# CNS STIMULANTS AND MAOIS, PART 2


## Abstract

This commentary reviews papers updating knowledge about how MAOI interactions with amphetamine, pseudoephedrine and ephedrine, phentermine, adrenaline, midodrine, pramipexole, ropinirole, rotigotine, and caffeine manifest. It reviews the evidence concerning whether such interactions are problematic or risky.


## Introduction

Part one dealt with the reuptake inhibitors, methylphenidate, modafinil, and bupropion. This second part deals with amphetamine, ephedrine, pseudoephedrine, adrenaline, pramipexole, midodrine, caffeine.

Ecstasy (MDMA) is dealt with separately because it induces serotonin toxicity.

## Releasers

### Amphetamine

Recent papers about the mechanisms of action of amphetamine at the molecular level suggest why the combination of amphetamine with MAOIs is not unduly risky, as has been supposed. Care (**start low, go slow, and only change one drug at a time**), experience, and blood pressure monitoring are needed, but it can be done safely and with benefit for some patients, although increases in dose can have disproportionate effects.

> Good pharmacological practice — start low, go slow, change only one drug at a time

### Mechanisms

Amphetamines elevate extracellular dopamine — and therefore produce increased stimulation at post-synaptic receptors — via mechanisms that, until recently, remained unclear. Amphetamine is a potent DA releaser, and somewhat weaker NA releaser, at low nano-molar concentrations.

Its mechanism(s) of action, at a molecular level, and how it interacts with the monoamine transporters, principally the dopamine re-uptake transporter DAT and the vesicular monoamine transporter (VMAT), are now clearer [1-4], see also Part 1.

**At pharmacologically relevant concentrations** (human and rodent plasma levels of ~500-1,000 nM [5]), it is actively transported into the neurone via the DAT, and into the neuronal storage vesicle via VMAT, and exchanged with DA, thus raising DA in the neuronal cytosol. That diminishes the vesicle pH-gradient (vesicle 5.6 vs cytosol 7.2). It is then removed from the cell via the DAT in the process referred to as reverse transport.

Thus, to produce its effects, it must be actively transported by both the DAT and VMAT in tandem.

It now seems that neuronal trans-membrane lipophilic diffusion alone cannot deliver enough amphetamine to vesicles for these effects to occur, therefore amphetamine is a substrate of DAT and VMAT; it is not an inhibitor.

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Specific VMAT inhibitors, which have been developed (CYY477), block the effects of amphetamines [1] — note, reserpine, tetrabenazine, and valbenazine are relatively non-specific, which is why this mechanism has only been clarified recently, since the development of a specific VMAT inhibitor.

Dopamine synthesis occurs in the cytosol, it is concentrated in vesicles via VMAT by ~100,000-fold to a concentration of ~0.1M.

It acts as a weak competitive inhibitor of NAT & DAT (this is not a significant therapeutic effect) because it utilises the transporter to enter the neurone. Amphetamine has further actions once within the pre-synaptic cytoplasm, via the DAT[1], by promoting **extra-cellular efflux of DA (called reverse transport).** Furthermore, it increases cytoplasmic levels of DA by disrupting storage of DA in the vesicles through the vesicular monoamine transporter (VMAT).

Other reviews outline progress of relevance and importance, particularly aspects of TAA receptors and VMAT [1, 6-8]. The latest understanding of this is evolving, is complex, and a detailed analysis of that is beyond the scope of this commentary. Further details are in the references herein: [2-4, 9], Sulzer summed it up by saying:

> Dopamine neurotransmission is generally initiated by fusion of synaptic vesicles in axonal boutons, with the exception of release by amphetamine-like drugs that can release DA via reverse transport through the DA uptake transporter (DAT).

In brain areas (like the prefrontal cortex), with low expression of DAT, dopamine is handled by the NAT: note that may have implications for the effectiveness of NRIs in depression, and their interactions with MAOIs.

Sulzer's review of Amphetamine (and other drugs of addiction) is an intoxicating Pierian spring of knowledge* [3].

> A little learning is a dangerous thing; Drink deep, or taste not the Pierian spring
>
> ~ Alexander Pope

Amphetamine is 50-100 times **less** potent as a releaser for serotonin, than it is for dopamine (see table). Its 5-HT transporter affinity (~3800 nM) is inconsequential. However, unlike methylphenidate, there is animal work indicating amphetamine does modestly increase serotonin levels [10, 11] — the degree of this elevation is probably mild, see [12], except where an overdose has been ingested.

