

# The role of classic Monoamine Oxidase Inhibitors in treatment-resistant depression: proposal for the inclusion of Phenelzine in the Complementary List of Essential Medicines

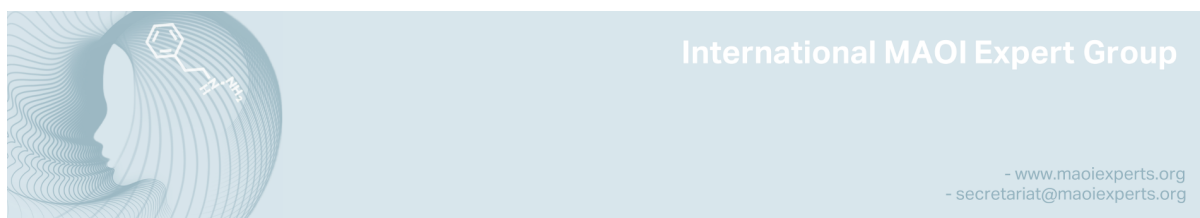
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Submitted on behalf of:

- PsychoTropical Research Institute, Queensland, Australia



- The International MAOI Expert Group (<https://maoiexperts.org>)



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Appended on the next page is a summary introduction document approved by the Presiding Council of the International MAOI Expert Group, which includes some of the most eminent academic psychiatrists and psychopharmacologists of recent decades.

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This submission is structured in accordance with the provided template document, entitled 'INFORMATION FOR APPLICANTS PREPARING A SUBMISSION FOR THE 2023 MEETING OF THE WHO EXPERT COMMITTEE ON SELECTION AND USE OF ESSENTIAL MEDICINES'.

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Having met with the Technical Department and having prepared an 'Executive Summary' in response to their comments, and regarding our submission to include phenelzine, a classic monoamine oxidase inhibitor (MAOI) antidepressant, in the EML for use in treatment-resistant depression:

Through the EML, the WHO can influence favourable outcomes regarding the continued use of out-of-patent and orphan-type drugs [1]. We request that they approve our initiative, which comes from the International MAOI Expert Group, whose members include eminent psychopharmacologists from leading institutions worldwide. This submission is also supported by the ECNP, EBC, and BAP (see below). We note that psychopharmacologists are not well-represented on the relevant EML committees and decision-making bodies; as such, we believe the supporters of the submission provide an additional balancing perspective.

MAOIs are potent antidepressants widely acknowledged as essential agents for treatment-resistant depression in most guidelines. Their underuse in practice is the result of complex influences, including the impact of pharmaceutical companies in promoting the latest patented medications and the enduring (and to a significant extent, misplaced) apprehensions about the supposed difficulties with MAOIs, which are dealt with in detail in our submission.

We emphasise that these drugs are essential for patients who do not sufficiently respond to first and second-line antidepressants. The increasing recognition of the limitations and risks of newer antidepressant drugs have given rise to concerns about their safety and tolerability. This has led to a greater appreciation of the number of patients receiving superior benefits from MAOIs.

The severe and chronic nature of the suffering and morbidity endured by these patients put them at high risk of general ill-health (YLD) and higher suicide risk from enduring insufficiently treated illness. Clinicians weigh the risk-benefit ratio with these considerations in mind, knowing that a substantial number of patients receive dramatic improvement with these drugs when little or no improvement has eventuated from previous treatments.

In our detailed submission report, we summarise the evidence that there are fewer and milder side-effects than previously supposed and that MAOIs have a positive risk-benefit balance:

- 1 the diet is now simpler than in the past, largely because foods are subject to better hygiene standards and therefore have lower tyramine levels;
- 2 the drug-drug interactions, including serotonin toxicity (formerly known as serotonin syndrome), are now well understood and reliably avoided by the educating of prescribers;
- 3 the toxicity in overdose (including deaths) is similar to the EML-approved amitriptyline;
- 4 the side-effect burden is generally of the same degree as other commonly used antidepressants;
- 5 withdrawal effects with usual clinical doses are rare and likely less than with the widely used serotonin reuptake inhibitors (due to the mechanism of MAO enzyme inhibition).

**The inclusion of phenelzine in the EML is a key step towards ensuring that individuals worldwide have adequate access to this essential medication.**

Yours sincerely,

Dr. Ken Gillman,  
Chairman of the Presiding Council

### Presiding Council

Chittaranjan Andrade © David Nutt © Gordon Parker © Elliott Richelson © Stephen Stahl © Allan Young © Michael Berk (vc) © Ken Gillman (c)

1. Bazargani, Y. T., Ewen, M., de Boer, A., Leufkens, H. G. M., & Mantel-Teeuwisse, A. K. (2014). Essential Medicines Are More Available than Other Medicines around the Globe. *PLoS One*, 9(2), e87576.

## 1. Summary statement of the proposal

This submission advocates the inclusion of phenelzine (PLZ) as an individual medicine in the Complementary List of Essential Medicines (EMLco) for use in treatment-resistant depression (TRD).

PLZ is an antidepressant (AD) of the classic monoamine oxidase inhibitor (MAOI) class. There is a broad consensus among psychopharmacologists that the classic MAOIs—which include PLZ, tranylcypromine (TCP), and isocarboxazid (ISO)—are often strikingly effective in treating severe depressions that did not sufficiently respond to other pharmacological interventions using tricyclic or modern ADs, i.e., TRD.

