

MAOI and TCA combinations: which first?

Abstract

Many of the myths concerning MAOI drugs can be traced back to the earliest writings from the late 1950s and early 1960s, before anything much was known about the pharmacology of either MAOIs or TCAs (by psychiatrists, that is) and well before any understanding of serotonin toxicity. To make matters worse, these myths were based solely on case reports, many of which were, by any standards, poor — indeed, most case reports still are poor. In the 60 intervening years, there is not one reliable report of serious ill-effects where therapeutic doses of MAOIs combined with TCAs (excepting CMI and IMI) have ever caused any major serious or toxic side-effects. Yet the myth persists and is reproduced in supposedly authoritative texts.

Understanding the origins of these myths remains important — if we are to learn from history, we must stop repeating these same mistakes.

Introduction

Just the place for a Snark! I have said it twice:
That alone should encourage the crew.
Just the place for a Snark! I have said it thrice:
What I tell you three times is true

~ The Hunting of the Snark, Lewis Carroll

It is a long poem and full of delightful nonsense, much like the story about MAOI/TCA interactions, which is so closely intertwined with reports about **serotonin toxicity ST**; the last verse is gloriously apposite:

In the midst of the word he was trying to say,
In the midst of his laughter and glee,
He had softly and suddenly vanished away—
For the Snark was a Boojum, you see

The quotation is concordant with comments I have made previously about describing non-existent entities: like using case reports to elucidate which drugs might cause **serotonin toxicity ST**. That is doubly misleading as so many people do not know what the well-defined features of ST really are.

It is like going ghost hunting in an old house. Your group, wandering around in the darkness, where supposed manifestations are said to occur, will doubtless have one person who swears they have felt a presence or seen something they cannot describe. No scientist would conclude ghosts existed from such stories when there is no reason to suppose they exist, no conceivable physical explanation, and no reliable or reproducible evidence.

Yet this is what is happening with imprecise reports of supposed ST and similar strange reactions associated with MAOI/TCA combinations.

The answer to the particular question — does it make any difference which one you give first — is rooted in the historic misunderstandings about the pharmacology, interactions, and the side effects of MAOI drugs — this is explained further in various other commentaries, especially this [commentary about the history of MAOI drugs](#).

Science and mythology

Science must begin with myths, then progress to the criticism of myths
Karl Popper, [1]

The answer to our question is most unlikely to be found by looking at case reports; one would have to look at the case series or trials where one or other technique was employed, study the dropout rate for the side-effects and compare any more dramatic toxic effects. This has already been done. There are various reports of groups of patients treated with combinations; such reports show no evidence of an increased incidence of side-effects; indeed quite the opposite is the case, e.g. see Razani [2].

The objection has been raised that one is looking at unpredictable and idiosyncratic effects; therefore, such small studies are not helpful because large numbers of patients must be studied for idiosyncratic effects to emerge.

That is incorrect. It is incorrect because **ST interactions are predictable, not idiosyncratic**. Faulty methods and poor logic have been applied to this question.

Generalisations made about 'the TCAs' are inevitably wrong because TCAs are a heterogeneous group of drugs — indeed, lumping them together pharmacologically makes no sense whatsoever. **Insufficient knowledge of their pharmacology was the root of earlier misunderstandings**, and was only partly resolved in the report of White and Simpson. Indeed, until recently, most reports failed to distinguish between the use of different TCAs in combinations, even after the variation in pharmacological profile and side-effects between different TCAs became scientifically established. These factors make many comments difficult to interpret because the TCA involved is not always specified, nor is the initial dose or rate of increase; these are crucial factors determining the level of side-effects experienced. Therefore, imprecision is heaped upon chaos.

Lumping TCAs together makes no sense whatsoever: they are pharmacologically a markedly heterogenous group

The idea that adding a TCA to an established course of an MAOI is, in way that has never been clearly specified, more likely to cause problems than vice versa, is a complete myth. It originated from poor quality data in the 1960s and has been unthinkingly reproduced, sometimes word for word, in various sources ever since. Never has there been any analysis or explanation of any reason why this might be so, nor has there been any new supportive evidence adduced since those early poor quality case reports in the 1960s. Indeed, a massive body of evidence, reviewed elsewhere, attests to the opposite view, the safety of these combinations, irrespective of the order in which they are given.

The nature of myths is that they are hard to reliably attribute to any single person or time. Nevertheless, we can deduce with some confidence how this significant misconception started. As Popper [1] said, science must start with myths:

The history of science, like the history of all human ideas, is a history of irresponsible dreams, of obstinacy, and of error. But science is one of the very few human activities — perhaps the only one — in which errors are systematically criticized and fairly often, in time, corrected.