Amphetamine causes NA increases of a lesser magnitude (400–450% of baseline) compared to dopamine (700–1500% of baseline). This suggests that, used carefully, the risk of precipitating hypertension is low (as practical experience indicates, see Israel for a recent report and review [13]).

The advent of lisdexamfetamine may now add a layer of safety because its slow conversion to the active form (d-amphetamine) occurs in red blood cells by rate-limited enzymatic hydrolysis. This means the time to $T_{max}$ is longer and peak levels are lower, about half [14]. It also has a low potential for cytochrome P450 interactions [15, 16]. Not only that, but also the inter- and intra-subject plasma

[1] The DAT may face inwards into the cell cytosol, or outwards into the extra-cellular space — it flips between those two positions in order to translocate a dopamine molecule from an extra-cellular binding site to a cytosolic site, where it can dissociate from the transporter and diffuse within the presynaptic space

levels are less variable which produces a smoother and more predictable response [17]: how good does it get! An unusual example of the usefulness of a pro-drug. It is to be confidently expected that this combination (with MAOIs) will be safer than previous preparations [13, 15, 18-22].

Note that releasers can increase intra-synaptic transmitter concentrations by more than 100-fold, compared to a maximum closer to 10-fold with reuptake inhibitors [9] — cf. see Gillman [23] concerning such mechanisms of interactions involving RIs, releasers and MAOIs in the serotonin toxicity triangle in the introduction to ST.

## Clinical

Amphetamine and MAOIs have been in use together for 60 years, it is perhaps surprising there are few deaths, either from serotonin toxicity, or NA/DA toxicity, reported with the combination. Amphetamine has only weak serotonin-mediated effects [11]; there seems to be little or no risk of precipitating serotonin toxicity with therapeutic doses, if combined with MAOIs [24], and low risk with SRIs (see Prior et al [12][2]).

Deaths that only involve amphetamine (without MAOIs) are generally related to cardiac problems or cerebral bleeds without signs of serotonin toxicity (and about half of these cases seem to show pre-existing vascular CNS lesions). Elevated dopamine by itself can cause hyperthermia. The occurrence of hyperthermic deaths following amphetamine does not suggest, *per se,* involvement of serotonergic mechanisms [25, 26]: and, as with MDMA, it is rare, and usually related to other physical or environmental factors that promote hyperthermia, see Gillman [27] for a review of hyperthermic mechanisms.

There are various case reports of fatalities with over-doses of MAOIs and Amphetamine [28-34].

Clinical reviews with some general background are Feinberg, Rothman and Markowitz [13, 35-38]. These reviews illustrate the desirability of ensuring the clearest possible understanding of the distinction between different toxidromes; especially blood pressure elevation, due to tyramine or other releasers, as opposed to serotonin toxicity [35-38].

Markowitz has offered the opposing opinion [39] that: '*The interactions of monoamine oxidase inhibitors with psycho-stimulants represent one of the few strict contraindications*'. That is an ill-defined and poorly informed over-generalisation (based on outdated pharmacology (i.e. use of the term stimulant), and a small number of poor case reports, e.g. [40]).

As Paracelsus stated, '*the dose makes the poison*' and that certainly applies to amphetamine.

## Amphetamine summary

In summary, amphetamine may not be without some risk in combination with MAOIs at therapeutic doses, and would seem to produce noradrenergic

[2] Note that this last case (Prior) comes out of the stable of Professor Whyte who is a sort-of-colleague of mine (in that we have co-operated and written together because of our shared view and interest about serotonin toxicity). These guys are expert physicians, pharmacologists, and toxicologists who spend their time looking after overdoses in intensive care units, and they know what they are talking about. That makes this case report worth reading [12], as will be obvious if you note the meticulous reporting of key symptoms that are, or are not, present. The probable response to large doses of cyproheptadine is the icing on the cake, which suggests whatever the mix of elevation of noradrenaline and serotonin and dopamine, there was enough elevation of serotonin to justify suggesting the clinical picture was substantially mediated by serotonin. One would conclude that significant serotonin toxicity is indeed possible in certain circumstances with SRIs and amphetamine.

potentiation, and even toxicity; presumably in the same way as tyramine does, by acting as a releaser. There is now a lot of accumulated experience of the concurrent administration of MAOIs and amphetamine for therapeutic purposes in depression. It is safe when done carefully. Early concerns about frequent hypertension have not materialized and recent clinical reviews indicate judicious use is safe [35], and reports by members of the MAOI expert group accord with that conclusion.

Since amphetamine is substantially more potent than ephedrine it appears, by extension, that concerns over ephedrine may also have been over-stated. If taken in supra-therapeutic doses or overdose the situation may be different.

