**Monoamine Oxidase Inhibitors (MAOIs) in psychiatric practice: how to use them safely and effectively**

Samuel R Chamberlain 1,2,3,4, David S. Baldwin 1, 2, 5

1 Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, UK

2 Southern Health NHS Foundation Trust, Southampton, UK

3 Department of Psychiatry, University of Cambridge, Cambridge, UK

4 Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

5 University Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa

Address for correspondence: Professor David Baldwin, University Department of Psychiatry, University of Southampton, College Keep, 4-12 Terminus Terrace, Southampton, UK. SO14 3DT. Tel: +44 2382 310 764; Fax: +44 2382 310 766; d.s.baldwin@soton.ac.uk.

Abstract

Monoamine oxidase inhibitors (MAOIs) were among the first licensed pharmacological treatments for patients with depression, but over time have fallen out of mainstream clinical use. This has led to a loss of clinician training opportunities and reduced availability of MAOIs for prescribing. This article provides a concise and practical overview of how to use MAOIs safely and effectively in psychiatric practice. We consider the history of MAOIs, why they are not used more frequently, their mechanisms of action, availability, indications and efficacy, general tolerability, withdrawal symptoms, and safety considerations (including hypertensive reactions and serotonin syndrome). Practical advice is given in terms of dietary restrictions, interactions with other medications (both prescribed and non-prescribed), and how prescribers can stop and switch MAOIs, both within the drug class and outside of it. We also provide advice on choice of MAOI and treatment sequencing. Lastly we consider emerging directions and potential additional indications. (149 words)

Key points:

* MAOIs can be beneficial in the pharmacological treatment of some patients with previously treatment-resistant depression, or with certain other conditions, including social anxiety disorder and post-traumatic stress disorder
* MAOIs have become over-looked in clinical practice, but psychiatrists should remain familiar with their pharmacological properties and potential applications
* Although there are important tolerability and safety considerations with MAOIs before, during and immediately after treatment, including the potential for drug interactions, potential MAOI treatment should still be considered as an option in some patient groups

1. **Introduction**

As with many psychiatric treatments, the realization that monoamine oxidase inhibitors (MAOIs) might show efficacy was serendipitous. Iproniazid was developed and explored as a treatment for tuberculosis, but was found to have incidental and unexpectedly beneficial effects on mood in treated patients. An initial clinical trial in 1958 showed that iproniazid had efficacy as “a psychic energizer” in the treatment of depression [1], and it was granted a license for the treatment of that condition. MAOIs were among the first licensed pharmacological treatments for depression (amphetamine had been licensed for ‘mild depression’ two decades previously). Although iproniazid was later withdrawn due to hepatotoxicity concerns, this pivotal clinical observation led to the development of a number of other MAOIs, including isocarboxazid, phenelzine and tranylcypromine.

Currently, a range of MAOIs are available for clinical use, which differ in their mechanism of action (preference for one, the other, or both isoforms of the monoamine oxidase enzyme) and in whether they reversibly or irreversibly bind to this enzyme: their mechanisms of action are addressed later. MAOIs are recommended as a potential treatment option in patients with refractory depression in National Institute for Health and Care Excellence (NICE) and British Association for Psychopharmacology (BAP) guidelines [2, 3]. American Psychiatric Association (APA) depression guidelines indicate that MAOIs should in general be reserved for use in patients who have not responded to other treatments [4]. MAOIs are listed as third-line treatment options for depression in the Canadian Network for Mood and Anxiety Treatments (CAMAT) depression guidelines [5, 6] and in the Royal Australian and New Zealand College of Psychiatrists (RANZCP) depression guidelines [7]. Therapeutic use of MAOIs is dwindling in the United Kingdom and worldwide. A recent study conducted in European tertiary psychiatric treatment centres found that MAOIs were used as the primary treatment in only 0.3% of patients with unipolar depression [8]. A UK-based clinical audit of patient records from 55 mental health services (n=2082) indicated that MAOIs were prescribed to less than 1% of patients [9]. Declining rates of MAOI prescribing have been observed in other geographical areas such as in New Zealand [10], though objective data are lacking in many regions.

The reasons for these diminishing prescribing rates are multifold, but include the need for careful safety considerations, relative complexity of prescribing, insufficient clinical training and sharing of clinical experience with others, and the growing availability of other pharmacological options (some with potential safety advantages) [11]. Additionally, the modern widespread use of selective serotonin reuptake inhibitors (SSRIs) makes use of MAOIs more challenging, because of the wash out and prescribing gap needed between stopping SSRIs and commencing an MAOI. The great reduction in clinical use of MAOIs is unfortunate as evidence supports their use in the context of treatment-resistant and ‘atypical’ depression, certain anxiety disorders, and post-traumatic stress disorder (PTSD). In addition to reduced rates of prescribing in clinical practice, the number of clinical trials being conducted on existing and novel MAOIs for psychiatric indications has declined markedly (**Figure 1**), though the exploration of MAOIs for potential non-psychiatric indications is seeing a resurgence, which may aid in retaining their availability in prescribing formularies.

1. **Mechanisms of action and currently available MAOIs**

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.

