PS03/20

Use of monoamine oxidase inhibitors (MAOIs) in psychiatric practice

July 2020

POSITION STATEMENT

Working group

Royal College of Psychiatrists' Psychopharmacology Committee

Samuel R. Chamberlain
Antonio Metastasio
Paul R. A. Stokes
David S. Baldwin

With additional input from

Hamish McAllister-Williams
Royal College of Psychiatrists' Psychopharmacology Committee

Julia Sinclair
Chair, Royal College of Psychiatrists' Addictions Faculty

Michael Browning
British Association for Psychopharmacology

Allan Young
British Association for Psychopharmacology

Scope

This Position Statement provides clinicians with practical advice relating to the use of monoamine oxidase inhibitors (MAOIs) in treating adult patients with moderate-to-severe depression or anxiety disorders.

Background

MAOIs were one of the first classes of antidepressant medication to be discovered, but have fallen out of mainstream clinical use. Data collected from European tertiary treatment centres indicated that MAOIs were used as the primary treatment in just 0.3% of the patients with unipolar depression (Dold et al., 2016). The reasons for low prescribing rates of MAOIs include safety concerns, the relative complexity of prescribing them, a lack of sufficient clinician training (Shulman, Herrmann and Walker, 2013), and potential problems in the continuity of drug supplies.

MAOIs are not a first-line pharmacological treatment for depression or anxiety, for several reasons: if compared to selective serotonin reuptake inhibitors (SSRIs), they are less safe in overdose, their prescribing is not straightforward, and there are important safety issues that need to be carefully addressed for each patient (including drug–drug interactions, and dietary restrictions).

A consideration regarding the use of MAOIs, and particularly irreversible MAOIs, is to minimise the risk of adverse reactions, which have sometimes been fatal; these can occur if an MAOI is taken in combination with food or drink that has a high tyramine content.

Approximately two thirds of patients with depression do not experience adequate symptom relief from first-line pharmacological treatments, such as SSRIs, and MAOIs can be effective in some patients with treatment-resistant depression, especially in people with ‘atypical’ symptoms.

Atypical depression is characterised by some or all of the following features: over-eating, over-sleeping, mood reactivity, and rejection sensitivity (Angst et al., 2002; Henkel et al., 2006).

Mechanism

Monoamine oxidase (MAO) is an important enzyme in the degradation pathway of the monoamines (serotonin [5-hydroxytryptamine], dopamine, and noradrenaline), and exists in two forms (isomers): MAO-A and MAO-B. Both isomers degrade dopamine and tyramine, whereas MAO-A has additional effects serving to deactivate serotonin, noradrenaline, and melatonin (Shulman, Herrmann and Walker, 2013). Different MAOIs are available: some irreversibly deactivate the enzyme (e.g. phenelzine), whereas others are reversible (e.g. moclobemide); some are non-selective (e.g. phenelzine), whereas others selectively inhibit either MAO-A (e.g. moclobemide) or MAO-B (e.g. selegiline, when given in standard dosages). MAO-A inhibition is thought to be important for anti-depressant properties (Figure 1), and MAOIs differ in their propensity to act on each isoform.

