

OVERVIEW: MAOI AND TCA INTERACTIONS

Abstract

This paper traces and analyses the historical origin of the mistakes and misconceptions surrounding the misinformation promulgated concerning the interactions between MAOI and tricyclic antidepressant (TCA) drugs. This is an object lesson in the importance of thorough teaching of pharmacology to psychiatrists, and of the importance of well-written and up-to-date reference texts which doctors can consult. A report to the American College of Neuropsychopharmacology, *The Combined MAOI-tricyclic antidepressant treatment: A reevaluation*, in 1980, stated clearly that most of the cautions and prohibitions concerning MAOIs were without foundation and even ‘mythical’ — yet 40 years later that report remains ignored and forgotten, despite its findings having been further validated and consolidated since then.

Introduction

In 1981 the Council of the American College of Neuropsychopharmacology (ACNP) endorsed and adopted as its official policy the views about the safety of MAOI/TCA combinations explicated in this paper by White and Simpson [1]. They expressed the view that **‘the riskiness of the combination is largely superstition.’** They noted the view of the eminent psycho-pharmacologist of the time, Frank Ayd, that the prohibition [of MAOI/TCA combinations] was **‘one of several myths and unscientific generalisations that plague contemporary psychopharmacology’**. We should note that Ayd was essentially correct in his assertion, but only because, at that time, clomipramine — which is a definite risk for precipitating serotonin toxicity (ST) — had not yet been marketed in the USA.

In 1980 the Council of the American College of Neuropsychopharmacology adopted a report about MAOI/TCA combinations that stated that ‘the riskiness of the combination is largely superstition’

Since then, a deeper understanding of pharmacology and serotonin-related phenomena has emerged which revealed that there is a greater than 1000-fold difference in potency for serotonin reuptake inhibition between the different TCAs: knowing the hSERT potency, as we now do, allows reliable predictions about which combinations of drugs may constitute a risk of ST.

This commentary reviews the historical record relating to these matters and explains our current understanding (with relevant accompanying references), by explaining why there has been a considerable degree of confusion in the literature as a result of an imperfect understanding of pharmacology, interactions, and toxicology.

Why the ACNP position statement was overlooked by psychiatrists and regulatory authorities remains something of a puzzle.

This commentary is intended to assist those who are not already familiar with these issues to grasp the overall picture. Contrary to most of the (mis)information still in some standard texts, **there is an enormous amount of published evidence demonstrating such combinations are perfectly safe.** How the contrary view got into the literature and common teaching is an object lesson in misinformation, overreliance on inadequate-quality case reports, biasing influences, and poor scholarship, which I have discussed elsewhere, e.g., [2].

My international group of MAOI experts have published a position statement about MAOIs [3]

The lengthy report by White and Simpson in 1980 which was ratified by the ACNP is discussed in the appendix. That report, although still essentially correct according to our current understanding, is now largely of historical interest; it is a useful source of references. Its timing was unlucky, because it was shortly after 1980 that much of the modern human-cloned receptor (HCR) data on drug affinities, including data on TCA pharmacology, became known. Those data form the substance of my series of papers [4-7] explaining the interaction as a manifestation of ST.

[This list of references on MAOI/TCA interactions below is the most comprehensive list ever compiled.¹](#)

Pharmacology updated

What is published in the scientific literature is but the tip of the iceberg in terms of the totality of clinical practice experience, and what is published gives a misleading impression of clinical reality. RCTs can be unrepresentative and misleading.

The categorisation of these 'TCA' drugs has changed as a result of improved pharmacological knowledge, accelerated by the move towards neuroscience-based classification of drugs [8]. The group of drugs referred to as tricyclic antidepressants (TCAs), which were brought into use in the early 1960s, were named merely on the basis that they all had a three-ring central structure. However, subsequent pharmacological research has made it clear that their pharmacological properties and actions differ greatly, by more than one-thousand-fold [7]. Pharmacologically, they are a markedly heterogeneous group. Generalisations made about 'the TCAs' are usually wrong. Insufficient knowledge of their pharmacology was the root of the earlier misunderstandings, as illustrated in the report of White and Simpson below.

