PsychoTropical Commentaries (2022):11;20-29

Posting key	2/2022
Currently posted	[post this updated version]
Faux-paper pdf	No
Menu listings	1 MAOIs (& 2 prof pages) & Position No 5
Correct header	[i.e. Page No. if to be formatted as pdf]
Keywords	
Meta description (<300 char/~50 words)	

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 supposed interactions between MAOI and TCA drugs. This is an object lesson in the importance of thorough teaching of pharmacology to psychiatrists and of the importance of production of well written and up-to-date reference texts which doctors can consult. A report to the American College of Neuro-psychopharmacology, 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 has been ignored and forgotten about, despite the fact that its findings have been further consolidated since then.

Introduction

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 [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 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, "the riskiness of the combination is largely superstition."

Since then, a deeper understanding of pharmacology and serotonin-related phenomena has emerged which reveals that there is a greater than 1000-fold difference in potency for serotonin reuptake inhibition between the different TCAs: that 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

Address for correspondence: ken.psychotropical@gmail.com
Website: https://psychotropical.com

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.

Quite 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].

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

Below is a footnote about the lengthy report by White and Simpson in 1980 which was ratified by the American College of Neuropsychopharmacology. 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 serotonin toxicity.

This list of references on MAOI/TCA interactions below is the most comprehensive such list yet to be compiled*.

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, speeded 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 heterogenous 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, for instance, their potency as sedative antihistamines (H1 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]). Both trimipramine and doxepin are still used as antidepressants, in my opinion misguidedly.

* 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.

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.

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 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 or recognised 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) — 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 tricyclics are at least one or two orders of magnitude less potent for this SRI effect. There are no reports of excessive serotonin mediated side-effects, nor of serotonin toxicity, 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 then 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 also there is 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 TCA/MAOI combinations.

The contraindications given in the product information 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 the explanation is simple and contributed to by not reviewing the overall picture and the underlying pharmacology, and by dealing with drugs on an individual basis.

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 of which drugs are potentially a risk from 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 serotonin toxicity.

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

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

The evidence that these 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 serotonin toxicity 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.

Commented [LG1]: Could use a heading somewhere above to break up this text, as the last heading used is 'Introduction' but this all makes up the bulk of the commentary so it obviously goes beyond an introduction.

Addendum

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

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 they 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. 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 with within a week or two after starting the MAOI**
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 [24])**.

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].

References

1. White, K. and G.M. Simpson, *Combined MAOI-tricyclic antidepressant treatment: A reevaluation.* A report to the American College of Neuropsychopharmacology, 1980. **Oct**: p. 1-54.

2. Gillman, P.K., *"Much ado about nothing": monoamine oxidase inhibitors, drug interactions, and dietary tyramine.* CNS Spectr, 2017: p. 1-3.

3. Gillman, P.K., S. Feinberg, and L. Fochtmann, *Revitalizing monoamine oxidase inhibitors: A call for action.* CNS spectrums, 2019: p. http://dx.doi.org/10.1017/S1092852919001196.

4. Gillman, P.K., *A reassesment of the safety profile of monoamine oxidase inhibitors: elucidating tired old tyramine myths.* J Neural Transm (Vienna), 2018. **125**(11): p. 1707-1717.

5. Gillman, P.K., *CNS toxicity involving methylene blue: the exemplar for understanding and predicting drug interactions that precipitate serotonin toxicity.* Journal of Psychopharmacology, 2011. **25**(3): p. 429-3.

6. Gillman, P.K., *Advances pertaining to the pharmacology and interactions of irreversible nonselective monoamine oxidase inhibitors.* Journal of Clinical Psychopharmacology, 2011. **31**(1): p. 66-74.

7. Gillman, P.K., *Tricyclic antidepressant pharmacology and therapeutic drug interactions updated.* British Journal of Pharmacology 2007. **151**(6): p. 737-48.

8. Nutt, D.J. and P. Blier, *Neuroscience-based Nomenclature (NbN) for Journal of Psychopharmacology.* J Psychopharmacol, 2016. **30**(5): p. 413-5.

* 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 [25], see here for further analysis.
The mantra 'start low, go slow' should always be observed as part of the practice of good clinical pharmacology.

** I concur with this view.

9. Gillman, P.K., *Serotonin Syndrome: History and Risk.* Fundamental and Clinical Pharmacology, 1998. **12**(5): p. 482-491.

