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## The prescriber's guide to classic MAO-inhibitors (phenelzine, tranylcypromine, isocarboxazid) for treatment-resistant depression

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# The prescriber's guide to classic MAO inhibitors (phenelzine, tranylcypromine, isocarboxazid) for treatment-resistant depression

## Guidelines

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## Abstract

This article is a clinical guide which discusses the “state-of-the-art” usage of the classic monoamine oxidase inhibitor (MAOI) antidepressants (phenelzine, tranylcypromine, and isocarboxazid) in modern psychiatric practice. The guide is for all clinicians, including those who may not be experienced MAOI prescribers. It discusses indications, drug–drug interactions, side-effect management, and the safety of various augmentation strategies. There is a clear and broad consensus (more than 70 international expert endorsers), based on 6 decades of experience, for the recommendations herein expounded. They are based on empirical evidence and expert opinion—this guide is presented as a new specialist-consensus standard. The guide provides practical clinical advice, and is the basis for the rational use of these drugs, particularly because it improves and updates knowledge, and corrects the various misconceptions that have

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hitherto been prominent in the literature, partly due to insufficient knowledge of pharmacology. The guide suggests that MAOIs should always be considered in cases of treatment-resistant depression (including those melancholic in nature), and prior to electroconvulsive therapy—while taking into account of patient preference. In selected cases, they may be considered earlier in the treatment algorithm than has previously been customary, and should not be regarded as drugs of last resort; they may prove decisively effective when many other treatments have failed. The guide clarifies key points on the concomitant use of incorrectly proscribed drugs such as methylphenidate and some tricyclic antidepressants. It also illustrates the straightforward “bridging” methods that may be used to transition simply and safely from other antidepressants to MAOIs.

## MAOIs: Introduction

The classic monoamine oxidase inhibitors (MAOIs), which include phenelzine, tranylcypromine, and isocarboxazid, inhibit monoamine oxidases (MAOs; A and B) in a nonselective and irreversible manner, resulting in the reduced breakdown of the neurotransmitters serotonin, norepinephrine, and dopamine.<sup>1</sup> The absolute amount of neurotransmitters is therefore increased *within* as well as outside the neuron (in contrast to treatment with selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRIs], or tricyclic antidepressants [TCAs], which yields only a relative, extracellular increase in the concentration of neurotransmitters within the synaptic cleft). This mechanism (affecting all 3 major neurotransmitters)<sup>2</sup> may explain, at least in part, the antidepressant effect of these medications (see also point 4.7.4).

### 1 Indications

- 1.1 Following insufficient response to a modern antidepressant (eg, an SSRI/SNRI, mirtazapine, bupropion) and/or a TCA, either as monotherapy treatment or with an augmentation agent (eg, lithium). MAOIs should always be considered in cases of treatment-resistant depression, including<sup>1</sup> those melancholic in nature (see point 2.4).
- 1.2 MAOIs are typically indicated prior to electroconvulsive therapy (ECT),<sup>3</sup> except when a rapid response to treatment is imperative (eg, imminent suicide risk, inanition, and catatonia).

*Note:* MAOIs can prove effective even after (failed) ECT treatment<sup>4</sup> or ketamine infusion.

- 1.3 MAOIs may also be effective for treatment-resistant anxiety and panic disorders.<sup>5,6</sup>
- 1.4 MAOIs can also be considered in the treatment of other diagnoses based on individualized considerations and patient preferences.

### 2 Selection criteria

- 2.1 Both phenelzine and tranylcypromine are highly effective antidepressants, although individual responses can differ significantly.<sup>7</sup> Fewer comparative data are available for isocarboxazid; it is therefore considered as a third/final choice among MAOIs, and is further discussed in Appendix A.<sup>11</sup>
- 2.2 This guide does not discuss other (nonclassic) MAOIs, such as the selective MAO-A inhibitor moclobemide (rather ineffective in treatment-resistant depression) and the selective

MAO-B inhibitor rasagiline (not indicated for use as an antidepressant).<sup>8</sup>

*Note:* At high doses, the selective MAO-B inhibitor selegiline also exhibits activity as an MAO-A inhibitor, and appears to be an effective (nonselective MAOI) antidepressant. As a trade-off for its (presumably) reduced efficacy compared with the classic MAOIs, selegiline may present with a better tolerability profile, and may in the future have a significant role to play in the treatment of mood disorders in selected patient populations, both as an (“off-label”) oral antidepressant<sup>9</sup> and in its approved form as a transdermal antidepressant<sup>10</sup> (available in 3 doses ranging from 6 to 12 mg/24 hour, which come with a variable, dose-dependent degree of dietary restrictions; at the lowest dose, there are none).<sup>11</sup>

- 2.3 In the case of premorbid anxiety disorder, or in the case of comorbid panic disorder, phenelzine (GABA activity) may be indicated over tranylcypromine (see also the “*note*” under point 2.4).
- 2.4 If psychomotor retardation is a prominent symptom, or in the case of a predominantly endogenous (melancholic) depression, tranylcypromine<sup>12</sup> may be indicated over phenelzine.

*Note:* Several clinician members of the Workgroup wish to emphasize that the clear-cut categorization observed in much of the original literature—reserving phenelzine for states of anxious depression and tranylcypromine for the more lethargic, melancholic manifestations—does not correlate with the weight of decades-long clinical experience, and is therefore no longer strictly tenable. They refer to severe cases of anxious depression responding to treatment with tranylcypromine (complete and sustained remission; no exacerbation of anxiety symptoms). They note, in addition, that phenelzine treatment remains particularly indicated for patients whose anxiety predates their depression.

- 2.5 The side-effect profiles of phenelzine (a hydrazine derivative) and tranylcypromine (nonhydrazine) differ considerably.<sup>13,14</sup> The side effects of phenelzine may be experienced as more troublesome:<sup>15</sup>
  - 2.5.1 With both phenelzine and tranylcypromine, there is a high probability of dose-dependent orthostatic hypotension (certainly during treatment initiation and following dose increase) due to the blood pressure (BP)-lowering effect of MAOIs (see also point 4.4).
  - 2.5.2 With phenelzine, possible side effects include weight gain, edema, somnolence, insomnia, hypoglycemia, sexual dysfunction, constipation, urinary retention, pyridoxine-deficiency, CYP450 interactions, and (rarely) hepatotoxicity.