PLZ and the other classic MAOIs irreversibly and non-selectively inhibit both MAO-isoforms A and B. They have a unique pharmacological profile as a result, in that they increase the availability of the three major neurotransmitters (serotonin, norepinephrine, dopamine), all of which are implicated in the aetiopathophysiology of major depressive disorders (MDD). None of the other classes of ADs have this triple-action profile.

There are historical misconceptions in relation to the side-effect profile of MAOIs, owing to the occurrence of the ‘cheese effect’, a hypertensive reaction from tyramine ingestion, which was not understood in the early years of MAOI availability; these were the 1950s and early ‘60s, when the field of psychopharmacology was in its infancy. This initial uncertainty introduced the perception of MAOIs as dangerous, which has since proliferated—but has in recent years been decisively rebutted in the specialized literature. MAOI treatment is perfectly safe if properly administered. There is no element of unpredictability to the dietary and drug-drug interactions; they are typically avoidable and always controllable.

This submission requests the inclusion of PLZ in particular to the EMLco, as it is one of only two hydrazine-derivative MAOIs, the other being ISO, and has more high-quality literature in support of its efficacy, as well as more literature detailing its mechanisms of action. These include the effectuation of increases in brain GABA-levels, which may explain PLZ’s potent anxiolytic properties. The third classic MAOI, TCP, is a cyclopropylamine rather than a

hydrazine-derivative, and has a significantly different (side-)effect profile, making it non-interchangeable with PLZ.

This summary statement emphasises the widely acknowledged fact that a considerable proportion of patients treated with existing ADs experience a failed or incomplete response, which leads to chronic suffering, debilitation, huge health service related costs, and impairment of family and societal functioning. The main alternative option to MAOI treatment is electroconvulsive therapy (ECT), which can have serious side-effects, including cognitive and amnesic deficits.

Both the hydrazine (PLZ) and non-hydrazine (TCP) MAOIs thus occupy crucial niches in the treatment of depressive disorders. Their continued availability and affordability worldwide are *conditions sine qua nons* for the optimal and evidence-based treatment of TRD.

## 2. Consultation with WHO Technical Departments

A draft version of this application report was submitted for consultation purposes to the WHO Technical Department on *October 31<sup>st</sup> 2022*. Upon receipt of their initial response, we (International MAOI Expert Group) further engaged in fruitful discourse via written communication and via a video-meeting. This resulted in our writing for your consideration a summary introduction (attached, *cf. supra*, p. 2) to address the most immediately compelling topics that have arisen in said preliminary discussions relating to the potential inclusion of PLZ in the EMLco.

## 3. Other organizations and experts consulted and/or supporting the submission

- (A) The International MAOI Expert Group (Addendum A)
- (B) The European College of Neuropsychopharmacology (Addendum B)
- (C) The British Association for Psychopharmacology (Addendum C)
- (D) Members of the University of Alberta Faculty of Medicine & Dentistry (Addendum D)
- (E) Gordon Parker, Scientia professor of UNSW Sydney (Addendum E)
- (F) *Pending*

## 4. Key information for the proposed medicine

### 4.1. International Nonproprietary Name (INN) and molecular formula

The International Nonproprietary Name (INN) of the medicine is: phenelzine. The molecular formula is:  $C_8H_{12}N_2$ .

### 4.2. Anatomical Therapeutic Code (ATC) of the medicine

The Anatomical Therapeutic Code (ATC) of the medicine is: N06AF03.

### 4.3. Dosage forms and strengths of the proposed medicine

PLZ is available in the form of (a) tablets, and (b) capsules; both forms are equipotent:

- (a) Each tablet contains PLZ sulphate (phenylethylhydrazine hydrogen sulphate)<sup>1</sup> equivalent to 15 mg of PLZ base.<sup>2</sup>
- (b) Each capsule contains 25.8 mg of PLZ sulfate.<sup>3</sup>

### 4.4. Indications

#### 4.4.1. Introduction

PLZ may be used to treat a variety of psychiatric disorders. They are summarily listed hereunder to illustrate PLZ's broad pharmacological action. Following this section, the submission will focus on PLZ use in TRD, as there is no suitable alternative for PLZ in this indication (other than ISO, the only other hydrazine-derivative MAOI, which is unavailable in most countries).

#### 4.4.2. Depressive disorders

PLZ is indicated for use in depressive disorders that may be categorized by ICD-11 criteria as 'recurrent depressive disorders' (6A71), 'mixed depressive and anxiety disorders' (6A73), and as other 'specified' (6A7Y) and 'unspecified depressive disorders' (6A7Z).

By DSM-5 criteria,<sup>4</sup> PLZ is indicated for use in major depressive disorders (MDD) 'with anxious distress', 'with mixed features', 'with melancholic features', and 'with atypical features'; PLZ may also be indicated for use in other MDD subtypes (e.g., with psychotic features<sup>5</sup>).

The literature concurs that PLZ is indicated for use in TRD. Although there is some dispute as to what precisely constitutes TRD<sup>6</sup>, the term is generally used to describe a heterogeneous subset<sup>7</sup> of particularly serious MDD cases, the diagnosis of which requires the fulfilment of several operational criteria, i.e., the clinical observation of insufficient response to at least two trials with different classes of modern or tricyclic ADs<sup>8</sup>.

#### 4.4.3. Bipolar disorders

PLZ is indicated for use in bipolar disorders that may be categorized by ICD-11 criteria as ‘bipolar type I disorders’ (6A60), ‘bipolar type II disorders’ (6A61), and as other ‘specified’ (6A6Y) and ‘unspecified bipolar disorders’ (6A6Z)—albeit with a note of caution regarding the risk of a hypomanic switch if PLZ is administered without a mood stabilizer (e.g., lithium).