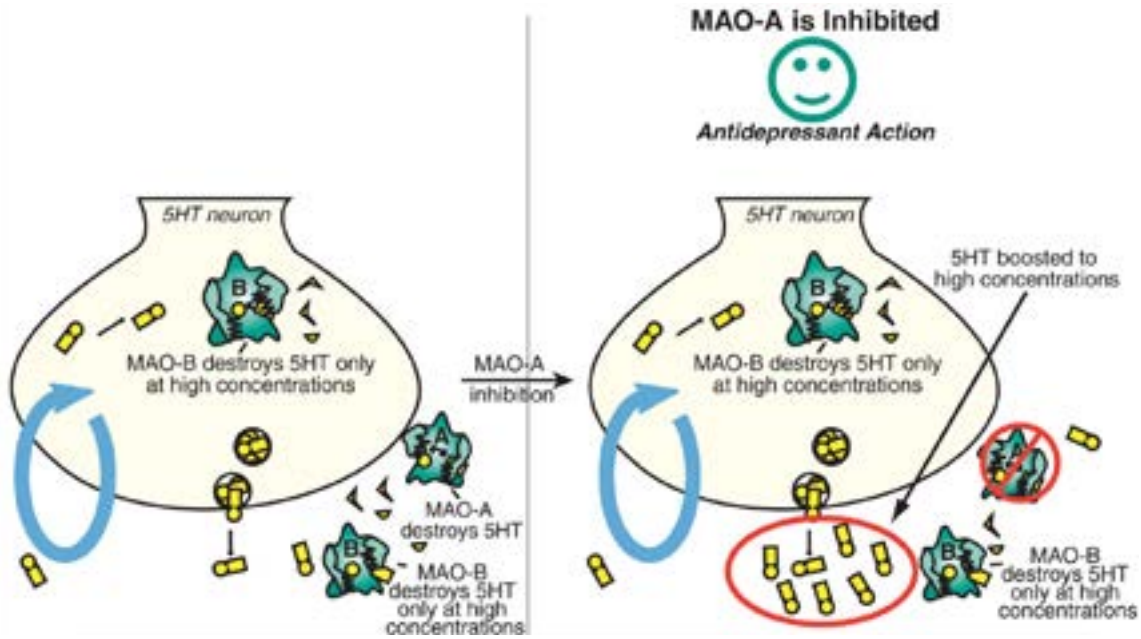

Figure 1. Enzyme MAO-A metabolises serotonin. By blocking this enzyme, MAOIs act to increase serotonin levels (and noradrenaline). MAO-B's role in breaking down serotonin (and noradrenaline) is much less prominent, because it only does so at high concentrations. From (Stahl S.M., 2008), with permission.

When should MAOIs be considered?

The 2015 British Association for Psychopharmacology guidelines for depression recommend that MAOI treatment is generally reserved for patients where first-line antidepressant therapy has not been effective, and should be initiated only by practitioners with expertise in treating mood disorders (Cleare et al., 2015). MAOIs may provide advantages for the treatment of depression with atypical features (Ricken et al., 2017). A 2006 meta-analysis indicated that MAOIs had greater efficacy than placebo in the treatment of atypical depression, with medium-to-large effect sizes (Henkel et al., 2006). MAOI efficacy effect sizes were higher than for tricyclic medication and were similar to those with SSRIs (Henkel et al., 2006). However, the number of data trials was relatively small.

In people with treatment resistant depression, a paper from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) group found that, in those patients who had not achieved remission from three previous antidepressant trials, 6.9% remitted after being treated with the MAOI tranylcypromine, compared to 13.7% who remitted on the combination of extended release venlafaxine plus mirtazapine (McGrath et al., 2006). This difference in remission between the two groups was not statistically significant. A study of people with treatment resistant depression found that use of MAOIs while an in-patient was independently associated with both remission at the point of discharge after controlling for other treatments, particularly for unipolar treatment-resistant depression, and with being in full remission at the time of final follow-up (Fekadu et al., 2012).

A number of randomised controlled trials have indicated that MAOIs can also be effective in the treatment of patients with panic disorder, social anxiety disorder (social phobia), or post-traumatic stress disorder (Menkes, Bosanac and Castle, 2016; Cipriani et al., 2018). The 2014 British Association for Psychopharmacology guidelines for anxiety disorders recommend that MAOIs are considered as potential treatments after non-response to more conventional pharmacological (e.g. SSRI) and psychological (e.g. cognitive behaviour therapy) approaches (Baldwin et al., 2014).

Tolerability and side effects

In a network meta-analysis, MAOIs did not differ significantly from SSRIs or serotonin-noradrenaline reuptake inhibitors (SNRIs) in how likely patients are to discontinue treatment due to adverse events (Meister et al., 2016). Nonetheless, the differing classes of antidepressants vary in their characteristic side effect profiles. The most common adverse effects of MAOIs occurring early in treatment are orthostatic hypotension, daytime sleepiness, insomnia, and nausea; later common effects include weight gain, muscle pain, myoclonus, paraesthesia, and sexual dysfunction (Fiedorowicz and Swartz, 2007). More serious adverse reactions include hypertensive crisis (see below), persistent hypotension and overstimulation (activation and nervousness). Other important safety considerations include potential drug–drug interactions, and the need for dietary restrictions. These are considered below.

For safety reasons, MAOIs should not generally be prescribed in people with a history of substance use disorders, over-use of prescribed medications, or overdoses. Other contraindications to MAOIs include: cerebrovascular disease, history of recurrent or frequent headaches, hepatic disease/dysfunction, blood dyscrasias, and phaeochromocytoma.