<sup>1</sup>Several Workgroup members wish to emphasize that MAOIs may be especially effective in melancholic depressions.

<sup>11</sup>While isocarboxazid is an effective antidepressant, availability and affordability may be issues in some countries.

- 2.5.3 With tranylcypromine, possible side effects include insomnia, dry mouth, and transient increases in BP postdosing (duration: 1 to 3 hours; often asymptomatic, sometimes accompanied by palpitations or headache, which may be managed by spreading out the daily dose, or by reducing the rate of dose increases—additionally, ambulatory monitoring of BP by patient or physician is advised). Although such transient hypertension is often seen as problematic, treatment cessation is rarely necessary (see point 4.5).

*Note:* While some older literature noted a significant risk of hypoglycemia with MAOI treatment, including tranylcypromine (as derived from research in the animal model),<sup>16</sup> the later implication of the hydrazine group (present in some other MAOIs, eg, phenelzine and isocarboxazid) as the causal factor,<sup>17</sup> and the absence of this observation in the subsequent decades of tranylcypromine use in clinical settings,<sup>18</sup> imply that the risk was likely overstated: significant hypoglycemia is unlikely to manifest at therapeutic doses of tranylcypromine (in contrast to the hydrazine MAOIs).

- 2.6 A tyramine-restricted diet is required with all classic MAOIs—this is an important measure to prevent potentially significant hypertensive reactions<sup>19</sup> (see point 5).

### 3 Contraindications

#### 3.1 Absolute contraindications

- 3.1.1 The patient is incapable or unwilling to adhere to dietary and other (medication- and drug-related) restrictions.

*Note:* This includes some cases of active substance use.

- 3.1.1 Concomitant use of certain medications, supplements, or drugs that have significant activity as serotonin reuptake inhibitors (SRIs), or have significant activity as serotonin releasers at therapeutic doses. The risk is serotonin toxicity. See also point 6.1.1.
- 3.1.2 Pheochromocytoma (risk: hypertensive urgency or emergency).

#### 3.2 Relative contraindications<sup>20</sup>

- 3.2.1 Uncontrolled hypertension or hypotension (BP medication may need adjustment due to the hypotensive effect of MAOI).
- 3.2.2 Diabetes mellitus (clinical conference advised; MAOIs may cause hypoglycemia and/or can interact with insulin and other agents that lower blood glucose; therefore, the monitoring of blood glucose levels is required to decide if dose reduction of diabetes medication is necessary).

*Note:* Tranylcypromine may be indicated over phenelzine, given the difference in side-effect profiles, pertaining specifically to the relative risk of significant hypoglycemia<sup>21</sup> occurring (see point 2.5.3).

- 3.2.3 Pregnancy<sup>22</sup> (MAOIs can cross the placental barrier; risk of teratogenic abnormalities cannot be ruled out).
- 3.2.4 Breastfeeding<sup>22</sup> (MAOIs may be present in breast milk; risk unclear due to lack of literature data).
- 3.2.5 Bipolar disorder (MAOI treatment may be indicated according to randomized controlled trials, although

caution is advised relating to the risk of manic switch<sup>23</sup> if used without a mood stabilizer, eg, lithium).

- 3.2.6 Lack of recent data concerning patient health status (it is recommended to first perform a physical examination and laboratory tests to rule out/treat potential contraindications).<sup>20</sup>
- 3.2.7 Concomitant use with certain other medications (see point 6: “Interactions” for nuanced discussion), eg, monoamine releasers without significant serotonergic activity (certain indirect sympathomimetics; see point 6.1.2). The risk is a hypertensive urgency or emergency.

## 4 Treatment initiation

### 4.1 In advance

- 4.1.1 The patient must follow a tyramine-restricted diet when MAOI treatment is initiated (consult a dietitian if necessary). The diet must be maintained until 2 weeks after cessation. Awareness concerning additional restrictions (medications + supplements/drugs) is also required. The prescribing physician provides the necessary information during consultation, cautions the patient about the likely occurrence of orthostatic hypotension (limit risk of falling), makes sure the patient understands and consents, and gives him/her written educational materials, such as the *Patient Information Brochure* (see Appendix B). Additional caution is warranted in caring for geriatric patients: the prescribing physician considers both using a lower starting dose than is outlined in point 4.2, as well as slowing the rate of subsequent dose increases (points 4.3, 4.6, and 4.7); such precautions may reduce the degree of orthostatic hypotension in the treatment initiation stage.

*Note:* While proper caution is warranted, undue apprehension of MAOIs is likewise to be addressed: they are effective and safe antidepressants, provided that proper consideration is given to the basic (dietary and comedication-related) principles outlined in this guide.

- 4.1.2 It is recommended to have BP measurements prior to treatment initiation (sitting/lying, followed by standing); this way, the degree of orthostatic hypotension (and of the potential transient BP increase following dosing) can be quantified relative to baseline (see also points 4.4 and 4.5). Again, additional caution is warranted in geriatric patients.
- 4.1.3 The patient has a calibrated BP monitor at home, and is willing (especially during the treatment initiation phase and following dose increase) to regularly take his/her BP (sitting or lying, followed by 2 successive measurements while standing).
- 4.1.4 If the patient was taking an SSRI/SNRI (or other SRI, including clomipramine and imipramine) or an agent with significant activity as a serotonin releaser, then a washout period is required (duration is 5 times the half-life of the SRI or serotonin releaser) prior to MAOI treatment initiation.