MAOIs differ in their propensity to act on each isoform. Both isomers degrade dopamine and tyramine, whereas MAO-A has additional effects serving to deactivate serotonin, noradrenaline, and melatonin [11]. Different MAOIs are available: some irreversibly deactivate the enzyme (e.g. phenelzine), whereas others do so reversibly (e.g. moclobemide); in addition, some are non-selective (e.g. phenelzine), whereas others are selective, inhibiting either MAO-A (e.g. moclobemide) or MAO-B (e.g. selegiline, also known as deprenyl, when given in standard dosages). MAO-A inhibition is thought to be important for antidepressant properties (**Figure 2**): using platelet MAO inhibition as a proxy marker for the presumed degree of central nervous system MAO inhibition, antidepressant efficacy appears optimal when between 80-90% MAO inhibition is achieved [12]. MAO-A is mostly found in the liver, gastrointestinal tract, and respiratory epithelium; whereas MAO-B is mostly located in blood platelets. However, both are found throughout the body, including in the central nervous system. As will be considered later, MAO enzymes (primarily MAO-A) degrade tyramine, and so patients taking non-selective MAOIs need to follow certain dietary restrictions (including avoidance of tyramine-containing cheese) to avoid the so-termed ‘cheese effect’ (ranging from headache to hypertensive crisis).

At present, phenelzine is more than ten times cheaper to prescribe in NHS settings than either tranylcypromine or isocarboxazid: clinicians should consult the latest edition of the country-specific formulary for accurate pricing, such as the *British National Formulary* (BNF) in the UK. The acquisition cost of MAOI antidepressants is often high (and higher than with alternative antidepressants), and supplies of MAOIs to pharmacies can be unpredictable: patients who are benefiting from MAOI treatment should be encouraged to ensure that prescriptions are regularly filled, so that treatment interruptions can be avoided. While data are limited, there are some differences between the MAOIs in terms of likelihood of particular side effects: for example, phenelzine appears relatively more likely to lead to weight gain, and tranylcypromine less likely [13].

Phenelzine is a non-selective and irreversible inhibitor of monoamine oxidase which prevents the breakdown of the monoamine neurotransmitters 5-HT, adrenaline, noradrenaline, dopamine and melatonin. It also prevents the breakdown of ‘trace amine neuromodulators’ such as phenylethylamine and tyramine. A metabolite (PEH) inhibits GABA-transaminase and increases GABA levels, but the clinical significance of this is uncertain. It is efficacious in dysthymia, unipolar depression, and bipolar depression, though probably less effective than tricyclic antidepressants in severely depressed inpatients: it has been thought to have possible superiority in patients with ‘atypical depression’ (see below) [14, 15]. It is also efficacious in panic disorder, social phobia, and PTSD [16]Early recognition of a high incidence of dizziness and hypotension [17] was followed swiftly by awareness of the risk of severe hypertensive reactions [18]. Its overall tolerability is comparable to that of tricyclic antidepressants [14], and its longer-term tolerability in patients with persistent depression is comparable to that of SSRIs [15]. It is occasionally associated with hepatoxicity [19] and vitamin B6 (pyridoxine) deficiency [20].

Tranylcypromine is a non-selective and irreversible inhibitor of monoamine oxidase, and ‘substituted amphetamine’ (but with low potency as a dopamine releasing agent), and possesses noradrenaline reuptake inhibitory properties at higher doses (40/60 mg/day) [21]. It has broadly comparable efficacy to other antidepressants in patients with (non-treatment-resistant) depression and has efficacy in treatment-resistant depression (following tricyclic antidepressant and SSRI treatment) with a response rate of 58.1% [22] – although a lower response rate was seen in the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study (12.1% response *vs*. the 24% response seen with the combination of venlafaxine and mirtazapine) [23]. It acts as an MAOI at doses of 10-20 mg/day, noradrenaline reuptake inhibitory effects are seen at 40-60 mg/day, and acts as a dopamine-releaser at dose of around 100 mg/day [22]. An optimal response is typically obtained in patients who can tolerate doses of between 40-60 mg/day [14]. ‘Dizziness’ relating to postural hypotension is the most common reason for stopping treatment, and other common adverse effects include insomnia, increased anxiety, agitation, and dry mouth. Weight gain and sexual dysfunction are infrequent. A tyramine-restricted diet is essential during and after tranylcypromine treatment. The actuarial risk of severe cerebrovascular events (including deaths) due to hypertensive reactions is low, variously estimated as lying between 0.0014-0.007 per cent [24-26] (i.e. 140-700 events per 100,000 patients treated) .

Isocarboxazid is an irreversible non-selective inhibitor of MAO enzymes. Early randomised controlled trials did not establish its efficacy in depressed patients, though it was marginally superior to moclobemide in a clomipramine-controlled study [27]. It is used only rarely, in patients with treatment-resistant depression [28]. Adverse effects include dizziness, orthostatic hypotension, headache, and oedema. It inhibits activation of pyridoxine to pyridoxal 5′-phosphate (PLP, the active metabolite) and B6 supplementation reduces treatment-emergent oedema [29].