The history: 1960s

First, one has to appreciate that in the 1960s, few psychiatrists had much knowledge of pharmacology; indeed, pharmacological knowledge was at an inchoate stage and such knowledge as existed was not understood by the writers of these opinions — for instance, it is clear that the writers of the American

Medical Association report of 1964 were entirely unaware of the relevant pharmacology research that was then available because they failed to cite a single relevant reference: see '[Overview: MAOI and TCA interactions](#)' for details of the references they should have cited, yet failed to cite.

Many of the patients treated with MAOIs at that time were given the most commonly used TCA, imipramine. We now know from *in vitro* work, animal experiments, and analysis of human toxicology, that IMI has sufficiently weak SRI potency such that it is only sometimes potent enough to cause the serious drug interaction of ST (when given in conjunction with MAOIs). Thus, many of the patients treated with this combination suffered few problematic symptoms or major toxicity (i.e., rarely experienced full-blown ST) — it was precisely because it was an uncommon complication, and nobody appreciated its association with IMI as a cause, nor recognised the as yet and undelineated picture of ST, that it was not understood at the time.

Here is a list of reports of such reactions, illustrating the confusion that existed just from the years 1960 and 1961 [3-14]; if I listed all the references in the years after that, the list would be absurdly long. I reviewed all these cases when I first wrote about ST 20 years ago [15], so I am intimately familiar with the story. As I have discussed in detail, the reports in the last 10 or 15 years are no better; there has been a complete failure to learn from history and to understand the [misleading nature of case reports](#). Unfortunately, there is a vast expansion of journals publishing nothing but case reports, which is causing confusion and misdirection in the literature.

Because the TCAs were thought of as a homogenous group, there was no understanding of the mechanistic basis for these reactions, and thus the myth grew that adding a TCA was dangerous.

Without a good understanding of mechanisms and causality,
clinical science is difficult and chaotic

In reality, it was only IMI that was the culprit (CMI is 50 x more potent as an SRI [16] and often causes fatal ST, but did not exist then). The case reports, apparently implicating other TCAs in diverse types of reactions, if only rarely, were enough to cement the confusion.

In retrospect it is clear from analysis of these old 'non-IMI' case reports that they were not ST and that the interactions of an unfavourable nature had little or nothing to do with the use of therapeutic doses of the TCA but with other factors — such as straightforward toxicity from using hundreds of milligrams of a TCA daily in patients who were not subject to therapeutic drug monitoring, thus causing, *inter tot alia*, anti-muscarinic toxicity (delirium), co-ingestion of other drugs etc. The case reports from that time also illustrate that anti-muscarinic delirium was not usually recognised for what it was. All the TCAs, with the possible exception of DMI, possess significant anti-muscarinic potency to induce delirium in large doses and overdoses.

I have previously discussed at length the misleading nature of case reports [17-19] which cause misdirection, a deal of misinformation, and wasted clinical time and effort, especially for less experienced practitioners — and now that they are incorporated into computerised drug interaction systems the potential for misinformation and misdirection is massively multiplied — such is progress.

The first indication that CMI was clearly more toxic (vs IMI) was from Beaumont, who was the Medical Adviser for Geigy Pharmaceuticals in the UK (where CMI was introduced in 1968, not in USA till 1988) [20]. He summarised **four reports of fatalities**, clearly from ST, that had been made to the company. Note that, like others, he reported these patients as exhibiting 'convulsions' which were most probably severe clonus, not epileptic seizures — clonus being one of the most reliable signs of excessive elevation of serotonin and impending

ST. This was the dawn of the realisation that SRI potency was the key to toxicity between MAOIs and TCAs and the new generation of SSRIs.

Case for the prosecution

In 1964 Atchley summarised the American Medical Association's 'Council on drugs' report, '*Reevaluation of Tranylcypromine Sulfate*' [21] — this was after TCP had been withdrawn from the market (in the USA, not the UK) for several months earlier that year.

As I have pointed out before, the Council on drugs report makes some dubious and unfounded statements which even then were out of keeping with current knowledge and did not cite relevant pharmacology research, which justifies the assumption that they were not experts. They opined that the order of administration might be a factor and also expressed the following dubious statements in that document which seem to have caused these unfounded myths to be pseudo-authoritatively promulgated:

Tranylcypromine should not be administered to any patient with a confirmed or suspected cerebrovascular defect or to any patient with cardiovascular disease hypertension, or pheochromocytoma. It should be used cautiously in patients with epilepsy or impaired liver function. [MAOIs] and other antidepressant drugs (e.g. amitriptyline, imipramine) should not be given concomitantly or soon after the administration of another agent in this group since, in addition to the hypertensive reaction, such combinations may cause severe convulsive seizures [wrong]. ...hypertension can also be precipitated when tranylcypromine is used with ... methyldopa, ... or tryptophane [wrong].