*Note:* In practical terms, this means for most SSRIs and SNRIs that 8 days will suffice as a washout period, with vortioxetine and fluoxetine being notable exceptions:

- (a) Vortioxetine has a median elimination half-life of approximately 66 hours.<sup>24</sup> The calculation of the minimum washout duration comes out to 14 days.
- (b) Fluoxetine has an elimination half-life of 1 to 4 days, but that of its active metabolite, norfluoxetine, ranges from 7 to 15 days<sup>25</sup>; therefore, the calculation of the minimum washout duration comes out to 10 weeks,<sup>26</sup> although a cautious start of MAOI after 6 weeks is deemed permissible in most guidelines.<sup>27,28</sup>

*Note:* a longer washout (>6 weeks) is recommended if high doses of fluoxetine were used.

4.1.5 The requirement (in the discussed cases) of a washout period prior to MAOI initiation may have important clinical implications. The patient is likely to be severely ill, so that even a short time with no antidepressant relief may prove intolerable. The addition of a different, “bridging” agent may be considered—nortriptyline (TCA), lithium, and low-dose ( $\leq 15$  mg) mirtazapine are prime candidates for this role, as they can safely be added both to the serotonergic agent that is being (or has been) tapered off, and to the MAOI that will be started after the washout period.

4.1.6 The prescribing physician alerts the patient’s primary care doctor, and directs him/her to this *Prescriber’s guide*.

*Note:* Before undergoing dental work, the patient needs to alert the dentist that he/she is taking a classic MAOI. When administering a local anesthetic, the dentist exercises the proper care concerning the choice of an appropriate anesthetic agent and dose (eg, avoids cocaine, considers using lower doses of adrenaline and reducing treatment duration, or uses felypressin instead of adrenaline in patients with cardiovascular or cerebrovascular conditions). If possible, additional measures may be employed to avoid intravascular injection of the local anesthetic (fractionated injection and aspiration test).

*Note:* In the case of phenelzine treatment, supplementation with pyridoxine hydrochloride (vitamin B6) is advisable; see also point 6.6.3(e). It may be added either at the start of phenelzine treatment, or if/when related side effects appear (clinician’s choice).

#### 4.2 Starting dose

4.2.1 The starting dose is one daily tablet of 10 mg tranylcypromine or one tablet of 15 mg phenelzine (if a compounded preparation is used, the equivalent dose is 25.8 mg phenelzine sulfate).

4.2.2 The patient takes his/her BP 3×/week, 2×/day (sitting/lying, followed by 2 successive measurements while standing for  $\geq 1$  minute;<sup>29</sup> this is to assess the degree of orthostatic hypotension).<sup>20</sup>

*Note:* Early side effects may include gastrointestinal symptoms and sedation; they are likely to improve (or resolve) with continued treatment.

#### 4.3 First dose increase

4.3.1 In principle, a slow regimen of dose increases is advised, certainly in ambulatory patients, to reduce

the burden of side effects. If the severity of the depressive episode requires a faster dose increase regimen, this can also be considered, particularly in an inpatient context.

4.3.2 If the starting dose is well tolerated, the first dose increase can take place 3 to 5 days later (dose increase to 20 mg tranylcypromine or 30 mg phenelzine).

4.3.3 If the starting dose elicits significant orthostatic hypotension (possible but unlikely), then one can consider slowing the rate of further dose increases. See also point 4.4.

4.3.4 If transient BP increase is observed (possible, certainly with tranylcypromine), see point 4.5.

#### 4.4 In the event of orthostatic hypotension

4.4.1 Significant orthostatic hypotension ( $\geq 10$  to 15 mmHg systolic BP) is a predictable effect of MAOI treatment. From clinical observation, this hypotensive effect has been shown to occur shortly after a dose increase, and typically reaches its peak 10 to 14 days later. Thereafter, a gradual lessening of the hypotensive effect is observed. Even in initially severe cases, patients often note significant improvement over time (typically after 3 to 4 weeks). To bridge this period, maintaining the dose (or even temporarily lowering it) is advised. Additionally, one may consider the following options: spreading the MAOI daily dose, increasing water intake, increasing dietary salt intake<sup>30</sup> (or using salt tablets),<sup>31</sup> the use of compression stockings, as well as temporarily adding fludrocortisone<sup>III</sup> if the current rate of improvement is inadequate. The cessation of MAOI treatment is only rarely necessary.

*Note:* Several clinician members of the Workgroup mention the successful treatment of exercise-induced hypotension in MAOI patients with propranolol. This is a novel treatment strategy in expert clinical practice; there is no relevant literature at present (this means confirmatory research is required; implement with care).

#### 4.5 In the event of a transient BP increase

4.5.1 This side effect can arise shortly after MAOI dosing (mostly with tranylcypromine).<sup>32</sup> A rise in BP is then observed for a couple of hours (the rise in BP is often limited, although in extreme cases it can reach 180 to 200 mmHg systolic). Considering the limited duration of this BP increase, the risk is most often limited; therefore, treatment is typically not indicated—although it may still be advisable in more severe cases. In the first instance, administration of a benzodiazepine (alprazolam or lorazepam) and/or propranolol is useful.

*Note:* This side effect may be observed incidentally in the context of self-recorded BP measurements by the patient, and should be reported to the physician. Given the limited duration of this BP increase, a cautious approach to treatment is in order (to avoid the risk of hypotensive overshoots). One may consider the following

<sup>III</sup>Some clinicians prefer to treat orthostatic hypotension with dopamine antagonists, such as domperidone or metoclopramide (see Zandee *et al.* 2017), but risk-benefit balance must be considered (same with fludrocortisone).

options: spreading out the daily dose of tranylcypromine (lowers peak plasma concentrations), temporarily reducing the dose, and/or administering propranolol. Long-term treatment with a benzodiazepine is inadvisable. In case of insufficient improvement, consider swapping (after washout of 14 days) to phenelzine.

#### 4.6 Second dose increase

4.6.1 If side effects are well tolerated, then—after 3 to 5 days on 20 mg tranylcypromine or 30 mg phenelzine—one can increase the dose to 30 mg tranylcypromine or 45 mg phenelzine. It is useful, given the potential occurrence of significant orthostatic hypotension, to maintain this dose for 10 days (certainly in ambulatory settings). If partial response is observed, one can maintain this dose for 2 to 4 weeks to see if further improvement occurs.