By DSM-5 criteria, PLZ is indicated for use in various subtypes of both bipolar I and II disorders (e.g., ‘with anxious distress’, ‘with mixed features’, ‘with rapid cycling’).

#### 4.4.4. Anxiety disorders

PLZ is indicated for use in anxiety disorders that may be categorized by ICD-11 criteria as ‘generalized anxiety disorders’ (6B00), ‘panic disorders’ (6B01), and ‘social anxiety disorders’ (6B04).

By DSM-5 criteria, PLZ may be useful in various anxiety disorders, including generalized anxiety disorders,<sup>9</sup> social anxiety disorders,<sup>10,11</sup> panic disorders,<sup>12,13</sup> and agoraphobia.<sup>14,15</sup>

#### 4.4.5. Other disorders

PLZ may be useful in the treatment of other indications, including post-traumatic stress disorders,<sup>16</sup> schizophrenic disorders,<sup>17</sup> attention deficit hyperactivity disorders, and bulimia<sup>18</sup>. But there is a paucity of reliable evidence, so that further confirmatory research is required.

### **5. Proposal for an individual medicine or representative of a pharmacological class/therapeutic group**

This submission advocates the inclusion of PLZ as an individual medicine in the Complementary List of Essential Medicines (EMLco), rather than as an MAOI class representative. This is because PLZ is a hydrazine-derivative<sup>19</sup> MAOI, whereas the other commonly used classic MAOI, tranylcypromine (TCP) has a cyclopropylamine structure<sup>20</sup>. Although they are both effective MAOI ADs, their structural dissimilarities make it so that they are not fully interchangeable, i.e., PLZ and TCP present with different therapeutic- and side-effect profiles. It is therefore not advised to select one of them as the representative of a pharmacological class.

## 6. Information supporting the public health relevance

### 6.1. Definition of TRD

This section provides a more detailed overview of definitional aspects of TRD by revisiting and adding nuance to the statement made in section 4.4.2.: ‘Although there is some dispute as to what precisely constitutes TRD<sup>6</sup>, the term is generally used to describe a heterogeneous subset<sup>7</sup> of particularly serious MDD cases, the diagnosis of which requires the fulfilment of several operational criteria, i.e., the clinical observation of insufficient response to at least two adequate trials with different classes of modern or tricyclic ADs<sup>8</sup>’.

#### Points of clarification:

- The classification TRD provides no information on the specific symptomatology of the depressive disorder (e.g., melancholic or non-melancholic depression)—hence the heterogeneous nature of TRD cases. Clinical symptoms may vary significantly in presentation, and may be indicative of aetiological distinctions<sup>7</sup> that allow for evidence-based treatment differentiation strategies. An example of this would be the preferential treatment response of ‘atypical’, non-endogenous depressive symptom clusters to MAOIs over tricyclic ADs (TCAs). This is further explored in section 8.
- The adequacy of an AD trial is determined by evaluating three key factors: dosage, duration, and patient compliance.<sup>21</sup> These factors must be assessed, and serve to differentiate true TRD from cases of pseudo-resistant depression.<sup>22</sup>
- The stipulation that trials with at least two different AD classes are required for the diagnosis of TRD is not without contention. Some authors assert that switching to an AD

from a different class is not proven to result in superior treatment outcomes when compared to an intra-class switch.<sup>21,23</sup> This assertion is buttressed by the fact that the terminology ('AD class') is pharmacologically imprecise. This is illustrated by the class of TCAs, which is comprised of medicines with distinct mechanisms of action (e.g., clomipramine and imipramine have significant serotonergic activity at therapeutic doses, whereas nortriptyline and desipramine do not).

## 6.2. Prevalence of TRD

The prevalence rates of (a) non-response and (b) incomplete response to an initial AD trial are estimated at (a) 30-50% and (b) 60-70% of MDD patients.<sup>22</sup> Estimates of the prevalence rate of TRD vary significantly: Berlim and Turecki (2007) estimate TRD prevalence at 'up to 15% of depression patients'<sup>21</sup>; both Al-Harbi (2012)<sup>23</sup> and Zhdanova et al. (2021)<sup>24</sup> provide higher estimates, placing TRD prevalence at around 30% of all medication-treated MDD cases.

## 6.3. Public health burden of TRD

The personal, societal, and economical burden of TRD is tremendously high. In a seminal cross-disciplinary study, Hays et al. (1995) quantified the effects of depression on well-being by comparing the resulting level of impairment with that of several somatic illnesses; they found that '[d]epressed patients have substantial and long-lasting decrements in multiple domains of functioning and well-being that equal or exceed those of patients with chronic medical illnesses'—including diabetes and congestive heart failure.<sup>25</sup> The quality of life in TRD patients is significantly diminished, with substantial reductions in work productivity and general activity levels.<sup>26</sup> There is a high risk of psychiatric and somatic comorbidities, including anxiety disorders, hypertensive diseases, and diseases of the central nervous system.<sup>27</sup> TRD incurs an increased suicide risk, 'greater direct and indirect healthcare resource utilization, and greater costs'.<sup>28</sup> In a six-year population-based cohort study in Hong Kong, Chan et al. (2022) established the difference in healthcare resource utilisation between non-TRD and TRD patients, and found that the latter subset accessed both psychiatric and non-psychiatric services to greater extents, leading to an 'additional \$41000 annual healthcare cost per patient'.<sup>29</sup>



6.4. Comparisons of PLZ and ‘alternative medicines currently included in the EML’  
Section 24.2.1. of the 2021 EML lists two ADs under the heading *Medicines used in depressive disorders*.<sup>30</sup> These are (a) amitriptyline and (b) fluoxetine.