Moclobemide (not currently available in the USA) is a reversible inhibitor of monoamine oxidase-A (RIMA), inhibition lasting less than 24 hrs [30]. It is somewhat selective, as a 300 mg dose of moclobemide inhibits 80% of MAO-A but only 30% of MAO-B [31]. The potentiation of the pressor effect of tyramine is approximately 12% of that with irreversible MAOIs, and a hypertensive reaction is deemed unlikely if it is taken with tyramine-containing foodstuffs (24). In individuals taking 600 mg per day of moclobemide, significant rises in systolic blood pressure (30 mmHg or more) are seen following administration of 250 mg of tyramine ([32]: Cheddar cheese typically contains approximately 0.25 mg/g of tyramine, so around 1 kg of cheese would have to be eaten to achieve this pressor effect ([32]. It is efficacious in unipolar and bipolar depressive episodes and in dysthymia [33], has comparable efficacy to imipramine and clomipramine in hospitalised patients [34], but is not efficacious in recurrent brief depression [35]. There is some evidence of a dose-response relationship in patients with severe depression [36]. It is also efficacious in social phobia [37], and has possible efficacy at higher dosages in panic disorder [38]. Its more common adverse effects include dizziness, nausea, and insomnia (24) but treatment-emergent sexual dysfunction is less frequent (1.9%) than with SSRIs (21.6%) [39]. Animal models suggest it may potentiate the effects of pethidine (meperidine) [40] and there are occasional reports of serotonin syndrome if combined with clomipramine [41] or SSRIs [42, 43], though most cases occur following deliberate or inadvertent overdose rather than therapeutic use.

Selegiline is a ‘selective’ but irreversible inhibitor of MAO-B (although it inhibits MAO-A at high dosages). It exerts neuroprotective effects through inhibition of free radicals and has high affinity for sigma-1 receptors. Its metabolites include levomethamphetamine and levoamphetamine. Selegiline was originally developed for the treatment of Parkinson’s disease [44] where it delays the need for and the dosage of levodopa treatment. There are risks of serotonin syndrome if combined with an SSRI, and of hypertensive reactions with tyramine, especially with higher doses of selegiline (i.e. >10 mg / day). The selegiline transdermal system (administered via a skin patch, replaced every 24h) shows efficacy in the treatment of depression and is licensed for depression in the USA [45]. The transdermal system increases its bioavailability to 73% (from 4%) which results in non-selective inhibition of MAO-A and MAO-B, although MAO-A in the gastro-intestinal tract is available to metabolize tyramine. It is efficacious in both acute treatment [46-48] and in the prevention of relapse (38) of depression. The ‘number needed to treat’ for symptom reduction is around 11, and for remission is around 9. It is 3.6 times more likely to lead to remission than to drop-out due to adverse effects [49]. There is no difference from placebo in the incidence of weight gain or sexual dysfunction. 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*’ (CR210, December 2017), for advice about provisions relating to prescribing outside the terms of marketing authorisation (‘product licence’).

The availability of and licensing arrangements for MAOIs are likely to differ between countries, and change over time within a country: as such, it is always recommended to consult locale specific guidelines periodically.

1. **Indications for MAOI treatment**

MAOI antidepressants slowly came to be niched for the treatment of patients with ‘atypical depression’, but the precise nature of this condition has been disputed for decades. Current criteria for atypical depression (i.e. depression with atypical features in DSM-5) require the presence of mood reactivity (i.e. mood brightens in response to actual or potential positive events), together with two or more of the following features: significant weight gain or increase in appetite; hypersomnia (at least 10 hours/day or 2 hours more than when not depressed); leaden paralysis (i.e. heavy, leaden feelings in arms or legs, for at least an hour per day); and a long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment (this being a trait with early onset and persists throughout most of adult life). It is important that the criteria are not met for melancholic or catatonic features [50]. MAOIs may provide advantages for the treatment of depression with atypical features. A 2006 meta-analysis indicated that MAOIs had greater efficacy than placebo in the treatment of atypical depression, with medium-large effect sizes [51]. MAOI efficacy effect sizes were higher than for tricyclic antidepressants and were similar to those with SSRIs. However, the number of randomised controlled trials was relatively small. Furthermore, the notion that MAOIs as a class have preferential efficacy over other antidepressants in treating patients with atypical depression is somewhat erroneous: phenelzine may have superiority over the tricyclic imipramine, but comparative randomised controlled trials are limited in number and of relatively small size [51], and not all studies included the placebo arm which is necessary for establishing efficacy [52].

The 2015 BAP guidelines for depression recommend that MAOI treatment is generally reserved for patients where first-line antidepressant therapy has not been effective, and should only be initiated by practitioners with expertise in treating mood disorders [3]. In people with treatment-resistant depression, a paper from the STAR\*D group in the USA 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 [23]: however, this difference in remission between the two groups was not statistically significant. A UK-based study of people with treatment-resistant depression found that inpatient use of MAOIs was associated with higher remission at discharge, especially in patients with treatment-resistant illness [53]. In a recent network meta-analysis of treatment trials for depressive disorders, phenelzine showed the highest efficacy across all treatments considered (including non-MAOIs such as SSRIs); furthermore, the four MAOIs considered had favourable efficacy and tolerability versus those for other treatments [54]. The authors highlighted the need to revisit MAOIs as a treatment for depressive disorders.