TCAs are structurally related to the first-generation antihistamine drugs, which are all 'tricyclics', and to the first generation of neuroleptic drugs, represented by chlorpromazine. Indeed, those drugs share many properties, such as their sedative potency as histamine-1 (H1) receptor antagonists.

Some of the drugs that were marketed as antihistamines in the 1960s would now be classified as SRIs, and several of the TCAs would now be classified as specific and potent antihistamines, for example trimipramine and doxepin — indeed doxepin has recently been re-marketed as a sleeping tablet, as suggested in my TCA review paper some years ago [7]). Yet both trimipramine and doxepin are still used as antidepressants, in my opinion misguidedly.

[A full appreciation of this new pharmacological knowledge has still not percolated widely into standard texts, nor everyday clinical practice, nor into the product information approved by the EMA or FDA.](#)

¹ If anyone is aware of significant other references that I had missed please inform me, and I will add them — I daresay there is mention of such things in various older textbooks to which I do not have access; although some of that information will be of limited value, it is worth documenting it for the record.

History

The relevance of this is that the past reports of interactions between MAOIs and TCAs were not informed by an understanding of their neuro-pharmacology. Also, reports confused different adverse effects and toxicities [9].

Indeed, most of the past reports were poor-quality case reports of single cases, usually with incomplete and uncertain data and poorly informed discussion — there are several recent examples of this duplication of incorrect and unhelpful reviews of case reports [10, 11].

I have previously discussed at length the frequently misleading nature of case reports [12-14]. Such reports produce a great deal of misinformation and wasted clinical time and effort, especially for less-experienced practitioners.

Better-quality data has emerged from prospective monitoring of toxicity in toxicology databases. Foremost among such sources is the seminal data collected by Professor Whyte and colleagues, from Newcastle [15-22]. Unfortunately, such data are not well-known, recognised, or cited in the psychiatric literature.

We now understand that the only serious interaction between MAOIs and some TCAs (viz. only clomipramine and imipramine) is caused by excessive elevations of serotonin. Such great elevations of serotonin (5-HT) can only be produced if MAOIs are combined with therapeutic doses of **potent** serotonin reuptake inhibitors (SRIs), leading to severe ST — this does not occur after single-drug overdoses of SRIs. There are some other drugs that possess SRI properties to the extent that they are occasionally able to increase serotonin substantially [23], and therefore become risky (e.g. meperidine, tramadol, chlorphenamine).

Of the TCAs, the only ones that possess significant SRI potency are clomipramine and imipramine; however, imipramine is a less potent SRI and only occasionally causes a severe ST interaction. Indeed, interactions with imipramine are sufficiently uncommon and mild that some practitioners (incorrectly) consider the combination to be safe (see Gillman [9] for a full explanation).

All the other TCAs are about two orders of magnitude less potent for this SRI effect. There are no reports of excessive serotonin-mediated side-effects, nor of ST, when these have been combined with MAOIs, even in overdoses (and this agrees with experiments in animals, and much other data [23]).

The many references about the safety of MAOI/TCA combinations provided below refer to a considerable number of publications describing **thousands** of patients treated with such combinations. In addition to that, many experienced psycho-pharmacologists all over the world continue to use such combinations and find them to be safe. My own first-hand experience of such treatments encompasses several hundred cases without serotonin-mediated adverse effects.

The property of TCAs that is beneficial, potentially to an extent which will reduce, or even obviate, the need to follow a tyramine restricted diet, is their inhibition of noradrenaline reuptake (NRI); again, this property varies considerably in potency between different TCAs.

Ironically, not only is the risk of a tyramine pressor response reduced, but there is also a definite suggestion that some combinations of an MAOI and a TCA can have less ‘day-to-day’ side effects overall than either drug given separately. That is not as strange as it might at first seem, because sometimes one drug can mitigate the side-effects of another — that is what may be occurring with some MAOI/TCA combinations.