(a) Amitriptyline is a TCA with pronounced activity as a norepinephrine reuptake inhibitor (NRI) via its metabolite nortriptyline, and weak activity as a serotonin reuptake inhibitor (SRI).<sup>31</sup> It is not considered a suitable alternative for PLZ in TRD, as many patients diagnosed with TRD have already shown insufficient response to amitriptyline/NRIs/TCAs. PLZ, an MAOI, has a pharmacologically dissimilar, and potentially therapeutically superior effect in TRD.<sup>32,33</sup>

(b) Fluoxetine is a selective serotonin reuptake inhibitor (SSRI). In a systematic review and network meta-analysis by Cipriani et al. (2018), it was shown to be a less effective AD than other SSRIs such as escitalopram and sertraline—which were shown, in turn, to be less effective than amitriptyline (TCA).<sup>34</sup> It is not considered a suitable alternative for PLZ in TRD, as most patients diagnosed with TRD have already shown insufficient response to one or more SSRIs.<sup>35</sup> The pharmacological profile of MAOIs, including PLZ, is distinct from that of SSRIs, and is considered therapeutically superior in TRD.<sup>36</sup>

## 7. Treatment details

### 7.1. Introduction

This submission advocating the inclusion of PLZ in the EMLco is considered by the applicants to be an important and necessary step in a series of projects aimed at revitalizing MAOI use in TRD worldwide. An important prior step was the formulation and publication of a state-of-the-art guideline for the clinical use of classic MAOIs in July of 2022. The title of this guideline is *‘The Prescriber’s Guide to Classic MAO inhibitors (phenelzine, tranylcypromine, isocarboxazid) for treatment-resistant depression’*.<sup>37</sup> It is coauthored by 44 experts, and in total over 70 experts were consulted during the drafting process. It is regarded as the culmination of decades’ worth of peer-reviewed research and clinical experience in using PLZ and the other classic MAOIs in TRD. The guideline is available open access at

<https://doi.org/10.1017/S1092852922000906> , so that it may be freely consulted by all physicians worldwide.

#### **Abstract of the *Prescriber's guide to MAO inhibitors***

This article is a clinical guide which discusses the 'state-of-the-art' usage of the classic 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 (over 70 international expert-endorsers), based on six decades of experience, for the recommendations herein expounded. They are based on empirical evidence and on 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 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 ECT—whilst taking 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 TCAs. It also illustrates the straightforward 'bridging' methods that may be used to transition simply and safely from other antidepressants to MAOIs.

The recommendations in the guideline serve to inform clinicians on topics such as 'dosage regimen and duration of treatment' and 'requirements to ensure appropriate use of the medicine', which are discussed in the following subsections.

## 7.2. Dosage regimen and duration of treatment

### 7.2.1. Dosage regimen

The dosage regimen for PLZ is best tailored to the individual on the basis of effect and side-effect. This is discussed in the *Prescriber's Guide* for both PLZ and TCP in passages 4.2, 4.3, 4.6, and 4.7, which are provided hereunder.

#### 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 3x/week, 2x/day (sitting/lying, followed by two successive measurements while standing for  $\geq 1$  min; this is to assess the degree of orthostatic hypotension).

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 3–5 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.'

*[The passages 4.4. and 4.5. of the Prescriber's Guide are provided in section 7.3 on 'Requirements to ensure appropriate use of the medicine'.]*

#### 4.6 Second dose increase

4.6.1 If side effects are well tolerated, then—after 3–5 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 2–4 weeks to see if further improvement occurs.

#### 4.7 Additional dose increase(s)

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 30–60 mg tranylcypromine or 60–90 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 80–100 mg tranylcypromine is reached.

4.7.3 Whilst 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 4–6 weeks; with phenelzine this may even take 8–12 weeks (due to an assumed initial inhibition of its own metabolism, as phenelzine is both a substrate and inhibitor of MAO).

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 40–60 mg, and potential dopamine-releasing activity at 100 mg; phenelzine is metabolized on a dose-related basis to several metabolites, including  $\beta$ -phenethylamine (releases dopamine and norepinephrine) and  $\beta$ -phenylethylidenedihydrazine (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).

#### 7.2.2. Duration of treatment

PLZ and other MAOIs are typically considered late-line (or last-line) pharmacological treatment agents in TRD. Given the severity and refractory nature of the depressive disorder, long-term treatment is typically indicated. The *Prescriber's Guide* reads as follows on this topic:

## **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.

More concrete recommendations with regard to treatment duration were deemed inadvisable, as these are best decided by the treating physician on a case-by-case basis. The *Prescriber's Guide* also addresses the connected topic of 'treatment cessation':

## **10 TREATMENT CESSATION**

- 10.1 A gradual dose reduction is advised (e.g., reduce dose by 10 mg tranylcypromine or 15 mg phenelzine every 2 weeks), certainly after long-term treatment, in order to prevent (or limit the severity of) withdrawal effects—which may include 'severe anxiety, agitation, pressured speech, sleeplessness or drowsiness, hallucinations, delirium and paranoid psychosis', and (hypo)mania.

