medical literature for decades (NB I am not suggesting that they have not occurred). When De Villiers [59] reviewed this in the UK at the time Parnate was withdrawn in the USA (1964) he noted that of 21,582 treated with MAOIs (between 1960 and 1964), 2% developed headache, 0.27% had the 'hypertensive syndrome'. Fourteen deaths were reported in Great Britain out of an estimated one and a half million patients treated since the introduction of the drugs in 1960. The estimated risk for a patient treated with tranylcypromine was: for headache 2%; for hypertensive crises 0.5% and for death 0.001%. Note that this was when foods had much higher tyramine levels and *before* tyramine-restricted diets and an understanding of the pressor response.

Furthermore, if one considers the reduction of tyramine in foods these days, and the better dietary advice now available, then the incidence of *serious* hypertensive events is likely to be exceedingly low. Indeed, it is so low that it may be hard to distinguish from the background rate of spontaneously occurring subarachnoid haemorrhage in the general population.

The detailed commentary reviews many physical activities, both indoors and out of doors, which raise blood pressure to 200-250 mmHg, including marathon

running and vigorous sports and weight lifting (BPs are as high as 450 mmHg) [60-64], and the lack of association of any of these BP elevations with significant risk of SAH.

It is important to maintain a clear perspective on the issue of acute BP elevation (which is an over-concern with many doctors).

It is an irony that an SSRI side effect that most doctors do not even know about, or think about, may cause far more deaths than the feared 'hypertensive crisis'.

What the eye does not see, the heart does not grieve over, Proverb

Irony: SSRI increased bleeding risk may cause more deaths than MAOI induced hypertensive emergencies

Non-therapeutic/illicit drugs

Those requiring information about non-therapeutic/illicit drugs are advised to be wary:

1) there is a lot of misinformation in medical texts and on the net.
2) Some interact potently with MAOIs, because they are potent releasers of serotonin, dopamine and or noradrenaline [65]: e.g. the interaction of moclobemide and MDMA is predictably toxic (causing fatal ST) and has caused a number of tragedies [66, 67].

Note that combinations of releasers with re-uptake inhibitors will result in diminished effects/efficacy: for example, SSRIs will diminish the effects of 3,4-methylenedioxy-methamphetamine (MDMA, ecstasy). For further explanation about this see my review [43].

The following papers contain information and further references about 'designer' and novel psychoactive substances [65, 68-71].

Medically, such possible interactions are only likely to be seen as presentations to emergency departments and are unlikely to be relevant to usual therapeutic practice.

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