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 PTSD [55-57]. The 2014 BAP 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 [58]. MAOIs may have a particular role in the treatment of patients with PTSD or social phobia. In a network meta-analysis involving 51 double-blind randomised controlled trials for PTSD, which included 25 differing interventions and a total of 6189 patients, phenelzine was superior to many other drugs (and was the only drug superior to placebo in terms of all-cause drop-outs from treatment): although the authors noted the findings were probably not sufficient to suggest phenelzine as a drug of choice for this condition, they felt they reinforced the idea that phenelzine should be prioritised in future trials [57]. In another network meta-analysis, of 101 trials of 41 interventions in social anxiety disorder, which included 13,164 patients, the authors emphasised the superiority of SSRI and serotonin-noradrenaline reuptake (SNRI) medicines to pill placebo, and the superiority of cognitive behaviour therapy (CBT) to psychological placebo, but the largest effect size for pharmacological treatment was for MAOIs, mainly due to the robust effect size for phenelzine [37].

Clinical trials using MAOIs in the treatment of obsessive-compulsive disorder (OCD) are few in number. In one double-blind study, OCD symptoms improved significantly and similarly following treatment with phenelzine or clomipramine (clomipramine has a strong evidence base in the treatment of OCD); and improvements between the two treatments did not differ significantly [59]. In a double-blind study examining the MAOI clorgyline versus clomipramine, only clomipramine showed significant benefit overall, though the authors noted some patients had benefited from the MAOI [60]. In another double-blind study compared placebo, phenelzine, or fluoxetine, findings were mixed. Specifically, only fluoxetine was associated with symptomatic improvement on one measure, whereas other outcome measures did not differentiate across treatment arms (including placebo) [61]. The authors noted that a subset of patients did appear to benefit from phenelzine. Lastly, in a recent small case series of nine OCD patients where extensive first-line treatments had not resulted in sufficient symptomatic improvement, three patients experienced marked benefits after switching to phenelzine, three experienced some benefit, and three did not: of the three patients who did not, two individuals had discontinued due to side effects, and one had discontinued relatively early (after four weeks) due to lack of benefit [62].

The use of MAOIs in the context of bipolar disorder has received relatively little research. As with other antidepressants such as SSRIs, the possibility or inducing a manic switch with treatment should be considered, particularly in patients who are not taking mood-stabilising medication. In a double-blind study of patients with bipolar disorder who were experiencing an episode of anergic depression, tranylcypromine was associated with symptomatic improvements in depression versus imipramine, and no increased risk of treatment emerging hypomania/mania was detected [63]. In a double-blind study comparing moclobemide versus imipramine, both treatments were associated with marked improvement of depressive symptoms in around 50-60% of the patients with bipolar disorder [64] (based on subgroup analysis from a larger study of depressive disorders). Some caution is needed because manic switches may constitute a relatively uncommon event, and the sample sizes of patients with bipolar disorder in these studies were relatively small.

1. **General safety principles**

As with prescribing any psychotropic medication, it is important to consider and discuss benefits and risks with the patient on an individual basis. In a network meta-analysis, MAOIs did not differ significantly from SSRIs or SNRIs in how likely patients were to discontinue treatment due to adverse events [15]. 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 [65]. More serious adverse reactions include hypertensive crisis (see below), persistent hypotension, and ‘overstimulation’ (i.e. activation and increased nervousness). Other important safety considerations include potential drug-drug interactions and the need for dietary restrictions. These two topics are considered in further detail in sections 5 and 6.

Prior to prescribing MAOIs, there should be thoughtful consideration of a patient's willingness and ability to adhere to the necessary restrictions. 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: or who have marked impulsivity or hostility, or difficulty in understanding written information. Other contraindications to MAOIs include cerebrovascular disease, history of recurrent or frequent headaches, hepatic disease or 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 some other classes of antidepressant medication. 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.

Two distinct important safety issues when considering prescribing MAOIs are serotonin syndrome and hypertensive effects (including rare cases of hypertensive crisis) (**Table 1**). Serotonin syndrome is characterised by a combination of autonomic hyperactivity, neuromuscular hyperactivity, and/or mental state changes [66]: it can occur when MAOIs are inappropriately combined with other medications or substances that have overlapping effects on activating the serotonin neurochemical system. Should it occur, initial supportive measures (cooling, administration of a benzodiazepine) may need to be followed by hospital admission, intravenous (IV) fluids and administration of the potent 5-HT2 antagonist cyproheptadine [67]. Hypertensive effects range from mild and asymptomatic elevation of blood pressure, to rare cases of hypertensive crises (which are potentially life-threatening): they can occur when MAOIs are inappropriately combined with other medications or substances that have overlapping effects on the noradrenaline neurochemical system, although they can occur spontaneously, albeit very rarely [68]. Most instances of hypertension will resolve within a 1-2 hours, but if systolic blood pressure is raised above 180 mmHg patients should be admitted and blood pressure reduced steadily (not precipitously) [69]. Partly because of this potential risk, but mainly due to the more common problem of hypotension during treatment, it has been argued that patients should be encouraged to monitor their blood pressure at home [69]. If these principles are borne in mind, many contraindicated medication combinations become easier to understand. Also crucial is the need for patients to follow a low tyramine diet to minimise the likelihood of hypertensive effects (including potential hypertensive crises).

