

## MAOIs: swapping and combining

### Abstract

Swapping and combining to or from MAOIs and other anti-depressant drugs is simpler than many sources would lead one to suppose. It is useful to be confident about how to do this so that when patients need to transition from one treatment to another chance of relapse and exacerbation of distressing symptoms is kept to a minimum. The groups of drugs which must be avoided in combination, or close proximity, with MAOIs are those drugs that have potent activity as serotonin reuptake inhibitors. That is, the SSRIs, and the SNRIs. Other antidepressants are perfectly safe. Other supplementary treatments, including antianxiety drugs and sleeping aids, are all perfectly safe. As always, when combining different drugs, it is wise to adhere to the old mantra, start low, go slow, and only change one drug at a time.

### Introduction

This commentary covers swapping and combining from or to MAOIs and other AD drugs, (swapping from [MAOI>MAOI is discussed here](#)), it overlaps with various other commentaries, which is **inevitable\***. Also, that repetition and overlap consolidates ones knowledge and understanding.

**Myth: There are many drugs that are 'dangerous' if combined with MAOIs**

Interactions, swapping and combining involving MAOIs is not difficult.

There are *no* significant pharmaco-kinetic interactions that involve MAOIs [1, 2]. There are however many with the SSRIs and the SNRIs, in this respect MAOIs are superior and easier to use.

Learning about interactions is interesting (I think it is fun) and helps one to master the principles of clinical pharmacology that are of wide applicability.

Once interactions are understood then swapping and combining drugs is simply the practical application of that knowledge. There is a lot of misinformation in the psychiatric literature on this subject, largely because psychiatrists' knowledge of clinical pharmacology is not good.

There are no significant pharmaco-kinetic interactions and only two possible pharmaco-dynamic interactions: 1) ST and 2) pressor response. That is: nothing else.

How hard is that?

**Indeed, less potentially dangerous interactions than fluoxetine**

**1) ST** is the only serious interaction involving MAOIs that is ever likely to be encountered these days.

**2) The pressor response** of increased blood pressure (BP) is the other interaction that caused much consternation in the past. It involved the 'releasers' that in the past were found in over-the-counter drugs such as cough and cold remedies. These drugs have largely been withdrawn from the market and most cough and cold remedies now contain oxymetazoline (an  $\alpha_1$  adrenergic receptor

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\* Note: this is primarily about the non-selective irreversible inhibitors, tranylcypromine and phenelzine and isocarboxazid. Other MAOIs such as rasagiline, selegiline, and moclobemide have even less interactions (see below).

agonist, which is safe), but not ephedrine-like drugs: e.g. ‘Sudafed’ used to be pseudo-ephedrine but is now replaced by ‘oxymetazoline’, badged as ‘Sudafed OM’. Where ephedrine-like drugs are occasionally still available they should be avoided, but ordinary therapeutic doses are unlikely to lead to *serious* harm: it is overdoses of such drugs that are likely to be seriously harmful. As would be expected, from an understanding of the mechanism of action, the same applies to amphetamine.

**Serotonin toxicity (ST)** is caused *only* by the co-ingestion of **serotonin reuptake inhibitors (SRIs)**. Therefore, avoid ‘SRIs’ (with appropriate ‘washout’ intervals), i.e., both SSRIs and SNRIs, and you are 99% of the way there in terms of avoiding problems. There are one or two other drugs that are not generally regarded as SRIs, but which do have sufficient SRI potency to be problematic (see below, and other commentaries on my site for details).

Contrary to the opinions expressed in many texts, various other purportedly ‘and you should see a screen similar to the one **below**.’\* drugs are not significant SRIs — such as trazodone, mirtazapine, lithium, buspirone, tryptans etc., see below for full list — and are not a risk for ST interactions: these references contain detailed evidence relating to these issues [3-6].

The first general principle to keep in mind is that ST (when caused by MAOI/SRI combinations) is much more likely to lead to serious harm than is the pressor response to tyramine — or other releasers.

Even a single therapeutic dose of a potent SRI is likely to lead to a serious (i.e., putting someone in hospital) or even fatal ST reaction.