## Pseudoephedrine and Ephedrine

Ephedrine is a less potent releaser than amphetamine [37, 43, 44]. Pseudoephedrine is less potent than ephedrine.

Pseudoephedrine and Ephedrine, the archetypal drugs of concern, are still available for use in some countries, whereas, in others they have been replaced by oxymetazoline (which is a topically-used alpha-1A adrenoceptor agonist and does not interact with MAOIs). Previously they were components of cough and cold remedies. Reactions are unlikely to be severe or dangerous unless large (oral) doses are used (that usually means an overdose).

Adrenaline (epinephrine) and noradrenaline (norepinephrine) are (because they are the body's neurotransmitters that act at these receptors) direct post-synaptic agonists and therefore do not cause any problematic interaction with MAOIs — although downward dosage adjustment is likely to be appropriate, because of additive effects. Equivocation about that has been evinced repeatedly over the years in most standard texts and has caused mistreatment of patients e.g. [45], yet the lack of an interaction was established at the dawn of modern pharmacology by researchers whose names are prominent in history (Gaddum and Brodie, among others), early papers being [46-48]. That work has been forgotten.

The concern about cough and cold remedies and nasal decongestants is because of early confused reports in the 1960s, e.g., [49, 50] and because they may contain both SRIs (e.g. chlorpheniramine, and opioids like dextromethorphan, as well as releasers like ephedrine). Note that until the 1990s, and in some reports beyond, there was a failure to understand the toxidromic distinction between a risky pressor response and ST. That failure has caused much confusion — it endures in some (less-informed) circles.

The unrecognised irony was, until my 1998 review, it was not appreciated that the chlorphenamine (aka chlorpheniramine, an anti-histamine component in some OTC remedies) is an SRI, and therefore has definite risk for precipitating ST. Indeed, as I noted, chlorphenamine was a possible, but unrecognized, contributor to the death of Libby Zion in a much, but inaccurately, commented on case [41, 51, 52].[3]

As Rothman states,

> 'Historically, it has been difficult to distinguish whether drugs act as reuptake inhibitors or substrate-type releasers using simple test tube assays.'

[3] As a matter of record, I contacted the Doctor in charge of the inquiry report about the Libby Zion case. He was dismissive, rude, dogmatic, arrogant, and ignorant. It is a fatal combination when someone does not understand enough to understand how ignorant they are, and with the admixture of arrogance constitutes a disaster. Ignorance does not recognise itself in the mirror. The inquiry report was poorly informed.

But it seems established that ephedrine is only a weak 5-HT releaser [37, 43, 44].

Therefore, over-the-counter drugs are less of a problem now, because even pseudoephedrine has been taken off the market (at least, in many western countries).

The commonest 'non-releaser' nasal decongestant is oxymetazoline, which is a direct adrenergic alpha 2 agonist: it has no interaction with MAOIs and is not a problem.

Directly acting agonists, such as midodrine and adrenaline itself, are not a problem with MAOIs — clearly, additive pharmacological effects mean a downward dosage adjustment is required, but there is no major interaction. because there is no potentiation, something that was established over half a century ago.

## Phentermine

Phentermine has been around since 1959 (in combination dexfenfluramine) and was discontinued in the 1990s, then re-introduced in 2012 combined with topiramate.

It is an NA and DA releaser.

There is no specific data on combinations in humans, however, the data relating to other releasers suggests that co-administration should generally be avoided. If this preparation was taken accidentally in combination with an MAOI it is doubtful that a single-dose would cause serious adverse effects, but an overdose might have serious toxicity.

## Pharmacological Profile for 5-HT/NE/DA Release/Re-uptake

See full table in Rothman [37]

* sertraline- for comparison, not from Rothman

| | 5-HT | | NE | | DA | |
|---|---|---|---|---|---|---|
| | Release (EC50 nM) | Uptake (Ki nM) | Release (EC50nM) | Uptake (Ki nM) | Release (EC50 nM) | Uptake (Ki nM) |
| Amphetamine | 1765 | 3830 | 7 | 39 | 25 | 34 |
| Methamphetamine | 736 | 2137 | 12 | 48 | 24 | 114 |
| Ephedrine | >10,000 | >50,000 | 72 | 225 | 1350 | 4398 |
| Tyramine | 2800 | 1550 | 41 | 73 | 120 | 106 |
| Fenfluramine | 52 | 150 | 300 | 1300 | 10,000 | 22,000 |
| MDMA | 57 | 238 | 77 | 462 | 376 | 1572 |
| Cocaine | >10,000 | 304 | >10,000 | 780 | >10,000 | 478 |
| Desipramine | >10,000 | 350 | >10,000 | 8.3 | >10,000 | |
| Citalopram | >10,000 | 2.4 | >10,000 | | >10,000 | |
| Fluoxetine | >10,000 | 9.6 | | | | |
| Sertraline | -- | 0.29* | | | | |