MAOIs are not generally recommended for use in pregnant or breast-feeding patients, due to the lack of adequate safety data; more safety data are available for other classes of antidepressant. Nonetheless, there may be some patients for whom the benefits of continuing a MAOI in pregnancy and/or lactation, with close monitoring (including of blood pressure) might outweigh the risks of continued treatment. Specialist advice is particularly needed in this situation.

Drug–drug interactions

MAOIs must not be prescribed alongside SSRIs, or other substances with serotonin reuptake inhibition effects (including SNRIs, trazodone, and clomipramine), due to the risk of inducing serotonin syndrome. Serotonin syndrome is characterised by a combination of autonomic hyperactivity, neuromuscular hyperactivity, and/or mental state changes (for more detail see Volpi-Abadie, Kaye and Kaye, 2013). Other medications that have serotonergic effects should also not be concomitantly prescribed, including certain analgesics, opioids (e.g. tramadol), and some triptan migraine medications (Culpepper, 2013). Some non-prescribed substances taken by patients have SSRI-like properties, including St John's Wort, and so also must be avoided.

When switching a patient from an SSRI to a MAOI, clinicians must ensure there is a suitable washout period of at least five half-lives of the particular SSRI (Grady and Stahl, 2012). This would typically be approximately seven days for most SSRIs, but around six weeks for fluoxetine due to its much longer half-life.

A washout period of 2–3 weeks is always advised after stopping a MAOI, before commencing an alternative antidepressant. This includes when switching from one MAOI to another MAOI based on conventional practice.

As there are occasional reports of the emergence of features of serotonin syndrome even 10 weeks after an MAOI is stopped, introduction of medicines with serotonin-re-uptake inhibitor properties should be conducted cautiously with careful monitoring. MAOIs can be combined with some tricyclic medications (not clomipramine) (Pilowsky and Kerwin, 1997) but this should only be considered in psychiatric inpatient units, or specialist outpatient clinics for patients with treatment-resistant affective disorders, due to the need for cautious dose titration and close monitoring.

Medications with potent noradrenergic effects should also be avoided whenever possible in people taking MAOI, due to the potential risk of synergistic effects on blood pressure (Grady and Stahl, 2012). Examples of such medications include stimulant and stimulant-like medications (e.g. methylphenidate, amphetamine, modafinil), noradrenaline reuptake inhibitors (including atomoxetine and reboxetine), and certain anaesthetic agents. For surgical procedures needing local anaesthetic, a non-noradrenergic anaesthetic agent should be used. For surgical procedures needing general anaesthetic, input from an anaesthetist should be sought well in advance, as it is likely the MAOI will need to be discontinued at least 10 days prior to surgery. MAOIs can have serious (including life-threatening) interactions with anaesthetic medications such as certain opioid analgesics.

Patients should be advised to check carefully and discuss with a doctor or pharmacist before using over-the-counter cold remedies and/or anti-congestants (including nasal sprays). This is because some of these can interact with MAOI effects, and increase levels of noradrenaline and/or serotonin. In turn, this can increase the risk of high blood pressure or serotonin syndrome.

As with other antidepressant medicines, abrupt withdrawal of MAOIs can be associated with distressing psychological and physical symptoms. Particular caution needs to be exercised when considering potential further pharmacological management of patients with these symptoms, due to the risk of potential severe drug–drug interactions.

Dietary restrictions

Consuming high levels of dietary tyramine while also taking MAOI medication can lead to raised blood pressure, including in some cases serious life-threatening hypertensive crises. Tyramine is normally metabolised by MAO in the liver and intestinal cells. With MAO inhibition, tyramine is not metabolised in the gut and passes directly into the circulation, where it may release norepinephrine, so causing hypertension.

Even though reversible MAOIs theoretically have a lower risk of this reaction, current best practice is that all patients taking MAOI should be advised to follow the dietary restrictions. Table 1 provides a useful general guideline for common foods and drinks to avoid, and those that are allowed, in people taking MAOIs. Patients' individual dietary practices should also be considered on a case-by-case basis, in case their usual diet includes tyramine-containing food or drink not considered in the table.

Table 1. Foods and drinks to avoid, and those that are allowed, in people taking MAOI. Table reprinted with permission of the authors from the Sunnybrook Health Sciences Centre (Shulman, Herrmann and Walker, 2013).