Reminder — ST is not an idiosyncratic reaction but a **predictable dose-related interaction**. That is why for years it has been my contention that it is nonsensical to speak about ST being ‘rare’. Strychnine poisoning is rare, except in people who have taken strychnine.

In contrast, a single *therapeutic* dose of releaser is *extremely unlikely* to lead to a seriously harmful outcome due to a pressor response. In most cases of releaser-induced pressor responses nothing will be observed, and occasionally a brief episode of hypertension will result, which will not do any harm. There is a great difference in the risks produced by these two different reactions. Another noteworthy difference is that episodes of hypertension have potential serious or fatal consequences only for a small fraction of the population. That is because subarachnoid haemorrhage only occurs in those predisposed to it by virtue of a pre-existing vascular abnormality.

Everyone is susceptible to ST, only a fraction of the population are susceptible to SAH from a brief episode of hypertension

The other major difference between the two reactions (ST and pressor) is that potentially dangerous SRI antidepressants are frequently going to be encountered in patients who might be considered for treatment with MAOIs (like leftover supplies of SRI-type medication in the bath-room cabinet), whereas the need and frequency of use of drugs that are potent releasers is rare in modern practice. Therefore, the releaser/pressor-response scenario is both infrequent and unlikely to lead to serious trouble.

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\* Serotonergic is a poor and misunderstood term: strictly speaking it means effecting serotonin neurones. However, it is usually (mis)used to mean serotonin-enhancing (as opposed to serotonin-blocking). Add that to the pharmacological confusion and you have chaos. Yes, in a sense mirtazapine is a ‘serotonergic’ drug, but an anti-serotonergic one that lessens manifestations of ST, not exacerbates them.

## Swapping and combining

It is commonly thought and stated that it is problematic to change from one drug to another when one of them is an MAOI. In practice this is simply not a difficulty.

If you know how to combine drugs, then you know how to swap safely.

Combining TCAs and MAOIs serves as a good teaching example to illustrate some key points. These two classes can be safely co-administered, except for clomipramine and imipramine which have significant potency as SRIs. It is only SRIs that are a problem — nothing else.

Incidentally, I must mention here that there is no sound evidence that the order in which MAOIs/TCAs are given, if used in combined treatment, makes any difference to side-effects or safety. That notion was pure speculation contained in one of the reports in the 1960s. This became established in the literature with no facts to support it, promulgated by ‘ignorant experts’.

There continues to be a great deal of misinformation about combining drugs in the psychiatric literature, and as above, it is often without a factual or even a theoretical basis. Some recent examples of one or two basic errors are in a paper by Palaniyappan et al. that was specifically directed at professional education for specialists [7]. I published a response to that [8]. Anyone interested can read the relevant material, including the authors’ response to my criticisms, but I do not particularly recommend that as a good use of your time. [link to free pdfs in the references below].

It is not always individual psychiatrists who are solely to blame for their lack of knowledge, what they are presented with for educational reading, even by independent and supposedly authoritative sources, such as the UK Royal College (Palaniyappan [7], above), is not always of an impressive standard. That reflects the problem I often allude to — the poor pharmacological knowledge of most psychiatrists.

### *The example of imipramine*

Imipramine is a useful example to understand because throughout the history of psycho-pharmacology it has been a focus of confusion (likewise pethidine, aka meperidine). Some authorities (e.g., in Germany) still express the view that it is not contraindicated to combine imipramine with MAOIs.

The confusion about this arose in the early 1960s because a serious interaction with IMI occurred only infrequently, and it was not understood or distinguished from the pressor response to **tyramine**\*. The ST reaction only occurs sometimes because imipramine is a relatively weak SRI and therefore in smaller doses, or in people who have low blood levels, it does not cause excessive serotonin-mediated side effects or toxicity. However, the blood level only needs go up a little and then symptoms of increasing serotonin-mediated side-effects or overt serotonin toxicity *rapidly* develop. An *overdose* of imipramine combined with an MAOI will frequently lead to serious ST and may prove fatal. An example of a fatal case is provided in the report by Otte et al. [9].