### Reuptake inhibition

Reuptake inhibition is mediated by the effect of drugs on the transporters for serotonin, norepinephrine and dopamine (often abbreviated as SERT, NAT and DAT respectively). Drugs that affect the other transporters act as substrate releasers, VMAT2 inhibitors, and/or reverse transporters (see below). Reuptake inhibitors reversibly bind to, and inactivate, the re-uptake transporters, but are not transported into the pre-synaptic terminal. Releasers are transported into the pre-synaptic nerve terminals. Once there they promote neuro-transmitter release and thereby elevate extra-cellular neuro-transmitter levels.

Reuptake inhibitors prevent ingress of some releasers into the pre-synaptic terminal or block VMAT2 (vesicular mono-amine transporter 2) and thus increase synaptic release, see reviews for further information [8, 53].

Norepinephrine re-uptake inhibitors (NRI) block the ingress of tyramine into the pre-synaptic terminal, thus attenuating the pressor response, as many studies with TCAs, SNRIs, reboxetine etc. clearly demonstrate. An early elucidation of tyramine/amphetamine/DMI actions came from the famous lab of Bernard Brodie [54]. That early Brody paper in 1968 suggested that NRI dependence on tyramine was the case at lower concentrations, but that at high concentrations it was not solely dependent on the NAT (increased passive diffusion?).

NRIs have the effect of reducing release of noradrenaline from synaptic stores (VMAT). Therefore, NRIs thus attenuate/prevent the hypertensive response in a dose dependent manner, depending on their potency. Brodie showed that in rats desipramine 10 mg per kilogram intra-peritoneally produced complete inhibition, i.e., completely suppressed the pressor response.

For 5-HT pathways (attenuation of MDMA effects by SRIs) the same has been demonstrated [36, 55-57].

Tyramine acts as a releaser of noradrenaline — and to a lesser extent of DA — NRIs attenuate that response

## Direct agonists

### Adrenaline and midodrine

These are direct agonists, midodrine being selective for alpha-1 receptors. They have an additive effect when given together. All direct agonists can sometimes elevate blood pressure sufficiently to be associated with subarachnoid haemorrhage but that is extremely rare, thus, giving them together it is akin to giving a larger dose of one or the other, which will clearly raise effects, side-effects, and potential risks — the net effect is additive, not potentiating. Since MAOIs elevate noradrenaline and adrenaline it is appropriate to start midodrine at a reduced dose and titrate according to response.

Post-synaptic receptor agonists cause a lesser interaction with MAOIs than do releasers; hence, with usual therapeutic doses, ephedrine (a releaser) is more problematic than adrenaline (direct agonist) in combination with MAOIs [54, 58].

I would advise starting at ½ to ¼ of the normal starting dose

### Pramipexole, ropinirole, rotigotine

These drugs were developed for the treatment of Parkinson's disease and are direct dopamine receptor agonists.

There appear to be no major interactions with MAOIs, they do not seem precipitate hypertension.

They have been used for the augmentation of antidepressant treatments. It is advisable to use them with caution because of their propensity to facilitate problematic behaviours in the area of risk-taking, sexual behaviour, gambling, and suchlike.

It is to be hoped the psychiatrists will be more astute at picking up these potentially ruinous behaviours more quickly than neurologists who have taken an inordinate time to recognise them, see Boylan's editorial '*Don't ask, don't tell*' [59, 60].

## L-Dopa

Dopamine (DA) is present in many plants and plays a role in repelling pathogens. It is the precursor of the quinones that cause browning when they polymerise into melanin (e.g. bananas, avocados). Some legumes contain significant amounts of L-DOPA in some tissues, at some stages of growth, including *Vicia faba* L. varieties (aka fava beans, broad beans) and *Mucuna pruriens* (Cowhage, itching powder) [61-66]. Varieties of these plants are being genetically engineered to try to find a suitable dietary source for L-DOPA because it may be better than pharmaceutical L-DOPA (better absorption, more stable plasma concentrations). Various preparations are being sold on the internet. A search for 'mucuna aphrodisiac' or 'mucuna parkinson' returns many thousands of hits.

Maximum concentrations of 10-20 mg/g (dry weight) have been found in *Vicia faba* [61], equivalent to a wet weight concentration of approximately 100 mg/kg. However, the edible beans are lower.