- 10.2 Following treatment cessation, it is necessary to adhere for at least an additional 2 weeks (longer if an SRI is instated) to the dietary and medication guidelines.

Note: After irreversible inhibition, MAO needs to be regenerated through biosynthesis (and with tranylcypromine, possibly to some extent through biorepair). 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.

## 7.3. Requirements to ensure appropriate use of the medicine

### 7.3.1. Introduction

PLZ and the other classic MAOIs are best prescribed by a psychiatrist (initially, until the patient is stabilized on the treatment), as they require some expert knowledge with regard to management of the predictable early side-effect of orthostatic hypotension. Additionally, the appropriate and responsible use of PLZ requires that the patient adhere to certain dietary requirements, and that coadministration of certain medicines is avoided (and that the dosages of certain other medicines are decreased). These topics are discussed hereunder, following a passage in which the relatively few absolute and relative contraindications to starting PLZ treatment are considered. The *Prescriber's Guide* provides an in-depth explanation and guide to ensure the safe use of PLZ. The dietary considerations are elaborated on in its sister publication, '*The Prescriber's Guide to the MAOI Diet—Thinking Through Tyramine Troubles*'.<sup>38</sup> A number of relevant passages from both publications are provided hereunder. These passages are best read in conjunction with the information in the previous section 7.2.

### 7.3.2. Contraindications

Passages 3.1 and 3.2 of the *Prescriber's Guide* discuss the few absolute and relative contraindications that must be considered prior to starting PLZ treatment.

#### **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.

3.1.2    Concomitant use of certain medications, supplements, or drugs that have significant activity as serotonin reuptake inhibitors (SRI), or have significant activity as serotonin releasers at therapeutic doses. The risk is serotonin toxicity. See also point 6.1.1.

3.1.3    Pheochromocytoma (risk: hypertensive urgency or emergency).

##### **3.2      Relative contraindications**

3.2.1 Uncontrolled hypertension or hypotension (BP medication may need adjustment due to 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 occurring (see point 2.5.3).

3.2.3 Pregnancy (MAOIs can cross the placental barrier; risk of teratogenic abnormalities cannot be ruled out)

3.2.4 Breastfeeding (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 advised relating to risk of manic switch if used without a mood stabilizer, e.g., 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)

3.2.7 Concomitant use with certain other medications (see point 6: 'Interactions' for nuanced discussion), e.g., monoamine releasers without significant serotonergic activity (certain indirect sympathomimetics; see point 6.1.2) The risk is a hypertensive urgency or emergency.

### 7.3.3. Orthostatic hypotension

Passages 2.5.1. and 4.4.1 of the *Prescriber's Guide* discuss the likely occurrence of orthostatic hypotension and its suggested treatment:

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 BP-lowering effect of MAOIs (see also point 4.4).  
(...)

#### 4.4 In the event of orthostatic hypotension

4.4.1 Significant orthostatic hypotension ( $\geq 10$ – $15$  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 10–14 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 3–4 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), the use of compression stockings, as well as temporarily adding fludrocortisone if current rate of improvement is inadequate. The cessation of MAOI treatment is only rarely necessary.

#### 7.3.4. Dietary considerations

There are certain dietary considerations that must be taken into account with PLZ use. This is because PLZ and the other classic MAOIs exert a wide range of pharmacological actions, which explains both their superior therapeutic effect compared to other antidepressant classes, as well as the requirement for several dietary precautions. To clarify this point: PLZ inhibits both isoforms (A and B) of monoamine oxidase (MAO), thereby altering the metabolism of all monoamines; this includes the three main neurotransmitters (serotonin, norepinephrine, and dopamine), and also tyramine, a vasoactive monoamine that is present in some foodstuffs. The reduced breakdown rate of tyramine in the presence of MAO-inhibition may cause hypertensive reactions if ingested in excess. The cause-effect relationship of this interaction was first established in the 1960s by Blackwell and Marley<sup>39</sup>, and is often referred to as ‘the cheese effect’; this is because some (but certainly not all) cheeses contain elevated levels of tyramine, and must be either avoided or consumed in reduced quantities. Although some consideration is therefore warranted, the MAOI diet is not a highly restrictive one. In fact, many patients with healthy eating habits may hardly need to change their diet at all.



The abstract of the new 2022 *Prescriber's Guide to the MAOI Diet* (which is co-authored by Barry B. Blackwell, whose seminal work established the link between tyramine and hypertension in MAOI patients) is presented here:

#### **Abstract**

This review article features comprehensive discussions on the dietary restrictions issued to patients taking a classic monoamine oxidase inhibitor (phenelzine, tranylcypromine, isocarboxazid), or high-dose (oral or transdermal) selegiline. It equips doctors with the knowledge to explain to their patients which dietary precautions are necessary, and why that is so: MAOIs alter the capacity to metabolize certain monoamines, like tyramine, which causes dose-related blood pressure elevations. Modern food production and hygiene standards have resulted in large reductions of tyramine concentrations in most foodstuffs and beverages, including many cheeses. Thus, the risk of consequential blood pressure increases is considerably reduced—but some caution remains warranted. The effects of other relevant biogenic amines (histamine, dopamine), and of the amino acids L-dopa and L-tryptophan are also discussed. The tables of tyramine data usually presented in MAOI diet guides are by nature unhelpful and imprecise, because tyramine levels vary widely within foods of the same category. For this reason, it is vital that doctors understand the general principles outlined in this guide; that way, they can tailor their instructions and advice to the individual, to his/her lifestyle and situation. This is important because the pressor response is characterized by significant interpatient variability. When all factors are weighed and balanced, the conclusion is that the MAOI diet is not all that difficult. Minimizing the intake of the small number of risky foods is all that is required. Many patients may hardly need to change their diet at all.