Imipramine is ‘on the cusp’ SRI-potency-wise. Drugs more potent than imipramine as SRIs are likely to precipitate ST and drugs that are significantly less potent do not (there is more detailed consideration of this in various of my peer-reviewed papers).

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\* This patient would almost certainly not have died had they known how to diagnose and treat ST (which, frankly, they should have known, especially since the incident was at a ‘teaching’ hospital).

For the record, as it were, here are refs to some of the old cases of ST in the 1960s involving MAOIs with imipramine: [10-17]

Because the relative SRI potency of these different drugs (TCAs and opioids like pethidine etc.) was not recognized back in the 1960s, and those reactions were confused with the pressor response, this led to uncertainty and a blanket prohibition about combining these two classes of drugs (which is still repeated in many sources), and about analgesics and anaesthesia. Modern knowledge resolves these uncertainties even if some current texts have not caught up yet.

The simple requirement is to learn and remember which drugs are significantly potent SRIs — which competent clinicians probably know already. This would be easy if drugs were labelled correctly according to their pharmacological properties, but that is not the case, because they are labelled more according to marketing imperatives, not pharmacology. Nevertheless, it is not that difficult to sort the sheep from the goats (see below).

Obviously, the ‘SSRIs’ and the ‘SNRIs’ are ruled out.

There are a few drugs on the market in the last few decades which have been stated to be ‘serotonergic’ but which **do not significantly elevate serotonin and are therefore safe**. That is marketing for you. I have written extensively about that, and the proto-typical example is mirtazapine. It is not a ‘serotonergic’ drug and is perfectly safe with MAOIs.

Mirtazapine is safe with MAOIs

## Swapping and bridging candidates

When swapping drugs, it may sometimes be appropriate to stop one before starting the next one, with appropriate washout intervals. However, this is rarely **necessary**. It is often preferable to bridge or overlap the two, decreasing one whilst increasingly the other. I have done this in hundreds of cases without any problems.

It must be remembered that when both drugs are non-MAOI drugs then pharmacokinetic interactions may need to be taken into consideration. That is one of the reasons why nortriptyline is a good candidate, because it is less likely than most other drugs to have a significant pharmacokinetic interaction.

The only time when ‘overlapping’ cannot be done is when one wishes to swap from an MAOI to an SRI (and vice versa) and that is when a ‘bridging’ strategy is especially useful.

The TCA nortriptyline is, pharmacologically speaking, a good and flexible candidate to fulfil a ‘bridging’ role. For instance, if one is changing between an MAOI and (des)venlafaxine, which can have marked withdrawal symptoms, co-administering **nortriptyline\*** prior to reducing or ceasing the venlafaxine, may both reduce withdrawal symptoms and act as a bridge (to reduce the chance and severity of any relapse) prior to the initiation of the MAOI. The same process works in reverse where nortriptyline can be added to a pre-existing MAOI, the MAOI is then stopped and most subsequent treatments can then be initiated with ease.

The strategy I used frequently was to add **sertraline\*\*** to the nortriptyline, once the MAOI was out of the system, to get a good SNRI effect.

One should note here, that using two separate drugs (e.g., Sert + NTP, instead of an ‘SNRI’ like venlafaxine) makes ‘stopping and swapping’ easier because one

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\* One could equally use mirtazapine, doxepin, amitriptyline, quetiapine, (but not ziprasidone), mood stabilizers: in short, anything you favour that is not an SRI. And with no worries about pharmacokinetic interactions. How difficult is that!

\*\* Why sertraline? Because, like nortriptyline, it has the most favourable pharmacological and pharmacokinetic characteristics of the drugs in its group. That is something I have been saying for a long time, and I notice now that a number of more recent reviews put forward the same argument.

can raise and lower or cease each element separately. That may also assist in minimising side effects.

Some people seem to prefer using a single drug, such as (des)venlafaxine, milnacipran or duloxetine to get a dual effect, but I suspect that prejudice has got a lot to do with habit, and unfamiliarity with pharmaco-kinetic considerations concerning interactions.