The suggestion that it should not be used in those with '*cardiovascular disease, hypertension...**' and likewise, '*It should be used cautiously in patients with epilepsy***' are produced out of the blue with no justification or references.

The eminent psycho-pharmacologist Frank Ayd added to the discussion, following his report a couple of years previously [8] *Toxic somatic and psychopathologic reactions to antidepressant drugs*: that reported three cases of MAOI/IMI interactions with characteristics compatible with ST, none of which were fatal. This occurred when IMI was added to the MAOI. Most considered TCAs as a homogenous group, not as individual drugs, which led to the presumption about the sequence of administration and that all TCAs were equally liable. Big mistake. A mistake still repeated.

Because MAOIs were new and highly favoured in the early 1960s, most patients given combinations were already on an MAOI. IMI was the most used TCA, thus the most likely to be the one added. It occasionally gave rise to serotonin mediated side-effects (tremor, hyperreflexia) and, when used in higher doses, cases of frank ST, some of which were fatal (reviewed by me back in 1998 [15]).

The case for the defence

Someone nearly got it right

Rees and Pare suggested in 1963 that reporting should be drug-specific since individual drugs within these generic groups had different effects [22]. They seem to have been among the few who appreciated the importance of variation between different members of these two classes of drugs.

* This is doubly surprising because, at that time, MAOIs were being used to treat hypertension by cardiologists and general physicians!

** There is evidence that MAOIs raise the epileptic threshold rather than lower it

We feel that the dangers involved in using these drugs may have been exaggerated and that the issues involved have been clouded with irrelevancies. The risk of toxic effects must be weighed against the effectiveness of monoamine-oxidase inhibitors in relieving the morbidity of depression which has been proved in numerous controlled clinical trials.

... the morbidity arising from depression is considerable, and we feel that it should be left to the individual doctor to decide whether the condition of the patient justifies the use of antidepressants of this type.

Thus, they were ahead of the game in one way, but in other respects, they made the very mistakes they had themselves warned about. Pare subsequently thought his work with an NRI and an MAOI to try to prevent the tyramine pressor response had been a failure [23, 24]. That was because he did not understand the **thousandfold differences in the potencies of 'TCAs' at the NET** [16] — he lumped them all together and thus did not recognise his own positive findings.

However, in the book he wrote, Pare also speculated that giving the TCA second was less advisable [25], but adduced no cogent evidence to support that notion.

In 1981 the Council of the American College of Neuropsychopharmacology **endorsed and adopted as its official policy, the views about the safety of MAOI/TCA combinations** explicated in this paper by White and Simpson [26]. They concluded the combinations were safe, providing one avoided IMI (CMI had not reached the American market by then).

White and Simpson's report concluded that the combinations were safe

Many readers will not be surprised to hear that little notice appears to have been taken of it, as far as clinical practice was concerned, and it was not widely cited in the relevant literature.

In parallel with the report above, White and Simpson published a paper [27] analysing cases, in which they stated clearly:

Many of these case reports involved complicating factors of such magnitude as to render them nearly useless for assessing any toxicity unique to the MAOI/TCA combination

My subsequent analysis, which covered most of these cases and others of which they were unaware, concluded that none of the ones they considered were useful, especially without a clear understanding of the underlying pharmacology [15]. They suggested, tentatively, that introducing the TCA second might be less satisfactory. One or two of their suggestions demonstrate, unsurprisingly, the extremely unreliable nature of speculations derived from case reports. **These tentative suggestions have not been supported in the intervening years, yet they are still repeated uncritically in supposedly authoritative texts.**

It should also be noted that in the 60 years these drugs have been in use, there is no single reliable or convincing case report where therapeutic doses of MAOIs and TCAs*, used according to good clinical pharmacology practice, have ever caused any major serious or toxic side-effects.

In 60 years, there is not one **reliable** report where therapeutic doses of MAOIs and TCAs* have caused toxic side-effects — not one

* I am assuming my readers have learnt sufficient by now to understand that I am excluding CMI and IMI from that statement!

An instructive example of a misleading case report (they cited) was the report from Jarecki, which constituted an example of one of the toxic interactions that contained another unrecognised element [28]. Aside from the fact that the case was of an overdose, the patient had in fact ingested **chlorpheniramine****, which is a potent SRI, and would precipitate ST with an MAOI. Another similar case was the infamous Libby Zion incident which led to a great kerfuffle in New York [29]. Despite a committee of experts reviewing the Zion case, they failed to recognise the role of chlorpheniramine, as I explained in my review [15].

Davidson succinctly summarised his experience and opinion soon after Whyte and Simpson's report, in a brief letter [30], and reported other contemporaneous experiences of colleagues [31], who all **stated clearly that they had found both sequences of administration perfectly safe and satisfactory**, providing, as below, the general principles of good clinical pharmacology were followed.