As treatment with phenelzine or isocarboxazid is occasionally associated with pyridoxine (vitamin B6) deficiency - which can also appear during treatment of TB patients with isoniazid, which has mild MAO inhibitory effects – patients should be warned about this potential rare complication, and periodically reviewed for symptoms and signs of B6 deficiency such as skin rashes, glossitis and paraesthesia.

1. **Drug-Drug interactions**

MAOIs must not be prescribed alongside SSRIs, or other substances with significant serotonin reuptake inhibition effects (including SNRIs, trazodone, and clomipramine), due to the risk of inducing serotonin syndrome. Other medications that have serotonergic effects should also not be concomitantly prescribed, including certain analgesics, and opioids (e.g. tramadol) [70].Some non-prescribed substances taken by patients have SSRI-like properties, including St John’s Wort, so also must be avoided. Triptans (used for migraines) are broken down in the body by MAO-A, and so their plasma levels can be increased by MAOIs: therefore, co-prescribing a triptan and an MAOI should be avoided.

Opioids are potentially problematic, not only due to the risk of serotonin syndrome but also in some cases because of overlapping cytochrome enzyme interactions. NHS Specialist Pharmacy Service guidance on MAOIs and opioid co-administration [71] suggests that some opioids can be cautiously used with MAOIs if clinically necessary (such as morphine, codeine, oxycodone, or buprenorphine), starting with a minimal dose, and increasing the dose carefully whilst monitoring blood pressure, CNS effects, and respiratory status. The NHS Specialist Pharmacy Service also recommends that other opioids should be avoided completely (such as dextromethorphan, methadone, pethidine [meperidine]), tramadol, fentanyl or tapentadol) [71]. These should be avoided not only during MAOI treatment, but also for at least two weeks after MAOIs are stopped. Dextromethorphan and pseudoephedrine are included in some cough suppressants and over-the-counter cold formulations, which should 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 [72]. 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. 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-reuptake inhibitor properties should be conducted cautiously with careful monitoring. MAOIs can be cautiously combined with some tricyclic medications, such as amitriptyline (but not clomipramine) [73] 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. Such practice is supported cautiously by pilot data [74].

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 [72]. 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 before surgery. Very little is known about the potential safety or toxicity of combining MAOIs with bupropion [75], although as a pharmacokinetic drug-drug interaction study suggests that phenelzine administration can increase the bioavailability of bupropion [76] their combined use should probably be avoided.

The combination of an MAOI with ketamine or esketamine is not advised by their manufacturers, due to concern about potential additive monoaminergic effects on cardiovascular function (principally dopamine reuptake inhibitory effects with esketamine). As tranylcypromine and phenelzine are often prescribed in patients with otherwise treatment-refractory depression, there is interest in the safety and tolerability of MAOI medications when combined with ketamine/esketamine: observations described in case reports and small case series (often reported as letters to editors) suggest that effects on blood pressure are variable, though only transient [77-79]: but much more information is required before these combinations can be recommended outside of research studies.

1. **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 can lead to release of noradrenaline, so causing hypertension.

Even though reversible MAOIs theoretically have a much lower risk of this reaction, current practice is that all patients taking MAOIs are best advised to follow the dietary restrictions, except for the lowest dose (6 mg/24 hours) of the selegiline transdermal system. Studies in healthy volunteers have found that reversible MAOIs interact less with tyramine than do irreversible MAOIs [80]. 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. For the reversible MAOI moclobemide, current UK prescribing guidelines (*British National Formulary*) advise that patients should avoid consuming “large amounts” of tyramine rich foodstuffs. **Table 2** provides a useful general guideline for common foods and drinks to avoid, and those that are allowed, in people taking MAOIs. Individual dietary practices should also be considered on a per patient basis, in case a particular patient’s usual diet includes tyramine containing food/drinks not considered in the table.

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 and cold medicines for 2-3 weeks after treatment is withdrawn.

1. **Practical advice on choice of MAOI and sequencing**

Efficacy studies demonstrate that reversible MAOIs (principally moclobemide) are as effective as tricyclic antidepressants, but may be less effective than irreversible MAOIs [11]. Prescribed doses of moclobemide may need to be at the upper limit, as positron emission studies indicate that MAO-A occupancy is around 75% for doses between 300-600 mg/day, but around 85% for doses between 900-1200 mg/day [81] (new reference needed).