Unhelpful product information

The contraindications given in the product information (PI) sheets approved by the FDA for various drugs (often long ago) relates to the earlier period of

knowledge referred to above, when the pharmacological properties of these drugs were not precisely known. Why general texts and the PIs have not caught up with modern knowledge is not something I will expound on here. However, drug-regulatory agencies, e.g., the FDA and the EMA, deal with drugs on an individual basis and do not necessarily review the overall developments in pharmacology and clinical toxicology. I suspect therefore that the explanation is simple and contributed to by not reviewing the overall picture and the underlying pharmacology.

As a world expert in ST, I am well-placed to state that our theoretical knowledge about ST, derived from pharmacology and animal experimentation, is now thorough, well-established, and well-validated. It allows accurate predictions regarding which drugs present a potential risk for precipitating this interaction (cf. the methylene blue story [5]). This knowledge is congruent with an informed interpretation of clinical data, pharmacology, and toxicology. It is therefore possible to be extremely confident that TCAs other than clomipramine and imipramine have no significant effect on elevating serotonin, and no risk of precipitating ST.

A recent review of all deaths (a putative total of 56) related to ST published over the last 40 years reveals no cases related to TCAs other than clomipramine and imipramine [10].

Thus, there are no other serious or dangerous interactions between (therapeutic doses) of MAOIs and TCAs.

The evidence that MAOI/TCA combinations result in an improved antidepressant effect is a different question, which is not addressed in this commentary.

For those not familiar with my numerous papers on ST, it should be noted that these contain exhaustive details explaining the pharmacology of this interaction as it pertains to all relevant drugs and gives clear guidance on what is and is not safe.

Appendix

[Notes on 'Combined MAOI-tricyclic antidepressant treatment: A reevaluation' \[A report to the American College of Neuropsychopharmacology\] \[1\]:](#)

As discussed, this report (adopted as the ACNP position statement) is now mainly of historical interest, because its timing was unlucky. It was just after 1980 that important explanatory data about pharmacology and serotonin toxicity became known. Particularly, the better-defined clinical features of ST and its differentiation from other reactions, and the more precisely assayed potency of these drugs for different receptors, particularly the serotonin transporter. Those data provided the essential explanatory power to understand this interaction, which was not available to White and Simpson in 1980.

Nevertheless, certain comments these authors made are interesting and revealing, and some remain true today, as the following quotations reveal:

1. However, a number of factors have combined to reduce their apparent risk [MAOI+TCA] or at least make it seem more acceptable: appreciation of the rarity of such crises leading to severe complications; better understanding of the mechanism of these crises resulting in prevention and dietary and drug precautions; increased awareness of the toxicity of alternate antidepressant treatments and the risks involved with inadequately treated depression; and evidence that MAOIs may have a unique role in therapy many depressed patients poorly responsive to alternative treatments.
2. ... provides little support for the idea that TCP is more problematic when used in combinations with TCAs than our other MAOIs.

3. From informal discussions with many physicians it is obvious that thousands of patients have been thus treated with MAOI/TCA combinations.
4. Predicting responders from clinical attributes is unreliable.
5. The riskiness of the combination is largely superstition.
6. In 1977 Ayd commented that the prohibition was “one of several myths and unscientific generalisations that plague contemporary psychopharmacology”
7. [They agree] the hazards of been exaggerated, but that the risks are greater if the TCA is added within a week or two after starting the MAOI.²
8. There is little evidence of an increased rate of mild side-effects with the combination
9. They mention possible advantages in improving sleep and possibly reducing the tyramine pressor response (citing Ghose [25])³.

Complete list of references

The following list is as complete as I can make it and contains all known publications that attest to the safety of MAOI/TCA combinations and describes, or alludes to, a total of thousands of patients thus treated.

[1, 5, 7, 23, 26-78].

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² we can now be confident that statement is incorrect: there is no significant evidence that the order in which the drugs are given is relevant; that incorrect notion was initiated in the poorly researched report from the AMA 'Council on Drugs' summary of 1964, outlined in JAMA 24. Atchley, D.W., *Reevaluation of Tranylcypromine Sulfate*. *JAMA*, 1964. **189**: p. 763-4., [see here for further analysis](#). The mantra 'start low, go slow' should always be observed as part of the practice of good clinical pharmacology.

³ I concur with this view.

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