Since L-DOPA is a dopamine precursor, not a releaser, i.e. not an indirectly acting sympathomimetic like amphetamine is, it is likely to have an effect more analogous to L-tryptophan with MAOIs (i.e. moderate potentiation only). L-tryptophan does not cause serious problems with serotonin toxicity, and nor would one expect L-DOPA to do so with BP.

Despite the warnings on interactions with medicinal L-DOPA — early papers were [67-69], the evidence for serious hypertension (see below for discussion) with L-DOPA and MAOIs seems inconclusive.

Such amounts of L-DOPA may potentiate or precipitate moderate BP increases, but, in my opinion, it is unlikely that a seriously risky BP elevation would result.

### Caffeine

Caffeine is the most consumed stimulant worldwide. It is in coffee at high levels and in soft drinks also levels of hundreds of milligrams (Red Bull ~300 mg/L. In some countries the allowable levels are 150 mg/L. Caffeine tablets often contain 200 mg per tablet.

A typical espresso single shot contains between 100-250 mg [70].

The Scientific Committee on Food consider low caffeine doses (<200 mg/day) safe. They produce modestly enhanced alertness, energy, and concentration.

The UK Food Standards Agency recommend that pregnant women not have >300 mg/day (association with low birth weight and spontaneous abortion).

The main mechanism of action of caffeine occurs via the blockade of adenosine A1 and A2A receptors [71]. The motor stimulant effects relate to A1 receptors which inhibit, and A2A receptors, which stimulate, adenylate cyclase; which in turn effects dopamine. Since it affects drugs acting via dopamine, it can be considered as an atypical psychostimulant.

CYP1A2 has a major role in caffeine metabolism and is a good marker of CYP1A2 activity. The CYP1A2*1F variant appears to increase the clearance of caffeine in smokers; other variants may increase or decrease caffeine metabolism. 1A2 activity, measured by caffeine metabolism, shows a 70-fold variation among subjects, which results from exposure to drugs and xenobiotics that either induce or inhibit its activity [72].

The half-life of caffeine was increased from 5 to 31 hours by therapeutic doses of fluvoxamine, which is a potent inhibitor of CYP1A2.

Serious toxicities such as seizure and cardiac arrhythmias occur at plasma concentrations of ~15 mg/L or >3 mg/kg. Concentrations of 80–100 mg/L are considered potentially lethal [73, 74].

Features of intoxication, include anxiety, agitation, restlessness, insomnia, gastrointestinal disturbances, tremors, psychomotor agitation.

Although where are no serious interactions with MAOIs, it is clear that patients who get potentiation of the above side-effects and may need to restrain their intake of caffeine containing foods and beverages to minimize SEs.

# Summary

## NRI and DRIs

There is an interesting paradox in that, combined with MAOIs, SRIs potentiate serious ST, whereas, parallel inhibition of noradrenaline or dopamine appears to give rise to no major disturbances or problems. One supposes that might tell us something about how different neurotransmitters are handled in different areas of the brain — research needed?

Readers are referred to the serotonin toxicity triangle in relation to the interactions between these three different sorts of drugs, but in summary, it reduces the effect of releases and mildly potentiate the effect of MAOIs.

## Releasers

Inadvertent ingestion of OTC releasers is partly a problem of the past. First, in many countries they have been replaced by oxymetazoline, and second, they are in any case unlikely to produce severe hypertensive reactions unless used in excessive doses. Therefore, the degree of risk is not as great as has hitherto been assumed. There is a minute risk when releasers are taken alone, this is increased when combined with MAOIs, but they are unlikely to cause severe reactions in normal moderate therapeutic use; nevertheless patients should be advised to avoid them, especially since their benefit is only transient relief of a stuffy nose. Better and safer to take panadol, an antihistamine, and oxymeta nozoline nasal spray as necessary.

## Direct agonists

Alpha agonists like adrenaline and midodrine can be used, providing starting doses are reduced to compensate for the additive effect, and then adjusted upwards as indicated.

DA agonists like pramipexole, ropinirole, rotigotine do not appear to have major interactions with MAOIs, but need to use with care because of their inherent stimulatory properties that effect impulsiveness and hence behaviours like gambling etc.

If CNS stimulants are to be used to augment MAOIs, methylphenidate is safe (it does slightly elevate BP, which can be useful); amphetamine is a little riskier, and can precipitate toxicity, even at therapeutic doses; however, that appears to be rare in clinical practice. This combination does have a place in clinical practice for special cases and providing the old adage is followed of 'start low go slow', one can be confident that it constitutes an acceptable risk.

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