An irreversible MAOI may be preferred in patients with severe previously treatment-resistant depression, providing they are likely to comply with the necessarily strict dietary regime. Phenelzine doses may need to be as high as 90 mg/day in order to achieve the necessary level of MAO inhibition, as the lack of efficacy of phenelzine in a pivotal MRC-funded study [82] may have been due to its maximum dosage of 60 mg/day. Treatment response appears more likely in patients with ‘slow acetylator’ status [83]. 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 trial head-to-head comparisons are limited, phenelzine may be associated with weight gain, with some other MAOIs (such as tranylcypromine and moclobemide) being weight neutral [22]. In a recent network meta-analysis of trials for depressive disorders, phenelzine showed superior efficacy (based on the network meta-analysis metrics) as compared to other treatments that were examined, including other MAOIs and also non-MAOIs (e.g. SSRIs) [54]: the include MAOIs were reported to compare favourably to non-MAOIs in terms of efficacy and tolerability.

Intermittent supply issues occur with MAOIs, in part due to low prescribing rates. It makes sense to identify patients currently taking an MAOI, to organise their review within secondary care mental health services, and to consider whether there is scope for a planned gradual withdrawal of treatment. If antidepressant treatment withdrawal is not feasible (which is often the case in currently MAOI-treated patients), clinicians should consider switching from older MAOIs (phenelzine, tranylcypromine) to moclobemide, or switching to oral or transdermal selegiline, or switching to other classes of antidepressant medication: but unfortunately, patients and their treating clinicians must expect a rather bumpy course.

The MAOIs available for prescription in the UK, by way of example, can be distilled into a short list (**Table 1)**, and cost considerations have come to influence prescribing practice. Readers are advised to consult up-to-date local pricing and availability since these vary across countries and over time.

1. **Management of common side effects from MAOIs**

Management of common and bothersome side effects from MAOIs has a very limited evidence base; as such the following strategies are suggested based on clinical experience. In patients experiencing MAOI-related insomnia, consider where relevant discussing advice about sleep hygiene, adjusting dosing to earlier in the day, and/or adjustment to medication dosage. Where necessary, medications for insomnia can be considered, but it is important to consider safety issues including the potential for drug interactions. Treatment with non-selective MAOI is often associated with an asymptomatic postural decrease in blood pressure, although many patients experience an initial symptomatic and significant postural drop (between 10-15 mmHg): the latter often resolves within two weeks despite maintaining the same daily dosage [69]. Persistent symptomatic hypotension can sometimes be managed by dose reduction, although some patients will need to be switched to alternative treatments. The incidence of treatment-emergent sexual dysfunction with older MAOIs is uncertain, but sexual difficulties and dissatisfaction are less common with moclobemide than with SSRIs [39]: switching from an SSRI to moclobemide (of course, with appropriate washout) can sometimes be beneficial in enhancing sexual functioning in depressed patients [84].

1. **Symptoms whilst and after stopping MAOIs**

As with many other antidepressant medicines [85], abrupt withdrawal of MAOIs can be associated with distressing psychological and physical symptoms. Discontinuation or withdrawal symptoms were described in early case reports of treatment of patients with tranylcypromine [86, 87] and phenelzine [88]; and appear to be associated with a longer duration of phenelzine treatment [89]. Symptoms may include anxiety, mania, delirium, psychotic symptoms, and/or autonomic disturbances [90, 91]. Moclobemide appears less likely to be associated with such symptoms after stopping treatment, although its withdrawal has been linked to rebound rapid eye movement (REM) sleep (24), and ‘flu-like’ symptoms [92]. Particular caution needs to be exercised when considering potential further pharmacological management of patients with these emergent symptoms, due to the risk of potential severe drug-drug interactions.

1. **Future directions**

MAO inhibition is a proven mechanism for exerting antidepressant efficacy, yet for various reasons existing MAOIs are widely neglected, often misunderstood, and largely disappearing from clinical practice. Cohorts of psychiatry trainees - and possibly some consultants - have never seen a currently MAOI-treated patient. However, MAOIs are still recommended as a possible treatment option in patients with refractory depression in both NICE and BAP guidelines. As noted above, the MAOI phenelzine performed rather well in a network meta-analysis of randomised controlled treatment trials in patients with PTSD [57], and again in depression [54], leading to the suggestion that it should be prioritised in future trials for these disorders . Future work should aim to address ‘number needed to treat’ and ‘number needed to harm’ for MAOIs, since much of the literature to date does not permit evaluation of these parameters.

The efficacy and tolerability of the selegiline patch in some patients with treatment-resistant depression suggests there is scope for a renaissance of interest in MAOI treatment. There is certainly scope for the development of new compounds with MAOI as a core mechanism, but with pharmacokinetic and pharmacodynamic features which might lead to enhanced efficacy and improved tolerability and safety, when compared to other antidepressants. Furthermore, MAO-A and/or MAO-B inhibition is an established property in many plant-derived substituted flavonoids [93] suggesting the potential for development of novel pharmaceutical compounds.