10. Prakash, S., et al., *Fatal serotonin syndrome: a systematic review of 56 cases in the literature.* Clin Toxicol (Phila), 2021. **59**(2): p. 89-100.

11. Werneke, U., et al., *Conundrums in neurology: diagnosing serotonin syndrome–a meta-analysis of cases.* BMC Neurology, 2016. **16**(1): p. https://doi.org/10.1186/s12883-016-0616-1.

12. Gillman, P.K., *Extracting value from case reports: lessons from serotonin toxicity.* Anaesthesia, 2006. **61**: p. 419-422.

13. Gillman, P.K., *Lessons continue: serotonin toxicity.* Consulting Pharmacy, 2009. **24**: p. 398-399.

14. Gillman, P.K., *Combining antidepressants: Understanding Drug Interactions is the Sine Qua Non.* Advances in Psychiatric Treatment, 2010. **16**: p. 76-78.

15. Buckley, N.A., et al., *Greater toxicity in overdose of dothiepin than of other tricyclic antidepressants.* Lancet, 1994. **343**: p. 159-162.

16. Reith, D.M., et al., *Clinical features of self-poisoning with monoamine oxidase inhibitors and / or serotonin reuptake inhibitors.* Proceedings of the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists, 1996. **3**((Abstract)): p. 29.

17. Whyte, I.M. and A.H. Dawson, *Relative toxicity of venlafaxine and serotonin specific reuptake inhibitors in overdose.* Journal of Toxicology. Clinical Toxicology, 2001. **39**: p. 255.

18. Dawson, A.H. and I.M. Whyte, *Evidence in clinical toxicology: the role of therapeutic drug monitoring.* Ther Drug Monit, 2002. **24**(1): p. 159-62.

19. Whyte, I.M. and A.H. Dawson, *Redefining the serotonin syndrome.* Journal of Toxicology Clinical Toxicology, 2002. **40**: p. 668-669.

20. Dunkley, E.J.C., et al., *Hunter Serotonin Toxicity Criteria: a simple and accurate diagnostic decision rule for serotonin toxicity.* Quarterly Journal of Medicine, 2003. **96**: p. 635-642.

21. Isbister, G.K., et al., *Moclobemide poisoning: toxicokinetics and occurrence of serotonin toxicity.* British Journal of Clinical Pharmacology, 2003. **56**: p. 441-450.

22. Isbister, G.K., et al., *Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose.* Journal of Toxicology. Clinical Toxicology, 2004. **42**(3): p. 277-85.

23. Gillman, P.K., *A review of serotonin toxicity data: implications for the mechanisms of antidepressant drug action.* Biological Psychiatry, 2006. **59**(11): p. 1046-51.

24. Ghose, K., A. Coppen, and P. Turner, *Autonomic actions and interactions of mianserin hydrochloride (Org. GB 94) and amitriptyline in patients with depressive illness.* Psychopharmacology (Berl), 1976. **49**(2): p. 201-4.

25. Atchley, D.W., *Reevaluation of Tranylcypromine Sulfate.* JAMA, 1964. **189**: p. 763-4.

26. Beresford Davies, E., *MAOI TCA.* Lancet, 1963. **2**: p. 781.

27. Davies, E.B., *Combining the antidepressants.* Lancet, 1963. **2**: p. 781-782.

28. Watts, C.A., *Antidepressant Drugs.* Br Med J, 1964. **1**(5390): p. 1114.

29. Gander, D.R., *Combining the antidepressant drugs.* British Medical Journal, 1965. **1**: p. 521.

30. Gander, D.R., *Treatment of depressive illness with combined antidepressants.* Lancet, 1965. **1**: p. 107-109.

31. Hall, G.F., *Combining Antidepressant Drugs.* Br Med J, 1965. **1**(5431): p. 383-4.

32. Hynes, B., *Combining the Antidepressant Drugs.* Br Med J, 1965. **1**(5434): p. 589-90.

33. Marks, J., *Interactions involving drugs used in psychiatry*, in *The Scientific Basis of Drug Therapy in Psychiatry*. 1965, Elsevier. p. 191-201.