Foods and drinks to avoid	Foods and drinks allowed
Cheese	
All matured or aged cheese	Fresh cottage cheese, cream cheese, ricotta cheese, and processed cheese slices; all fresh milk products that have been stored properly (e.g. sour cream, yoghurt, ice cream)
All casseroles made with these mature/ aged cheeses e.g. lasagne	
Please note: all cheeses are considered matured or aged except for those listed opposite	
Meat, fish, and poultry	
Fermented/dry sausage: e.g. salami	All fresh packaged or processed meat, fish, or poultry; store in refrigerator and eat as soon as possible
Improperly stored meat, fish, or poultry	
Improperly stored pickled herring	
Fruit and vegetables	
Fava or broad bean pods	Banana pulp
Banana peel	All others
Drinks	
All on-tap beer	Other alcohol (NB: no more than two bottled or canned beers or two standard glasses of wine per day; this applies also for low alcohol / alcohol-free beer).
Miscellaneous	
Marmite concentrated yeast extract	Other yeast extract (e.g. brewer's yeast)
Sauerkraut	Pizza without aged cheeses
Soy sauce and other soy bean condiments	Soy milk, tofu
Tyramine-containing nutritional supplements	

When MAOIs are stopped, patients should be advised to continue their restricted diet (with avoidance of tyramine-containing foods and beverages) and their avoidance of some proprietary cough medicines for 2–3 weeks after treatment is withdrawn.

Studies in healthy volunteers have found that reversible MAOIs interact less with tyramine than an irreversible MAOI (Finberg, 2014). It follows that reversible MAOIs are less likely to cause a hypertensive reaction when combined with high levels of dietary tyramine. However, confirmatory prospective clinical data are not currently available.

Choice of MAOI

Efficacy studies demonstrate that reversible MAOIs (principally moclobemide) are as effective as tricyclic antidepressants, but maybe less effective than irreversible MAOIs (Shulman et al., 2013). However, there have been no recent systematic reviews or meta-analyses comparing the efficacy and safety of reversible MAOIs and irreversible MAOIs. As such, an irreversible MAOI may be preferred in patients with severe treatment-resistant depression, providing they are likely to comply with the necessarily strict dietary regime. An initial approach would be to trial phenelzine as it appears better tolerated; and then to switch to tranylcypromine (following washout) if there is not adequate symptom remission.

While head-to-head comparisons are lacking, phenelzine may be associated with weight gain, with some other MAOIs (such as tranylcypromine and moclobemide) being weight neutral (Ricken et al., 2017).

Intermittent supply issues occur with MAOIs, in part due to low prescribing rates. If other MAOIs are not available, the use of oral selegiline (an irreversible MAO-B inhibitor thought to have MAO-A inhibition effects at higher doses) can be considered for depression 'off-label', since supplies of this may be more readily available .

The selegiline transdermal system (administered via a skin patch that is replaced every 24h) shows efficacy in the treatment of depression and is licensed for depression in the USA (Bied, Kim, and Schwartz, 2015). The selegiline transdermal system is not currently available for licensed use in the UK for this indication. Prescribers are advised to consult the Royal College of Psychiatrist's College Report *Use of licensed medicines for unlicensed applications in psychiatric practice* (2nd Edition, CR210, December 2017), for advice about provisions relating to prescribing outside the terms of marketing authorisation (product licence).

Price and supply considerations

At present, phenelzine is more than ten times cheaper to prescribe on the NHS than either tranylcypromine or isocarboxazid. Prescribers are advised to consult the latest edition of the British National Formulary (BNF) for current pricing (www.medicinescomplete.com).

The acquisition cost of MAOI antidepressants is often high (and higher than with alternative antidepressants), and supplies of MAOIs to pharmacies can appear limited; patients who are benefiting from MAOI treatment should be encouraged to ensure that prescriptions are regularly filled, so that potentially upsetting treatment interruptions can be avoided.

References

Angst J, Gamma A, Sellaro R, Zhang H, Merikangas K (2002) Toward validation of atypical depression in the community: results of the Zurich cohort study. *J Affect Disord*, **72(2)**: 125–38.