It is somewhat ironic that the possible demise of MAOIs from mainstream psychiatric practice is occurring during a period when potential novel applications in non-psychiatric indications are being explored [94]. Phenelzine can disrupt androgen receptor signaling, so could be used in patients with recurrent prostate cancer [95]; tranylcypromine can induce myeloid differentiation and might be useful in the treatment of patients with acute myeloid leukaemia [96]; and selegiline can induce apoptotic cell death in melanoma lines and so might be useful in treating patients with that malignancy [97], in addition to its use in patients with Parkinson’s disease. In addition, MAOIs have indirect neuroprotective properties due to inhibition of hydrogen peroxide and aldehyde release, and individual drugs may also have direct neuroprotective effects [80]. Perhaps a subsequent repurposing of MAOIs into other areas of medicine might extend their availability for psychiatry, and so allow their continuing use in the original indications.

1. **Conclusion**

MAOIs are valuable medicines in the treatment of several common mental disorders, including treatment-resistant depression, and certain anxiety disorders (especially social phobia and PTSD). However, expertise in prescribing MAOIs, as well as availability of these medications, has been declining for a variety of reasons. This paper has provided a concise overview on the safe and effective prescribing of MAOIs, whilst noting the need for more research on their relative efficacy and safety profiles both within the medication class and between classes. The growing interest in using MAOIs for non-psychiatric indications was also mentioned, which we hope will support their continued availability. There should be greater emphasis on enabling psychiatrists to gain experience of prescribing MAOIs, so that patients continue to have access to the necessarily wide range of treatment options.

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***Table 1****. Common features of serotonin syndrome (left) and hypertensive crises (right). Adapted from Grady & Stahl, 2012. Note: only some features may be present.*

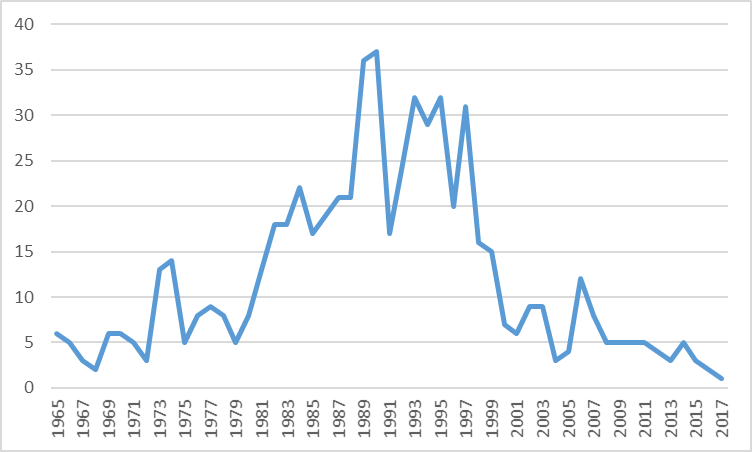
|  |  |  |
| --- | --- | --- |
| **Serotonin syndrome** |  | **Hypertensive crisis** |
| Psychomotor agitation |  | Elevated blood pressure (e.g. >120mmHg diastolic) |
| Excessive sweating |  | Bradycardia or tachycardia |
| Tremor |  | Palpitations |
| Hyperreflexia |  | Headache |
| Elevated temperature |  | Nausea and/or vomiting |
| Involuntary muscle contractions (clonus) |  | Neck pain or stiffness |
| Increased muscle tone and rigidity (hypertonia) |  | Excessive sweating |
|  |  | Ocular system changes such as photophobia or dilated pupils |
|  |  | Chest pain |

***Table 2.*** *Foods/drinks to avoid, and those that are allowed, in people taking MAOI. Table reprinted and adapted with permission of the authors from the Sunnybrook Health Sciences Centre.*