34. Pare, C.M., *Treatment of Depression.* Lancet, 1965. **1**(7392): p. 923-5.

35. Randall, J., *Combining the antidepressant drugs.* British Medical Journal, 1965. **1**: p. 521.

36. Sargant, W., *Combining the antidepressant drugs.* British Medical Journal, 1965. **1**: p. 1251.

37. Sargant, W., C. Walter, and N. Wright, *New treatment of some chronic tension states.* British medical journal, 1966. **1**(5483): p. 322.

38. Gander, D.R., *The clinical value of monoamine oxidase inhibitors and tricyclic antidepressants in combination.* In Garrantinis & Dukes. Antidepressant drugs, 1967: p. 336-343.

39. Sargant, W., *The treatment of depressive states.* Int J Neurol, 1967. **6**: p. 53.

40. Kelly, D., et al., *Treatment of phobic states with antidepressants. A retrospective study of 246 patients.* Br J Psychiatry, 1970. **116**(533): p. 387-98.

41. Sargant, W., *Safety of Combined Antidepressant Drugs.* British Medical Journal, 1971. **1**(6 March): p. 555-556.

42. Schuckit, M., E. Robins, and J. Feighner, *Tricyclic antidepressants and monoamine oxidase inhibitors.* Archives of General Psychiatry, 1971. **24**: p. 509-514.

43. Winston, F., *Combined antidepressant therapy.* Br J Psychiatry, 1971. **118**(544): p. 301-4.

44. Ray, I., *Combinations of antidepressant drugs in the treatment of depressive illness.* Can Psychiatr Assoc J, 1973. **18**(5): p. 399-402.

45. Shaw, D.M. and R. Hewland, *Correspondence: The management of resistant depression.* Br J Psychiatry, 1973. **123**(575): p. 489-90.

46. Davidson, J., *The management of resistant depression.* British Journal of Psychiatry, 1974. **124**(579): p. 219-20.

47. Sethna, E.R., *A study of refractory cases of depressive illness and their response to combined antidepressant treatment.* British Journal of Psychiatry, 1974. **124**: p. 265-272.

48. Abdala, E.N., *[Combination of tricyclic antidepressants and MAOI in the depressions].* Acta Psiquiatr Psicol Am Lat, 1975. **21**(1): p. 52-5.

49. Ashcroft, G.W., *Psychological medicine. Management of depression.* British Medical Journal, 1975. **2**(5967): p. 372-6.

50. Ayd, F.J., *Psychotropic drug combinations: good and bad.* Drugs in combination with other therapies

Greenblatt (Ed) pp 165-188 Grune & Stratton, New York, 1975.

51. Sargant, W., *Antidepressant drugs.* British Medical Journal, 1975(october): p. 101.

52. Shopsin, B., *Tricyclics and MAO inhibitors: rational poly-pharmacy in treatment-resistant depression.* Paper presented at the 10th Collegium Internationale Neuro-Psychopharmacologicum Congress,

Quebec, Canada, 1976: p. July 6.

53. Spiker, D.G. and D.D. Pugh, *Combining tricyclic and monoamine oxidase inhibitor antidepressants.* Arch Gen Psychiatry, 1976. **33**(7): p. 828-30.

54. Ananth, J. and A. Luchins, *A review of combined tricyclic and MAOI therapy.* Comprehensive Psychiatry, 1977. **18**: p. 221-230.

55. Ponto, L.B., et al., *Drug therapy reviews. Tricyclic antidepressant and monoamine oxidase inhibitor combination therapy.* American Journal of Hospital Pharmacy, 1977. **34**: p. 954-961.

56. Davidson, J., et al., *A comparison of electroconvulsive therapy and combined phenelzine-amitriptyline in refractory depression.* Arch Gen Psychiatry, 1978. **35**(5): p. 639-42.

57. Goldberg, R.S. and W.E. Thornton, *Combined tricyclic-MAOI therapy for refractory depression: a review, with guidelines for appropriate usage.* J Clin Pharmacol, 1978. **18**(2-3): p. 143-7.

58. Young, J., M. Lader, and W. Hughes, *Controlled trial of trimipramine, monoamine oxidase inhibitors, and combined treatment in depressed outpatients.* Br Med J, 1979. **2**(6201): p. 1315-1317.

59. Laska, E., C. Siegel, and G. Simpson, *Automated review system for orders of psychotropic drugs.* Arch Gen Psychiatry, 1980. **37**(7): p. 824-7.