One may also note Razani's trial (White and Simpson again) of combined MAOI and AMI [2]:

Of the 71 patients participating in the study, 11 dropped out prior to completing the fourth week. The dropout rate was highest in the amitriptyline only group (30%), lowest in the combination group (5%), and intermediate in the tranlycypromine group (19%).

Not only was the dropout rate lower in the combination group, but also most of the side-effects were less on the combination than they were on amitriptyline alone. No serious side-effects whatsoever were reported — that accords with other reports and experiences.

The most recent dataset, which allows comments on this question, comes from the work of Amsterdam et al. [32], who made a brief report on their extensive dataset of patients treated with these combinations. Sixty patients had combined treatment with no significant increase in side-effects and no suggestion of toxic effects of any sort. **They concluded that the order of administration made no difference to efficacy or side-effects.**

My experience of refereeing many case reports concerning ST, and analysing published reports about supposed ST, leads me to the clear opinion that many problems result from what I would call **'Psychopharmacology Cowboys'** — these are practitioners with insufficient knowledge of pharmacology and inadequate understanding of what constitutes good practical clinical pharmacology, as alluded to below.

Another view

Some people advocate starting both drugs together and increasing them gradually. This idea goes against **the usual precepts of sensible, practical clinical pharmacology**: start low go slow, only change one drug at a time, do not use two drugs where one drug may suffice.

First, if you start two drugs simultaneously, and some SE or reaction happens, you have little idea of which drug caused the problem. Second, another basic principle is avoid giving two drugs where one drug might suffice, so one is missing the opportunity to test or retest the notion that one drug alone will do the job.

Similarly, the idea is only a verisimilitude of reality, because you do not know when a drug reaches its true therapeutic level and the doses you are assigning as starting doses are somewhat arbitrary. There is little control over which drug reaches its therapeutic level first.

** Chlorpheniramine was the molecule that precipitated the development of Zimelidine, which was the first SSRI, preceding Prozac by years, although everyone seems to have forgotten that.

As a clinical pharmacologist, I cannot see sense in this idea. Besides that, there is, of course, no evidence whatsoever that it constitutes a superior approach.

Personal experience

In reviewing the old literature, whilst preparing this commentary, I only found one or two comments specifying which particular drugs might be most satisfactory. Nortriptyline is unquestionably, in the pharmacological sense, the most satisfactory TCA for combinations and bridging [16]. It has nearly linear pharmacokinetics, low interaction potential, a good level of potency versus other undesired effects (muscarinic activity etc.) and good safety in overdose (many people do not realise that it is safer than venlafaxine, which has been the most widely used SNRI, over the last couple of decades). If NTP is insufficiently sedative, it is logical to add a small dose of Doxepin (5-25 mg usually suffices) for that **effect***. I have added NTP, usually starting with 25 mg at night, and building up to the usual therapeutic dose of 50 to 125 mg daily, in hundreds of cases, to augment TCP — my experience is that the overall side-effect burden of this combination is often lower than either drug given individually. When I say augment, I mean that the most common reason for giving it was to improve sleep and reduce anxiety, in the knowledge that an NRI almost certainly attenuates the tyramine pressor response as a bonus. My experience was that the true anti-depressant augmentation effect was sometimes apparent but often marginal.

Conclusion

It is clear to me, tracing these threads of the story back to their origin, that the genesis of these misconceptions is clear.

There were few TCAs in the early 1960s and IMI was the only one which had sufficient SRI potency to cause problems. MAOIs were in common usage and IMI was the most used TCA. Thus, it was often added to an MAOI, creating the false impression that the order in which the drugs were given mattered because a proportion of patients would have experienced significant serotonin mediated side-effects and sometimes fatal ST*. Now that we understand ST [34], we can see that this reaction occurs no matter which way round the drugs are given, if one of them is sufficiently potent SRI.

Finally, because we understand the mechanism of ST, we know that it simply cannot occur in a severe or fatal form, unless an MAOI is combined with a potent SRI. We know that this is **not an idiosyncratic interaction but a predictable dose-related reaction**. For this reason, occasional reports of single instances of apparent toxicity with non-SRI drugs, e.g. mirtazapine, doxepin, or trazodone, cannot be used to support the idea that they have significant interactions with MAOI — such a notion makes no more sense than claiming that vitamin C precipitates strychnine toxicity. This is the most important scientific and logical principal to emerge from this understanding and analysis.

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* Many think that that is wrong and illogical because one is giving two different "TCAs" simultaneously. That goes to show they do not understand pharmacology.

* If anyone still clings to the idea that it is safe to give IMI with MAOIs, they should read this case report 33. Otte, W., T.K. Birkenhager, and W.W. van den Broek, *Fatal interaction between tranlycypromine and imipramine*. European Psychiatry, 2003. 18: p. 264-265.

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