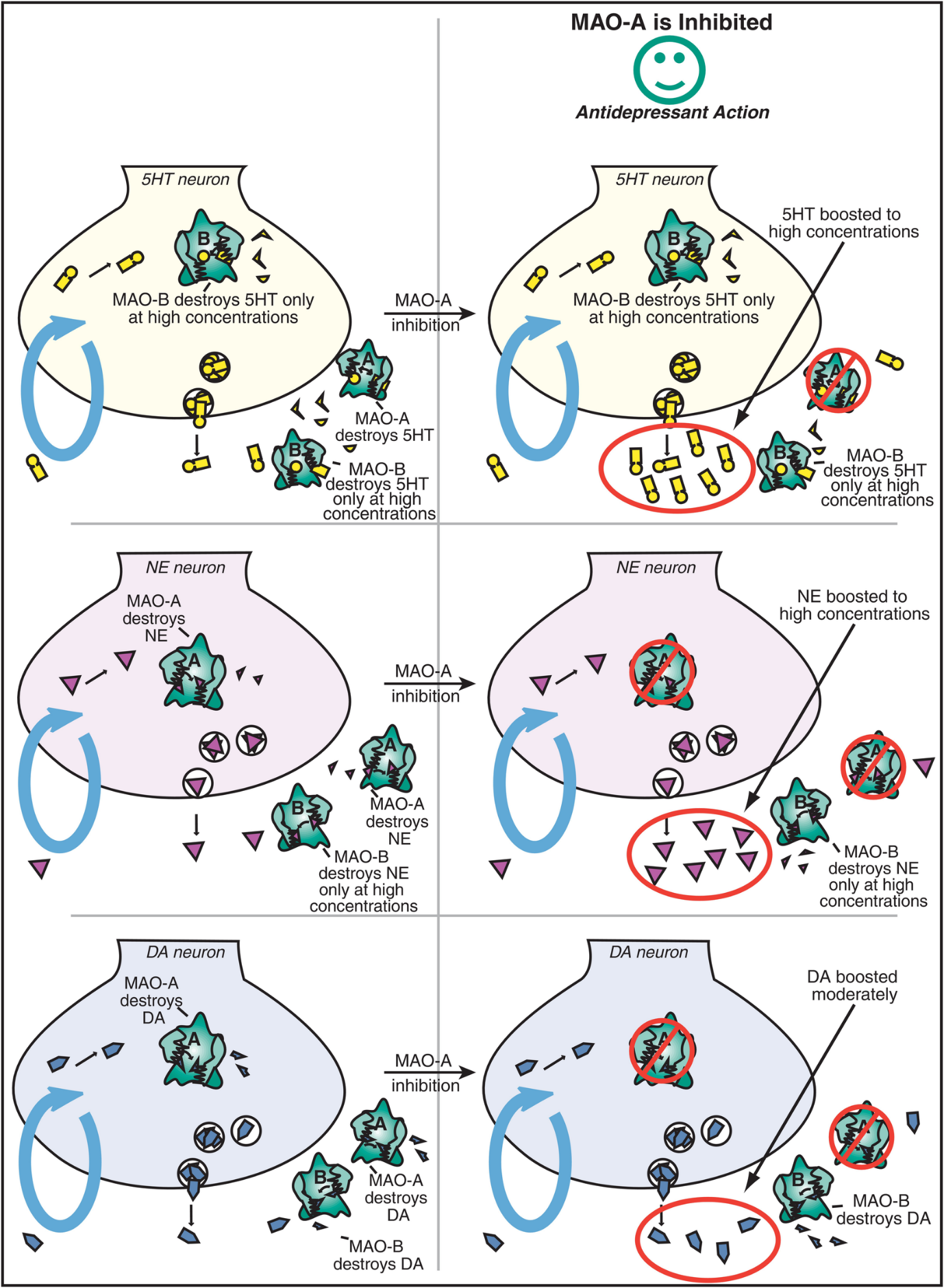
|  |  |
| --- | --- |
| **Foods and drinks to avoid** | **Foods and drinks allowed** |
| *Cheese* |  |
| All matured or aged cheese | Fresh cottage cheese, cream cheese, ricotta cheese, and processed cheese slices. All fresh milk products that have been stored properly (e.g. sour cream, yoghurt, ice 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 |

***Table 3****. Summary of MAOIs currently listed in the UK British National Formulary (BNF) available for prescription. Note that readers should consult local prescribing guidelines to check appropriate dosing and availability. Dosing suggestions are based on BNF guidelines and/or established clinical practice. Therapeutic dose refers to during acute psychiatric illnesses; maintenance doses may be lower.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Name of MAOI | Type | Major differentiation points | Current cost in British National Formulary | Relative cost to prescribe | Suggested dosing in physically healthy non-elderly adults |
| Tranylcypromine | Irreversible inhibitor of MAO-A and MAO-B | Greater stimulant-like activity than others. Insomnia, nausea, nervousness, elevated blood pressure may be more common. Less likely to lead to weight gain. | £288.36 / 28 10mg tabs | +++ | Initially 10mg twice daily, prior to 3pm. Usual therapeutic dose total of 20mg to 60mg per day in divided doses. |
| Phenelzine | Irreversible MAO-A inhibitor | Less hepatotoxicity; more common postural hypotension. Higher risk of weight gain. | £22.50 / 100 15mg tabs | + | Initially 15mg given three times daily (total daily dose 45mg per day). Usual therapeutic dose total 45mg to 60mg per day, given in divided doses. |
| Isocarboxazid | Irreversible MAO-A inhibitor |  | £217.75 / 56 10mg tabs | +++ | Initially 30mg per day in single or divided doses. Usual therapeutic dose 20mg to 40mg per day. |
| Mocolobemide | Reversible MAO-A inhibitor | Potential tolerability advantages. Theoretical safety advantages due to being reversible. | £10.00 / 30 150mg tabs | + | Initially 300mg per day, in divided doses. Usual therapeutic dose 150mg – 600mg per day. |
| (Selegiline) | MAO-B inhibitor | Marked MAO-A effects only at higher doses; available in ‘patch’ form in USA for depression (see ‘future directions’) | £32.23 / 100 10mg tabs | + | Initially 10mg in the morning, then increasing in 10mg steps cautiously, at least one week between dose increases.  Usual therapeutic dose for depression 30mg to 60mg per day. |



***Figure 1****. PubMed search for articles of type ‘clinical trial’ using search terms (monoamine oxidase inhibitor) and (depression OR anxiety OR PTSD). The Y-Axis shows the number of articles identified for each year (X-Axis). The graph exemplifies the decline of research into existing and new MAOIs for such psychiatric indications.*



***Figure 2****. 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 SM, Stahl’s Essential Psychopharmacology, 3rd edition, New York, 2008, with permission* (98)