#### 4.7 Additional dose increase(s)<sup>IV</sup>

4.7.1 After step 4.6, one can increase the dose, guided by clinical effect and side-effect tolerability. The typical effective dose range is 30 to 60 mg tranylcypromine or 60 to 90 mg phenelzine.

4.7.2 In the case of tranylcypromine, expert clinicians may increase the tranylcypromine dose if such is therapeutically indicated, until a maximum dose of 80 to 100 mg tranylcypromine is reached.

4.7.3 While some improvement in depressive symptoms may be observed within several days/weeks, the full antidepressant effect of a given dose may be achieved only after 4 to 6 weeks; with phenelzine, this may even take 8 to 12 weeks (due to an assumed initial inhibition of its own metabolism, as phenelzine is both a substrate and inhibitor of MAO).<sup>33</sup>

4.7.4 Aside from the known inhibition of MAO, both MAOIs likely have additional antidepressant mechanisms: with tranylcypromine, a working hypothesis (confirmatory research required) includes potential activity as a norepinephrine reuptake inhibitor at a dose of 40 to 60 mg,<sup>34</sup> and potential dopamine-releasing activity at 100 mg;<sup>35</sup> phenelzine is metabolized on a dose-related basis to several metabolites, including  $\beta$ -phenethylamine (releases dopamine and norepinephrine) and  $\beta$ -phenylethylidinedihydrizine (increases brain GABA levels).

*Note:* In older literature, it was advised to lower the dose gradually following antidepressant response, because a low “maintenance dose” would suffice for maintaining the achieved MAO inhibition. Because of a high chance of depressive relapse, this method is no longer advised. It is best to continue treatment with the same dose with which antidepressant response was achieved (exception: significant/persistent agitation or overstimulation may resolve with dose reduction).

### 5 Tyramine-restricted diet<sup>26</sup>

5.1 The patient must follow a tyramine-restricted diet, as the inhibition of MAO reduces the capacity for a breakdown of exogenous tyramine in the gastrointestinal tract and liver, leading to BP increases via peripheral norepinephrine

release (which can, in serious cases, result in a hypertensive urgency or emergency).<sup>36</sup> Tyramine is formed by the decarboxylation of tyrosine, and may be present in high quantities in some foodstuffs which have been fermented, matured, or spoiled. Examples include:

- some aged cheeses;
- some artisan beers which use natural yeasts instead of starter cultures, such as the Belgian “Lambic” beer;
- some fermented meats (eg, some salamis);
- fermented products such as tempeh, miso, soy sauce, sauerkraut, marmite, and kimchi.

For extensive elaboration, see “*The Prescriber’s guide to the MAOI diet—thinking through tyramine troubles.*”<sup>37</sup>

Additionally noteworthy:

- Thanks to modern food standards, the amount of tyramine present in many (but not all) foodstuffs has been considerably reduced (compared to the 1950s and the 1960s, when MAOIs were first on the market). This means MAOI treatment is safer now than ever, given the limited risk of excessive tyramine ingestion.
- Tyramine sensitivity differs significantly from person to person. In tyramine-sensitive MAOI patients, consumption of 10 mg of tyramine in a meal can cause a noticeable BP increase; in the “average” MAOI patient, this may require closer to 20+ mg of tyramine.
- BP increase after excessive tyramine consumption is typically maximal within 2 hours.

*Note:* For treatment advice in case of hypertensive urgency or emergency, see point 8.2.

### 6 Interactions<sup>14,26,38</sup>

#### 6.1 Pharmacodynamic interactions

##### 6.1.1 MAOIs should not be combined with:

SRI or agents with significant serotonin-releasing activity. The risk is serotonin toxicity.

*Note:* Serotonin toxicity<sup>39</sup> (or serotonin syndrome) is a dose-related response; symptoms (such as tremor, hyperreflexia, and clonus) are placed on a spectrum,<sup>40</sup> whereby the severity is determined by the elevation of intrasynaptic serotonin (which is mediated by serotonin reuptake inhibition and/or presynaptic release of serotonin).

##### 6.1.2 Great caution is advised when combining MAOIs with:

Monoamine releasers without significant serotonergic activity (certain indirect sympathomimetics). The risk is a hypertensive urgency or emergency.

*Note:* Combining MAOIs with certain other (direct or indirect) sympathomimetics is comparatively safer, and is therefore possible if therapeutically indicated (caution warranted; use low testing dose, slow dose increases, while considering the risk-benefit balance). See also points 6.4 to 6.6.

#### 6.2 Pharmacokinetic interactions

6.2.1 Tranylcypromine is an inhibitor of i.a. CYP2A6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, and CYP2B6; clinically significant interactions are unlikely at typical therapeutic doses, with possible exceptions being the inhibition of CYP2A6 (“low clinical relevance” due to

<sup>IV</sup>*Note:* For doses greater than those recommended in the product information, additional informed consent may be required in some jurisdictions.

the “very minor role” CYP2A6 plays in the metabolism of drugs),<sup>35</sup> and the inhibition of CYP2C19 (possibly clinically relevant in poor metabolizers or when high doses [ $>60$  mg/day] of tranylcypromine are used).<sup>41</sup>

- 6.2.2 Phenzazine<sup>42</sup> (a hydrazine derivative) is an inhibitor of i.a. CYP3A4, CYP2C19, CYP1A2, CYP2C9, CYP2D6, and CYP2B6; clinically significant interactions may potentially occur at typical therapeutic doses (lack of literature data; some studies exist suggesting the need for dose reductions of some medications, such as carbamazepine). Moreover, phenazine is an inhibitor of primary-amine oxidases, also referred to as semicarbazide-sensitive amine oxidases<sup>43</sup>—the relevance for clinical practice is unclear at present due to a lack of literature data.

*Note:* The inhibition of MAO can in a (very limited) number of cases involving concomitant medication give rise to pharmacokinetic interactions—namely if the medication in question is metabolized by MAO (eg, a lower dose of sumatriptan<sup>44</sup> is required due to significantly increased peak plasma concentrations and half-life).