60. White, K., T. Pistole, and J.L. Boyd, *Combined monoamine oxidase inhibitor-tricyclic antidepressant treatment: a pilot study.* Am J Psychiatry, 1980. **137**(11): p. 1422-5.

61. White, K. and G. Simpson, *Combined MAOI-tricyclic antidepressant treatment: a reevaluation.* Journal of Clinical Pharmacology, 1981. **1**: p. 264-281.

62. White, K., et al., *Combined MAOI-tricylic antidepressant treatment: a controlled trial.* Psychopharmacology Bulletin, 1982. **18**(4): p. 180-1.

63. Razani, J., et al., *The safety and efficacy of combined amitriptyline and tranylcypromine antidepressant treatment. A controlled trial.* Archives of General Psychiatry, 1983. **40**: p. 657-661.

64. Tollefson, G.D., *Monoamine oxidase inhibitors: a review.* J Clin Psychiatry, 1983. **44**(8): p. 280-8.

65. Feighner, J.P., J. Herbstein, and N. Damlouji, *Combined MAOI, TCA, and direct stimulant therapy of treatment-resistant depression.* Journal of Clinical Psychiatry, 1985. **46**(6): p. 206-9.

66. Kupfer, D.J. and T.P. Detre, *Tricyclic and monoamine-oxidase-inhibitor antidepressants: Clinical use*, in *Handbook of psychopharmacology*. 1987, Springer. p. 199-232.

67. Schmauss, M., et al., *Combined MAO-inhibitor and tri- (tetra) cyclic antidepressant treatment in therapy resistant depression.* Prog Neuropsychopharmacol Biol Psychiatry, 1988. **12**(4): p. 523-32.

68. Pande, A.C., M.M. Calarco, and L. Grunhaus, *Combined MAOI-TCA treatment in refractory depression.* . In: Amsterdam J, ed. Refractory Depression. New York, NY: Raven Press, 1991: p. 115-121.

69. O'Brien, S., et al., *Blood pressure effects of tranylcypromine when prescribed singly and in combination with amitriptyline.* Journal of Clinical Psychopharmacology, 1992. **12**(2): p. 104-9.

70. O'Brien, S., P. McKeon, and M. O'Regan, *The efficacy and tolerability of combined antidepressant treatment in different depressive subgroups.* Br J Psychiatry, 1993. **162**: p. 363-8.

71. Berlanga, C. and H.A. Ortega-Soto, *A 3-year follow-up of a group of treatment-resistant depressed patients with a MAOI/tricyclic combination.* Journal of Affective Disorders, 1995. **34**(3): p. 187-92.

72. Thase, M.E., M.H. Trivedi, and A.J. Rush, *MAOIs in the contemporary treatment of depression.* Neuropsychopharmacology, 1995. **12**(3): p. 185-219.

73. Amsterdam, J.D., F. Garcia-Espana, and M. Rosenzweig, *Clomipramine augmentation in treatment-resistant depression.* Depression and Anxiety, 1997. **5**(2): p. 84-90.

74. Schmauß, M. and T. Messer, *Kombinationstherapie tri-(tetra-) zyklischer Antidepressiva mit MAO-Hemmern.* Interaktionen und Wirkmechanismen ausgewählter Psychopharmaka, 2003. **2**: p. 125-135.

75. Amsterdam, J.D., *Monoamine Oxidase Inhibitor Therapy in Severe and Resistant Depression.* Psych Annals, 2006. **36**(9): p. 607-613.

76. Schmauß, M. and T. Messer, *[Combining Antidepressants: a Useful Strategy for Therapy Resistant Depression?] Kombination von Antidepressiva – eine sinnvolle Behandlungsstrategie bei therapieresistenten Depressionen?* Fortschr Neurol Psychiat, 2009. **77**(316-325): p. 125-135.

77. Ferreira-Garcia, R., et al., *Tranylcypromine Plus Amitriptyline for Electroconvulsive Therapy-Resistant Depression: A Long-Term Study.* J Clin Psychopharmacol, 2018. **38**(5): p. 502-504.

78. Amsterdam, J.D. and T.T. Kim, *Relative Effectiveness of Monoamine Oxidase Inhibitor and Tricyclic Antidepressant Combination Therapy for Treatment-Resistant Depression.* J Clin Psychopharmacol, 2019. **39**(6): p. 649-652.