I found using two different drugs, the individual doses of which could be adjusted to optimize efficacy vs side-effects, was a better strategy and more successful (and and you should see a screen similar to the one below.cheaper). Perhaps effects other than the NRI effect may contribute to the benefits conferred by nortriptyline. I have certainly seen many patients who have failed to respond to venlafaxine who have subsequently responded to the combination of sertraline and nortriptyline. But rarely the other way round.

It was postulated some time ago, on a sound pharmacological basis, that TCAs, by virtue of their NRI potency, attenuate the ‘cheese effect’ [28-30].

I assembled and explained the evidence for this in my TCA review [31] which concluded that the NRIs with the *high* affinity for the NAT (viz. reboxetine, atomoxetine, desipramine, oxypropraline, protriptyline and nortriptyline) have been demonstrated to block the pressor response to tyramine [28, 32-37], even when it has been potentiated in the presence of MAOIs [38-40]. Thank you! The early demonstrations of NRI attenuation of the pressor response to tyramine go back a long way, past learning seems to have been lost for a long time [41, 42]. NB Both those last 2 references are from the lab of the famous pharmacologist Bernard Brodie whose early papers are still worth studying.

This leads to the confident conclusion about an old and bitter-sweet irony: combinations of (non-SRI) TCAs or NRIs with MAOIs are not risky, they make MAOIs safer, not more dangerous, by attenuating the pressor response to tyramine, or any other NA releaser (ISA).

If a patient is more than usually tyramine sensitive, they will become less sensitive if a potent NRI like nortriptyline is added to the regime: the greater the dose the greater the attenuation of the pressor response. That is not a ‘theory’, it is pharmacological fact.

## Ceasing and half-lives

On ceasing any SRI-type antidepressant to start an MAOI, washout intervals varying between one and five weeks may be **required\***. No washout is needed for non-SRI-type drugs because it is safe to co-administer them (as above). The rule of thumb is to allow 5 half-lives to elapse, which is about one week for many of these drugs.

In practice 5 half-lives is a conservative approach. Most drugs will have lost sufficient SRI activity after two half-lives to allow cautious introduction of an MAOI — providing the patient can be observed for early signs of serotonin-mediated over-activity.

Such signs are: 1) specific; tremor, hyperreflexia and clonus. Less specific; GI overactivity, mydriasis, sweating, anxiety, restlessness.

Should such symptoms be apparent it is simple enough to withhold the MAOI for a few more days and then try again. ST is a dose related phenomenon, and the emergence of serotonin-mediated signs or symptoms is a cause for caution, not panic.

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\* Fluoxetine (via its metabolite norfluoxetine) has an elimination half-life in some people of up to two weeks (it can take up to 10 weeks to get out of the system). See any good pharmacology reference book for a table of half-lives, or on the net look at: <http://www.health.harvard.edu/diseases-and-conditions/going-off-antidepressants>

*Other drugs with significant SRI potency\*\**

Vortioxetine, vilazodone, ziprasidone

Chlorpheniramine (aka chlorphenamine) Brompheniramine.

Pethidine, tramadol, dextromethorphan, dextropropoxyphene (fentanyl is safe).

*Other safe drugs (with insignificant SRI potency)*

Mirtazapine, mianserin, doxepin (now re-badged — correctly — as an anti-histamine-type ‘hypnotic’), trazodone, nefazodone, buspirone, bupropion, reboxetine, atomoxetine, amoxapine, agomelatine, tianeptine.

Lurasidone, quetiapine, aripiprazole, olanzapine, asenapine, and other neuroleptics.

Methylphenidate (it is not a 5-HT releaser or uptake inhibitor), amphetamine (it is a releaser, but may be used cautiously, ‘start low, go slow’ is the mantra to remember), the new preparation ‘lisdexamfetamine’ may be an advantage owing to its better pharmaco-kinetic profile.

Lithium, carbamazepine, valproate, lamotrigine.

L-tryptophan (start low viz. 1 gram)

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\*\* Other than: ‘anti-depressant’ SRIs (viz. SSRIs and SNRIs). See more detailed info in other commentaries on website

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