### 6.3 Absolute contraindications

#### 6.3.1 Combinations that must be avoided (because of SRI activity).<sup>40,45</sup>

- All SSRIs (eg, paroxetine, fluoxetine, fluvoxamine, citalopram, escitalopram, sertraline, vortioxetine, vilazodone, and dapoxetine).
- All SNRIs (eg, venlafaxine, desvenlafaxine, milnacipran, levomilnacipran, duloxetine, and sibutramine).
- Imipramine and clomipramine (other TCAs are safe if appropriately/cautiously administered). The structurally similar drug cyclobenzaprine is also best avoided.
- Chlorpheniramine and brompheniramine (other antihistamines are safe).
- Some analgesics<sup>46</sup> (eg, dextromethorphan, dextropropoxyphene, levorphanol, pentazocine, meperidine (=pethidine), methadone, tramadol, and tapentadol).
- Ziprasidone<sup>47,48</sup> and lumateperone<sup>45</sup> (the only antipsychotics currently on the market with significant SRI activity).

*Note:* Washout period required prior to starting MAOI (typical duration is 5 times the half-life of the SRI).

#### 6.3.2 Combinations that must be avoided (because of serotonin-releasing activity):

- Amphetamines in medium/high doses
- Fenfluramine

*Note:* Washout period required prior to starting MAOI (typical duration is 5 times the half-life of the serotonin-releasing agent).

#### 6.3.3 Combinations that must be avoided (because of various/other mechanisms of interaction; paucity of literature data):

- Some antihypertensives (eg, methyl dopa and reserpine).

- Pancuronium (a muscle relaxant that is sometimes used with general anesthetics).<sup>49</sup>
- Various illicit drugs (eg, cocaine and MDMA) and some licit/illicit supplements (eg, ayahuasca and St. John’s wort).

*Note:* With *St. John’s wort* (*Hypericum perforatum*), the risk of serious interactions (eg, serotonin toxicity) is likely limited—but a lack of therapeutic rationale implies a negative risk-benefit balance.

- Concomitant use of other (classic or reversible/selective) MAOIs (eg, isocarboxazid, pargyline, selegiline, rasagiline, isoniazid, iproniazid, and moclobemide); there is often a lack of rationale for concurrent use of multiple MAOIs (as well as a paucity of literature data on the relative safety of such combinations). This absolute contraindication includes *all* agents with potent, albeit perhaps incidental, MAOI activity, such as methylthionium chloride (methylene blue) and linezolid.

*Note:* Washout period required when switching from MAOI to MAOI (most guidelines advise 14 days if the first agent was also an irreversible MAOI<sup>27</sup>—but expert clinicians have deviated from this precept in cases that allow for cautious/constant monitoring; see also point 7).

### 6.4 Relative contraindications (strong)

#### 6.4.1 Combinations that are, in principle, advised against because of activity as monoamine releaser (without significant serotonergic activity):

- Amphetamines in low doses

*Note:* Lisdexamphetamine is potentially safer than other amphetamines (including methamphetamine and dexamphetamine), owing to its lower peak plasma concentrations and longer  $T_{max}$ .

- Ephedrine and pseudoephedrine

*Note:* Caution is required concerning decongestants and cough medicines that contain these agents.

*Note:* Ephedrine is safer than amphetamine (lower potency), and pseudoephedrine is safer than ephedrine (same reason).

#### 6.4.2 Combinations that are, in principle, advised against because of resulting increases in neurotransmitter concentrations (lack of literature data):

- Precursors of monoamines (eg, 5-HTP, L-dopa, and L-tryptophan)

*Note:* The combination MAOI + L-tryptophan (as augmenting agent) is sometimes used by experienced clinicians.<sup>50</sup> Serotonin-mediated side effects may occur<sup>51</sup> if doses over 2 g of L-tryptophan are used; significant caution is advised.

#### 6.4.3 Combinations that are, in principle, advised against because of other mechanisms of interaction (paucity of literature data):

- Disulfiram;
- Bromocriptine;
- Hydralazine;
- Buspirone;

- (e) Guanethidine (may be administered at a lower dose if deemed clinically necessary).

6.4.4 *Combinations that are considered comparatively safe in reduced doses (although caution is advised because of possible potentiation):*

- (a) Epinephrine (=adrenaline), norepinephrine (=noradrenaline), phenylephrine, isoproterenol (=isoprenaline), and dobutamine

*Note:* These agents are nonselective adrenergic agonists (exerting direct sympathomimetic activity).

*Note:* Upon administration of epinephrine for anaphylactic shock in MAOI patients, a lowered initial dose is required because of potentiation (after which, uptitration based on effect is possible). If an MAOI patient carries an EpiPen, the dose of this EpiPen should likewise be adjusted.<sup>V</sup>

6.5 **Relative contraindications (weak)**

6.5.1 *Combinations that are considered mostly safe in reduced doses (although caution is advised because of possible potentiation):*

- (a) Triptans<sup>52</sup> (*note:* sumatriptan and zolmitriptan<sup>53</sup> are both metabolized by MAO; either avoid or use in significantly lower dose);  
 (b) Oxymetazoline and xylometazoline;  
 (c) Fentanyl.

6.6 **Safe to combine (although caution is advised because of possible potentiation of effect and side effect):**

6.6.1 *In general:*

- (a) Antipsychotics (other than ziprasidone and luma-teperone, because of SRI activity);  
 (b) Anticholinergics;  
 (c) Antihistamines (other than chlorpheniramine and brompheniramine, because of SRI activity);  
 (d) Benzodiazepines (note that additional BP-lowering effect may occur);  
 (e) Opioid analgesics that do not have significant serotonergic activity.