Baldwin DS, Anderson IM, Nutt DJ, Allgulander C, Bandelow B, den Boer JA, Christmas DM, Davies S, Fineberg NA, Lidbetter N, Malizia A, McCrone P, Nabarro D, O'Neill C, Scott J, van der Wee N, Wittchen H-U (2014) Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: A revision of the 2005 guidelines from the British Association for Psychopharmacology. *J Psychopharmacol.*, **28(5), pp. 403–439.**

Bied AM, Kim J, Schwartz TL (2015) A critical appraisal of the selegiline transdermal system for major depressive disorder. *Expert Rev Clin Pharmacol 8(6):673–81.*

Cipriani A, Williams T, Nikolakopoulou A, Salanti G, Chaimani A, Ipser J, Cowen PJ, Geddes JR, Stein DJ (2018) Comparative efficacy and acceptability of pharmacological treatments for post-traumatic stress disorder in adults: a network meta-analysis. *Psychol Med*, **48(12)**: 1975–84.

Cleare A, Pariante CM, Young AH, Anderson IM, Christmas D, Cowen PJ, Dickens C, Ferrier IN, Geddes J, Gilbody S, Haddad PM, Katona C, Lewis G, Malizia A, McAllister-Williams RH, Ramchandani P, Scott J, Taylor D, Uher R; Members of the Consensus Meeting. *(2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol*, **29(5)**: 459–525.

Culpepper L (2013) Reducing the Burden of Difficult-to-Treat Major Depressive Disorder: Revisiting Monoamine Oxidase Inhibitor Therapy. *Prim Care Companion CNS Disord*, **15(5).**

Dold M, Kautzky A, Bartova L, Rabl U, Souery D, Mendlewicz J, Porcelli S, Serretti A, Zohar J, Montgomery S, Kasper S (2016). *Pharmacological treatment strategies in unipolar depression in European tertiary psychiatric treatment centers – A pharmacoepidemiological cross-sectional multicenter study. Eur Neuropsychopharmacol.*, **26(12)**: 1960–71.

Fekadu A, Rane LJ, Wooderson SC, Markopoulou K, Poon L, Cleare AJ (2012). *Prediction of longer-term outcome of treatment-resistant depression in tertiary care. British Journal of Psychiatry*, **201**: 369–75.

Fiedorowicz JG, Swartz KL (2004) The role of monoamine oxidase inhibitors in current psychiatric practice. *J Psychiatr Pract*, **10(4)**: 239–48.

Finberg, J P (2014) Update on the pharmacology of selective inhibitors of MAO-A and MAO-B: focus on modulation of CNS monoamine neurotransmitter release. *Pharmacol. Ther*, **143**: 133–52.

Grady MM, Stahl SM (2012) Practical guide for prescribing MAOIs: debunking myths and removing barriers. *CNS Spectr*, **17(1)**: 2–10.

Henkel V, Mergl R, Allgaier AK, Kohnen R, Möller HJ, Hegerl U (2006) Treatment of depression with atypical features: a meta-analytic approach. *Psychiatry Res*, **141(1)**: 89–101.

McGrath J. *et al. (2006). Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: A Star*D Report. American Journal of Psychiatry*, **163(9)**: 1531–41

Meister R, von Wolff A, Mohr H, Härter M, Nestoriuc Y, Hölzel L, Kriston L (2016) Comparative Safety of Pharmacologic Treatments for Persistent Depressive Disorder: A Systematic Review and Network Meta-Analysis. *PLoS One*, **11(5)**: e0153380.

Menkes D, Bosanac P, Castle D (2016) MAOIs – does the evidence warrant their resurrection? Australasian Psychiatry, 24(4): 371–3.

Pilowsky LS, Kerwin RW (1997) Biological Treatments in Psychiatry in Murray R, Hill P, McGuffin P The Essentials of Postgraduate Psychiatry, Third Edition. *Cambridge University Press.*

Ricken R, Ulrich S, Schlattmann P, Adli M (2017) Tranylcypromine in mind (Part II): Review of clinical pharmacology and meta-analysis of controlled studies in depression. *Eur Neuropsychopharmacol*, **27(8)**: 714–731.

Shulman KI, Herrmann N, Walker SE (2013) Current place of monoamine oxidase inhibitors in the treatment of depression. *CNS Drugs*, **27(10)**: 789–97.

Stahl SM (2008) Stahl's Essential Psychopharmacology, 3rd edition, New York.

Volpi-Abadie J, Kaye AM, Kaye AD (2013) Serotonin syndrome. *Ochsner J*, **13(4)**: 533–40.