#### 7.3.5. Drug-drug interactions

As is the case with all potent psychopharmacological agents, drug-drug interactions may occur when combining PLZ with other drugs. This topic has been comprehensively addressed in the specialized literature, and the conclusion is that any potentially severe interactions are easily prevented by adhering to the two basic principles outlined below. With respect to this, it must be said that much of the non-specialized literature does not yet

reflect our enhanced understanding of MAOI pharmacology and drug interactions (e.g., serotonin toxicity), which has substantially increased over the last several years and decades. This is reflected in the fact that some journal articles and textbooks on general psychopharmacology, which may be written by physicians with broad expertise on AD treatments in general but with limited expertise on MAOI treatment specifically, are outdated on a number of key aspects. A prime example of this is the matter of combination treatment with PLZ (or other MAOIs) with TCAs; this is often listed as absolutely contraindicated in an undifferentiated sense.<sup>31</sup> However: the TCAs are grouped on the basis of their structural similarities, despite the fact that they have substantially differing pharmacological action profiles. Upon closer analysis, it becomes clear that there are only two TCAs that should under no circumstances be combined with PLZ; these are clomipramine and imipramine, the only TCAs with significant serotonergic potential at typical therapeutic doses. There is no such risk with the other TCAs, so that they may, in principle, be safely combined with MAOIs, provided that the fundamental tenets of good pharmacologic practice (e.g., start low, go slow) are properly adhered to. This is all addressed at length in the *Prescriber's Guide* in the passages on 'Interactions' (chapter 6). The text is provided hereunder, but is best read in conjunction with the other passages for context. (It is prudent to note, in addition, that the International MAOI Expert Group is in the process of contacting prominent textbook authors to offer advice on updating the section on PLZ/MAOI pharmacology and clinical practice.)

## **6 INTERACTIONS**

### **6.1 Pharmacodynamic interactions**

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

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

Note: Serotonin toxicity (or serotonin syndrome) is a dose-related response; symptoms (such as tremor, hyperreflexia, clonus) are placed on a spectrum, 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, whilst considering the risk-benefit balance). See also points 6.4–6.6.

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

6.2.2 Phenelzine (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). Also, phenelzine is an inhibitor of primary-amine oxidases (PrAO), also referred to as semicarbazide-sensitive amine oxidases (SSAO)—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 (e.g., a lower dose of sumatriptan 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):

- (a) All SSRIs (e.g., paroxetine, fluoxetine, fluvoxamine, citalopram, escitalopram, sertraline, vortioxetine, vilazodone, dapoxetine)
- (b) All SNRIs (e.g., venlafaxine, desvenlafaxine, milnacipran, levomilnacipran, duloxetine, sibutramine)

- (c) Imipramine and clomipramine (other TCAs are safe if appropriately/cautiously administered). The structurally similar drug cyclobenzaprine is also best avoided.
- (d) Chlorpheniramine and brompheniramine (other antihistamines are safe).
- (e) Some analgesics (e.g., dextromethorphan, dextropropoxyphene, levorphanol, pentazocine, meperidine (=pethidine), methadone, tramadol, tapentadol)
- (f) Ziprasidone and lumateperone (the only antipsychotics currently on the market with significant SRI-activity)

Note: Wash-out period required prior to starting MAOI (typical duration is five times the half-life of the SRI).

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

- (a) Amphetamines in medium/high doses
- (b) Fenfluramine

Note: Wash-out period required prior to starting MAOI (typical duration is five 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):

- (a) Some antihypertensives (e.g., methyldopa, reserpine)
- (b) Pancuronium (a muscle relaxant that is sometimes used with general anesthetics)
- (c) Various illicit drugs (e.g., cocaine, MDMA) and some licit/illicit supplements (e.g., ayahuasca, St. John's wort).

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

- (d) Concomitant use of other (classic or reversible/selective) MAOIs (e.g., isocarboxazid, pargyline, selegiline, rasagiline, isoniazid, iproniazid, 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 methylthioninium chloride (methylene blue) and linezolid.

Note: Wash-out period required when switching from MAOI to MAOI (most guidelines advise 14 days if the first agent was also an irreversible MAOI—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):

(a) 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<sub>max</sub>.

(b) Ephedrine, pseudoephedrine

Note: Caution 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):

(a) Precursors of monoamines (e.g., 5-HTP, L-dopa, 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 if doses over 2 g of L-tryptophan are used; significant caution advised.

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

(a) Disulfiram

(b) Bromocriptine

(c) Hydralazine

(d) 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 advised because of possible potentiation):

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

Note: These agents are non-selective adrenergic agonists (exerting direct sympathomimetic activity).

Note: Upon administration of epinephrine for anaphylactic shock in MAOI patient, a lowered initial dose is required because of potentiation (after which, up-titration based on effect is possible). If MAOI patient carries an EpiPen, the dose of this EpiPen should likewise be adjusted.

#### 6.5 Relative contraindications (weak)

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

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

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

6.6.1 In general:

- (a) Antipsychotics (other than ziprasidone and lurasidone, 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 (T3)
- (g) Pramipexole
- (h) Agomelatine
- (i) TCAs (other than imipramine and clomipramine, because of SRI-activity)

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, etc. with MAOIs. Nevertheless, caution is advised when administering this combination (MAOI+TCA), based on the specific properties of the selected augmenting agent (e.g., 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.