6.6.2 *As augmenting agents (low testing dose + slow rate of dose increases; monitoring of side effects advised):*

- (a) Lithium;  
 (b) Methylphenidate;  
 (c) Modafinil;  
 (d) Bupropion;  
 (e) Reboxetine;  
 (f) Triiodothyronine (T<sub>3</sub>)<sup>54</sup>;  
 (g) Pramipexole;  
 (h) Agomelatine;  
 (i) TCAs (other than imipramine and clomipramine, because of SRI activity)

<sup>V</sup>In patients on MAOIs with orthostatic hypotension, exogenous epinephrine may result in a reversal of the typical BP effect of large doses of epinephrine, from a pressor response (mediated by alpha receptors) to a depressor response (mediated by beta-2 receptors). If administration of epinephrine causes increased hypotension, further epinephrine is contraindicated and alternative pressors will be required.

*Note:* Of the remaining TCAs, amitriptyline has the most pronounced serotonergic activity; the combination (amitriptyline + MAOI) does not, however, result in serotonin toxicity. Therefore, there is no risk of serotonin toxicity when combining nortriptyline, desipramine, and so on with MAOIs. Nevertheless, caution is advised when administering this combination (MAOI + TCA), based on the specific properties of the selected augmenting agent (eg, desipramine is known to increase endogenous norepinephrine concentrations and to potentiate its vasoconstrictor effects). In counterpoint, the combination (MAOI + TCA) may offer some protection against excessive tyramine consumption, as NRIs attenuate the tyramine pressor response.<sup>13</sup>

*Note:* As TCAs are not a pharmacologically homogenous group, drug selection is of prime importance;<sup>55</sup> an exceedingly low starting dose and slow uptitration to a decreased maximum dose is required (suggested starting dose: ¼ of the typical starting dose). The order in which combination treatment is best administered (TCA first vs MAOI first vs simultaneous initiation and uptitration) remains a point of some contention. Much of the older literature that advocates against “MAOI first,” is based on case reports that (a) stem from a time when knowledge of serious drug-drug interactions was less extensive (eg, imipramine-induced serotonin toxicity in MAOI patients),<sup>56</sup> and (b) feature high starting doses for the TCA and/or an entirely too rapid rate of subsequent dose increases. Following a comprehensive reevaluation of the relevant data,<sup>57</sup> it was concluded that the efficacy and safety of the TCA + MAOI combination is unlikely to be governed by the order of treatment initiation. The Workgroup wishes to emphasize the need for strict adherence to the fundamental tenets of good pharmacology, as discussed above.

*Note:* Ketamine<sup>58</sup> and esketamine<sup>59</sup> appear, in principle, likewise safe to combine (sparse literature data at present; low starting dose, cautious uptitration, and BP monitoring advised).

While the above augmenting agents may be safely co-administered with an MAOI, the Workgroup wishes to underline once more that cautious introduction of the augmenting agent is in order.

6.6.3 *To manage side effects:*

- (a) For insomnia: trazodone<sup>VI,40</sup> (50 mg) or mirtazapine (7.5-15 mg) or doxepin (5-25 mg)

*Note:* These agents have no significant SRI activity at the doses mentioned.<sup>40</sup>

*Note:* Insomnia is a prominent side effect of MAOI treatment (and may be worse with tranylcypromine than with phenelzine). While the severity of this side effect may lessen during long-term treatment, it rarely dissipates fully. Patients may be advised to take the last dose earlier in the day<sup>VII</sup>; this may help somewhat. If improvement is insufficient, consider adding zolpidem or lorazepam.

<sup>VI</sup>We make mention of two recent case reports in the Dutch literature,<sup>89</sup> in which interactions (possible “serotonin syndrome”) were reported following comedication with low-dose trazodone (50-100 mg) in tranylcypromine patients. A response was formulated by a pharmacist at the “Geneesmiddelen Informatie Centrum” of the Royal Dutch Pharmacists’ Association (KNMP): “The case reports have insufficient information to ascertain whether these were cases of serotonin syndrome, and whether the symptoms occurred because of the tranylcypromine- and trazodone-comedication.” Additionally, *mechanistic substantiation of the interaction is hardly possible* (see Reinders 2014 for “citation” and paraphrase).

<sup>VII</sup>Seemingly paradoxically, for some patients it helps to take the daily dose(s) closer to bedtime (reason unclear; drug idiosyncrasy is a proffered explanation).



- (b) For severe/persistent orthostatic hypotension, see point 4.4.
- (c) For transient hypertension postdosing (mainly with tranylcypromine), see point 4.5.
- (d) For edema (mainly with phenelzine): sometimes improvement over time; consider additionally: dose reduction, use of compression stockings, and treatment with diuretics (caution is advised concerning the potential increase of hypotensive effect). If improvement is insufficient: consider stopping phenelzine and starting tranylcypromine (following washout).
- (e) For paresthesia and/or peripheral neuropathy (with phenelzine): supplement with pyridoxine hydrochloride (vitamin B6); recommended dose: 25 to 50 mg.<sup>60</sup>
- (f) For midday somnolence (more common with phenelzine): caffeine in moderation may help somewhat; consider cautious addition of low-dose methylphenidate or modafinil.

## 7 Interim conclusions

- (a) The above recommendations are aimed at preventing/limiting the risk of serious drug-drug interactions; they are formulated, as befitting of a specialist-consensus standard, in a general and undifferentiated sense. Several clinician members of the Workgroup wish, therefore, to reiterate the purpose of this document: it is a *guide*, not a rulebook. The best medical care is delivered on a case-by-case basis, and expert clinicians have been known to deviate from the precepts discussed in this *Interactions* section (or in this guide in general). For example:
  - Successful initiation of MAOI treatment in patients on disulfiram (strong relative contraindication). This combination may induce confusional states “akin to delirium,”<sup>20</sup> which may be explained mechanistically (unconfirmed) by comedication-induced increases in aldehyde concentrations.<sup>61</sup> Even so, expert clinicians report having used this combination without serious adverse events.
  - Successful comedication in MAOI partial responders with full-dose trazodone (200-400 mg), or mirtazapine (45-60 mg), or (in tranylcypromine cases) amitriptyline (80-150 mg).<sup>62</sup>
  - Successful, albeit cautious, coadministration of methadone without serious adverse events.
  - Successful, albeit cautious, comedication with either lisdexamphetamine or methamphetamine to remedy phenelzine-induced daytime somnolence that did not adequately respond to methylphenidate or modafinil.
  - Successful treatment with very high MAOI doses (that exceed the typically recommended maximum doses)—eg, 120 to 170 mg tranylcypromine<sup>63</sup> or 120 mg phenelzine.<sup>64</sup>
  - Successful cross-taper<sup>65</sup> (or even abrupt switch)<sup>66</sup> from MAOI to MAOI (note that additional research is required; this strategy remains highly controversial).

Note that these are treatment strategies used by experts; they are not to be used without great caution and consideration (and a second opinion).

In summary, this document is a detailed introduction to the use of classic MAOIs in clinical settings; it is meant merely to *guide*—not to restrain experienced practitioners, whose insights and intuitions may overrule these general considerations.

- (b) In the past, combining MAOIs with other pharmaceuticals was considered “too risky”—often without a solid clinical or pharmacological basis.<sup>67</sup> Assuming proper adherence to the discussed considerations, there is no sound reason to categorically exclude potentially effective combination therapies. It is wise to abide by the age-old adage “start low, go slow.” As a counterweight to the alleged risks of MAOI treatment—with or without the addition of an augmenting agent—one must consider the known risk of longstanding depression left improperly treated; the costs to the patient, to their loved ones, and to society are immense. It is vital, therefore, that treatment regimens are optimized<sup>68</sup> based on modern pharmacological literature and clinical insights.

## 8 Various

### 8.1 *In case of surgery*<sup>46</sup>

8.1.1 In past literature concerning (elective) surgery in MAOI patients, authors typically advocated for the cessation of MAOI treatment (at least 2-3 weeks beforehand), citing the risk of interactions in a perioperative setting. At present, drug-drug interactions have been elucidated to such an extent (see point 6), that it can be reasonably assumed that the psychiatric risk of depressive relapse often outweighs the somatic risk,<sup>VIII</sup> given that it is in most cases possible<sup>IX</sup>—via careful choice (or dose adjustment) of anesthetic and analgesic agents used before and during surgery (as well as in post-operative care)—to avoid potentially serious interactions.<sup>69</sup>

8.1.2 The MAOI should not be discontinued without conferring with the prescribing psychiatrist.

### 8.2 *Treatment of hypertension following excessive tyramine consumption*<sup>70</sup>

8.2.1 This BP increase is self-limiting (and is typically maximal within 2 hours), so that intensive treatment incurs a real risk of hypotensive overshoots (eg, use of sublingual nifedipine is strongly contraindicated).<sup>71</sup> For this reason, the recommendation (in some of the literature) to prescribe labetalol capsules for home use cannot be supported. It is likely better to opt instead for the administration of a benzodiazepine and to monitor BP. If the severity of the hypertensive episode warrants additional care, the emergency physician treats these cases with the best clinical judgment, taking into consideration the limited duration of the tyramine reaction (eg, considers infusing phentolamine, which has an elimination half-life of only 19 minutes).

8.2.2 The risk of a serious BP increase is limited (owing to improved food standards and increased clarity of dietary guidelines) but cannot be fully ruled out. In severe cases, there is a distinction made between hypertensive urgencies (systolic BP  $\geq 180$  mmHg and/or diastolic BP  $\geq 110$  mmHg without end-organ

<sup>VIII</sup> Additionally, there is some evidence indicating that cessation of MAOI treatment shortly before surgery may incur the risk of hemodynamic instability, presumably due to incomplete reversal—given the limited timeframe—of various MAOI-induced (neuro)physiological adaptations; we make mention, in this respect, of a case report<sup>91</sup> describing cardiovascular collapse (generalizability unclear).

<sup>IX</sup> For exceptions, see Wilting *et al.* 2009.

damage) and hypertensive emergencies (with end-organ damage).

## 9 Treatment duration and dose

- 9.1 Long-term treatment is typically advised for treatment-resistant depression responding to MAOIs.
- 9.2 For recommendations concerning initial dose and dose increases, see point 4.
- 9.3 It is advised to continue treatment with the same dose with which remission was attained.

## 10 Treatment cessation

- 10.1 A gradual dose reduction is advised (eg, reduce dose by 10 mg tranylcypromine or 15 mg phenelzine every 2 weeks), certainly after long-term treatment,<sup>x</sup> in order to prevent (or limit the severity of) withdrawal effects<sup>72,73</sup>—which may include “severe anxiety, agitation, pressured speech, sleeplessness or drowsiness, hallucinations, delirium, and paranoid psychosis,”<sup>74</sup> and (hypo)mania.<sup>75</sup>
- 10.2 Following treatment cessation, it is necessary to adhere for at least an additional 2 weeks (longer if an SRI is instated)<sup>76</sup> to the dietary and medication guidelines.

*Note:* After irreversible inhibition, MAO needs to be regenerated through biosynthesis<sup>77</sup> (and with tranylcypromine, possibly to some extent through biorepair).<sup>35</sup> This process may be marked by a high initial recovery rate that progressively decreases as more MAO is restored. It is generally accepted that sufficient MAO activity is restored after several weeks following treatment cessation to rule out dangerous interactions.

## Closing considerations

Classic MAOIs (phenelzine, tranylcypromine, and isocarboxazid) are of potentially life-saving efficacy in the treatment of otherwise intractable depression. Despite this, they are infrequently prescribed,<sup>26</sup> in part because of enduring misinformation regarding their risk profile. The aim of this *Prescriber's guide* is to provide a practical resource to support practicing physicians in confidently implementing MAOIs into their antidepressant armamentarium, and to ensure that trainee psychiatrists appreciate the distinctive clinical role of MAOIs.<sup>78</sup>

## Abbreviations

BP	blood pressure
ECT	electroconvulsive therapy
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
SNRI	serotonin and norepinephrine reuptake inhibitor
SRI	serotonin reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

<sup>x</sup>Protracted withdrawal syndromes<sup>92</sup> have been observed following antidepressant cessation (research data pertaining specifically to classic MAOIs are scarce); therefore, some patients may benefit from a very slow, individualized taper (eg, use of incrementally smaller dose decreases to mitigate withdrawal symptoms).