Note: As TCAs are not a pharmacologically homogenous group, drug selection is of prime importance; 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 which (a) stem from a time when knowledge of serious drug–drug interactions was less extensive (e.g., imipramine-induced serotonin toxicity in MAOI patients), 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, 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 and esketamine appear, in principle, likewise safe to combine (sparse literature data at present; low starting dose, cautious uptitration, and BP monitoring advised).

Whilst 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, (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.

Note: Insomnia is a prominent side-effect of MAOI treatment (and may be worse with tranylcypromine than with phenelzine). Whilst 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; this may help somewhat. If improvement is insufficient, consider adding zolpidem or lorazepam.

- (b) For severe/persistent orthostatic hypotension, see point 4.4.

- (c) For transient hypertension post-dosing (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, treatment with diuretics (caution advised concerning potential increase of hypotensive effect). If improvement is insufficient: consider stopping phenelzine, starting tranylcypromine (following wash-out).

- (e) For paresthesias and/or peripheral neuropathy (with phenelzine): supplement with pyridoxine hydrochloride (Vit. B6); recommended dose: 25–50 mg.

- (f) For mid-day somnolence (more common with phenelzine): caffeine in moderation may help somewhat; consider cautious addition of low-dose methylphenidate or modafinil.

#### 7.3.6. Other points of note

As discussed in the previous section, some of the general, non-specialized literature has not yet been fully updated in accordance with our increased understanding of PLZ pharmacology. Similarly, the various product information (PI) leaflets for PLZ (which are in essence closer to legal disclaimers than to state-of-the-art medical advice) are substantially



discordant with the current evidence-based data on several key aspects; we briefly discuss two examples of this.

The first example concerns the recommendation in the 2007 PI leaflet for PLZ to reduce the therapeutically effective dose ‘after maximum benefit’ has been reached—this is also referred to as the maintenance dose concept. However: aside from the pragmatic difficulties in assessing what precisely constitutes ‘maximum benefit’, this recommendation is not in accordance with the literature data, as the risk of depressive relapse is significantly increased when this ‘maintenance dose’ concept is put in practice. This is because the underlying reasoning is pharmacologically inaccurate, as it assumes that the only mechanism of action relevant to PLZ’s antidepressant effect is its capacity to inhibit MAO (the effect of which can indeed be maintained with a lower PLZ dose once a high level of about 80% platelet MAO inhibition has been achieved). But, as previously outlined in passage 4.7.4. of the *Prescriber’s Guide*, this line of reasoning ignores other pharmacologically relevant factors, because ‘PLZ is metabolized on a dose-related basis to several metabolites, including  $\beta$ -phenethylamine (releases dopamine and norepinephrine) and  $\beta$ -phenylethylidinedihydrazone (increases brain GABA levels)’; the actions of these metabolites contribute to PLZ’s antidepressant and anxiolytic effect. Therefore, the current expert consensus is that one should not reduce to a maintenance dose; instead, ‘it is best to continue treatment with the same dose with which antidepressant response was achieved’.

The second example concerns the connected statements in the 2007 PI leaflet for PLZ that patients ‘should not undergo elective surgery requiring general anaesthesia’, and that PLZ ‘should be discontinued at least 10 days prior to elective surgery’. This runs contrary to current expert consensus in that these statements mischaracterize the psychiatric versus the somatic risks involved with stopping MAOI treatment. The *Prescriber’s Guide* addresses this topic in passages 8.1.1 and 8.1.2, which are listed hereunder:

8.1 In case of surgery

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 peri-operative 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, given that it is in most cases possible —via careful choice (or dose adjustment) of anaesthetic and analgesic agents used before and during surgery (as well as in post-operative care)—to avoid potentially serious interactions.

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

## 7.4. Recommendations in other clinical guidelines

### 7.4.1. Introduction

PLZ and other classic MAOIs are indicated for use in many clinical guidelines on depression; they are typically indicated for use as a late-line treatment agent, i.e., when other ADs and combinations of ADs have failed.<sup>40</sup> We discuss here the recommendations on PLZ use featured in a number of prominent guidelines.

### 7.4.2. Prescriber’s guide to MAO inhibitors

The most prominent and up-to-date guideline on PLZ use (and on MAOI use in general) is the *Prescriber’s guide to classic MAO inhibitors*, which is referenced throughout this application report. The introduction describes the primary action mechanism of PLZ; it ‘inhibit[s] monoamine oxidases (MAOs; A and B) in a nonselective and irreversible manner, resulting in the reduced breakdown of the neurotransmitters serotonin, norepinephrine, and dopamine. 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 [PLZ].’

The indications for PLZ use are described in section 1 of the guideline:

## **1. Indications**

1.1. Following insufficient response to a modern antidepressant (e.g., an SSRI/SNRI, mirtazapine, bupropion) and/or a TCA, either as monotherapy treatment or with an augmentation agent (e.g., lithium). MAOIs should always be considered in cases of treatment-resistant depression, including those melancholic in nature\*.

1.2. MAOIs are typically indicated prior to ECT, except when a rapid response to treatment is imperative (e.g., imminent suicide risk, inanition, catatonia).

*Note:* MAOIs can prove effective even after (failed) ECT-treatment or ketamine-infusion.