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## Disclosures.

### A. In general

This guide is a best-effort blend of empirical evidence and expert opinion. It is, from an epistemological vantage point, a living document, based on the broad consensus that is both its vice and virtue. This is to say, the process was one of critical reflection and copious revision. Contentious topics are phrased in conditional terms; divisive topics were omitted—overall, the text is better for it. Given the pharmacological complexity, discussions in this *Prescriber's guide* relating to (side) effects, (contra)indications, and drug-drug interactions are by necessity merely indicative; the enumerations and lists of (co)medications are not exhaustive.

Further research on MAOIs in clinical practice is required so that in subsequent iterations of this guide, the balance of content may shift ever toward greater objectivity (as gleaned from high-quality research studies).

### B. Author-specific:

**Vincent Van den Eynde** (first author) is an external research consultant for, and receives or has received consulting fees from: PsychoTropical Research, NeuraWell Therapeutics, and Aristo Pharma GmbH; he has stock options in NeuraWell Therapeutics. He is the only author who received consulting fees (from PsychoTropical Research) specifically for the writing of this guideline.

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## Appendix A. Isocarboxazid

### Introduction

Like phenelzine, isocarboxazid is a classic (irreversible and nonspecific) hydrazine-derivative MAOI. It has been colloquially referred to as *phenelzine lite*, in that it exerts robust (albeit slightly lesser)<sup>79</sup> antidepressant effects,<sup>80</sup> and is generally better tolerated. This makes isocarboxazid a valuable addition to the short list of classic MAOI antidepressants,<sup>81</sup> to be used either as a second/third option (if phenelzine or/and tranylcypromine are not well tolerated), or indeed as a worthy first option—certainly at the higher end of the dose range (≥50 mg), at which point its efficacy may well rival that of phenelzine/tranylcypromine (although side effects are likewise increased).

There are 2 practical points of note: the first point centers on potential issues of affordability and availability (isocarboxazid is registered in Denmark, the UK, and the USA; it is also available in Iceland, the Czech Republic, and Iran); the second point centers on the relative paucity of literature data, so that the prescriber has fewer resources to consult regarding recommendations on dosing, management of side effects, and avoiding interactions. This appendix

provides an additional such resource, bearing in mind that the bulk of the main guide also applies to isocarboxazid. Here are some additional, more specific topics of consideration:

### Indications

Isocarboxazid is indicated for use in treatment-resistant depression. It has been used to great effect in various subtypes of depression,<sup>82</sup> including so-called “atypical” presentations (with symptoms that may include heightened interpersonal sensitivity,<sup>83</sup> mood reactivity, hypersomnia, feelings of excessive guilt, significant changes in weight, and/or appetite), as well as more melancholic (“endogenous”) manifestations (marked mainly by psychomotor retardation)—although in the latter case higher doses of isocarboxazid may be required.<sup>84</sup> For (relative/absolute) *contraindications*, see the main guide, point 3.

### Dosing

The recommended starting dose is 10 mg. In principle, a slow rate of dose increases is advisable, much like is outlined in the main guide (point 4). The typical effective dose range<sup>X1</sup> is 30 to 60 mg. Expert clinicians have raised the dose up to 80 mg—observing both superior antidepressant effects, and a greater incidence and severity of *side effects*<sup>85</sup> (most notably anticholinergic effects such as constipation, dry mouth, and urinary hesitancy, but also increased carbohydrate cravings, insomnia, and subjective feelings of weakness which may be attributable to MAOI-induced orthostatic hypotension).<sup>84</sup> Edema may also present as a side effect of isocarboxazid treatment; it may respond to supplementation with pyridoxine (vitamin B6).<sup>86</sup> In rare cases, hepatotoxicity has been noted.

The principles governing drug-drug *interactions* are outlined in point 6 of the main guide; they apply for all classic MAOIs. The same holds true regarding recommendations on *side-effect management*, *treatment duration*, and *cessation*, and various other aspects of MAOI use (eg, in cases of *dental work* and *elective surgery*).

## Appendix B. Patient information brochure

Your doctor has prescribed you a classic MAOI as a treatment for depression. This means you will be taking Phenelzine, Tranylcypromine, or Isocarboxazid.

MAOIs are effective and safe antidepressants, but there are 3 *rules* you must take into account:

1. The MAOI you are taking may lower your BP when you stand up (“orthostatic hypotension”). It is important that you follow your doctor’s instructions:
  - a. On when/how to take your BP, and on how to record the measurements.
  - b. On which dose you should take, and around what time you should take it.
  - c. On standing up slowly, because you may feel faint from the lowered BP. This side effect often improves or goes away when you keep taking the MAOI for a longer time.
2. While you are taking an MAOI, tyramine in your diet is not broken down as fast as it should be in your body. Tyramine is a substance that is present in some foods and drinks that are fermented or matured or (partially) spoiled. It is important that you:
  - a. Pay close attention to your doctor’s dietary instructions.
  - b. Read (together with your doctor) “*The Prescriber’s guide to the MAOI diet—thinking through tyramine troubles.*”<sup>87</sup> For specific recipes, see the *MAOI diet recipe book* ([sunnybrook.ca](https://sunnybrook.ca/)).<sup>87</sup>

<sup>X1</sup>Isocarboxazid is metabolized in the liver by hydrolysis, without involvement of CYP2D6; this is noteworthy in that it means no dose adjustments based on CYP2D6 genetic polymorphisms (prevalence of >7% in Denmark) are required.<sup>81</sup>

3. The MAOI you are taking may interact with certain other medications or health supplements. It is important that you:
  - a. Tell your primary care doctor that your psychiatrist has prescribed you a “classic MAOI.”
  - b. Pay close attention to your doctor’s instructions on which medications you should not take.
  - c. Do not take any health supplements or over-the-counter medications without asking either your doctor or pharmacist if it is safe (*note*: this includes cough medicines and nose drops).
  - d. Tell your dentist that you are taking a “classic MAOI” before having any dental work done.
  - e. Feel free to ask your doctor or pharmacist for extra advice or information.