1.3. MAOIs may also be effective for treatment-resistant anxiety and panic disorders.

1.4. MAOIs can also be considered in the treatment of other diagnoses based on individualized considerations and patient preferences.

\* The effectiveness of PLZ for treating melancholic (rather than only atypical) depressions is an important point to emphasise, as was established in the early research by Saunders et al. (1959): ‘Almost without exception, patients with endogenous (essential, true, primary) depression responded favorably to phenelzine’.<sup>17</sup> Additionally, we refer here to the summary conclusion of the forthcoming paper titled ‘*On the origins of MAOI misconceptions: reaffirming their role in melancholic depression*’, which reads as follows:

Throughout the decades since their inception, the general—and initially highly positive—sentiments surrounding MAOI use have been influenced by methodologically impure research (e.g., the STAR\*D trial, which used a low mean daily dose of 37 mg tranylcypromine and deemed it rather ineffective as a result) and by the success of marketing strategies for the selective-action ADs. The suffusion of erroneous beliefs regarding the limited effectiveness and the cumbersome side-effect profile of MAOIs jointly paved the way for their abandonment in favour of the newer and industry-backed SSRIs like sertraline and escitalopram, and the SNRI venlafaxine—a fate that was largely shared by the TCAs. The result is a relative scarcity of literature data on the use of MAOIs in melancholic depression, with much of the most compelling primary source material stemming from the 1950s-’80s.

Nevertheless, the current state of the research is sufficiently developed to allow for the statement that MAOIs have a clear and continuing role in treating SSRI- and TCA-resistant melancholic depression, although it may be noted that such ostensibly ‘treatment-resistant’ depressive conditions automatically enter the purview of MAOI treatment, regardless of their subtyping as melancholic or non-melancholic.

To summarise: PLZ and the other MAOIs are not only effective in atypical depression, as is well understood in the literature, but also in endogenous or melancholic depression, provided that higher doses are used (for PLZ: 75-90 mg).<sup>41</sup> Despite the fact that this was well-established in the 1950s and early 1960s,<sup>42</sup> the 1965 Medical Research Council mistakenly expressed serious doubts about the use of MAOIs in severe (endogenous) depressive disorders; however: this study is flawed because of the low dose used ( $\leq 60$  mg PLZ) and the inclusion of many patients with psychosis.<sup>41</sup> Nevertheless, it led to decades of distorted views on the proper use of MAOI ADs, which was only recently comprehensively rebutted by Van den Eynde et al. (forthcoming).

#### 7.4.3. American Psychiatric Association Guideline

The American Psychiatric Association (APA) affirms the use of PLZ and other classic MAOIs in TRD; this is outlined as follows in their Practice Guideline for the Treatment of Patients with Major Depressive Disorder on pages 35-36:

*‘MAOIs currently used as antidepressants include phenelzine, tranylcypromine, isocarboxazid, moclobemide, and the transdermally delivered formulation of selegiline. MAOIs have comparable efficacy to other antidepressants for outpatients with major depressive disorder and may be appropriate for patients with major depressive disorder who have not responded to safer and more easily used treatments. In fact, the role of MAOIs in major depressive disorder is now almost exclusively reserved for patients who have not responded to at least several other pharmacotherapies. Studies have demonstrated the effectiveness of MAOIs in patients who have not responded to other antidepressant medications, particularly TCAs. However, the effectiveness of MAOIs relative to other strategies for treatment-resistant patients in contemporary practice remains unclear, particularly for patients who have not responded to multiple sequential trials with SSRIs and*

*SNRIs. MAOIs have been shown to be particularly effective in treating depressed patients with atypical features, so psychiatrists should consider using these medications for patients with symptoms such as reactive moods, reverse neurovegetative symptoms, and sensitivity to rejection. There do not appear to be any significant differences in efficacy among the older MAOIs, although there are important individual differences in responsiveness, and these medications are not interchangeable.*<sup>43</sup>

#### 7.4.4. National Institute for Health & Clinical Excellence Guideline

The National Institute for Health & Clinical Excellence (NICE) Guideline on the treatment and management of depression in adults notes the following about MAOI use in TRD (pages 468-469):

*MAOIs have been used extensively in the management of 'treatment-resistant' depression for 4 decades but there is no randomised data on which to base recommendations. Most information and experience is with phenelzine. McGrath and colleagues treated patients in a cross-over design with high doses of phenelzine (maximum 90 mg), imipramine (maximum 300 mg) or placebo and found that of the non-responders only four of the 14 patients responded to a tricyclic crossover with 17 of the 26 patients responding to an MAOI crossover. There was some evidence of a preferential response in treatment-resistant patients with atypical symptoms of depression, but Nolen and colleagues (1988) subsequently showed that not only patients with atypical depressive symptoms but also patients with depression and melancholia responded to MAOIs, in particular tranylcypromine. It does not appear that moclobemide has the same spectrum of efficacy in treatment resistance as the classical MAOIs. Nolen and colleagues (1994) switched patients with resistant depression stabilised on tranylcypromine to moclobemide. About 60% of the patients showed deterioration and one-third relapsed.*<sup>44</sup>

#### 7.4.5. Other Guidelines

- The Malaysian Clinical Practice Guideline on the management of major depressive disorder recommends MAOI use in some settings, e.g., in atypical depression that did not respond to other ADs.<sup>45</sup>

- The National Clinical Guideline of Qatar on the diagnosis & management of depression lists MAOIs as ‘medications to be considered in secondary care’, with the mention that they ‘should be restricted to patients who do not respond to other pharmacotherapies’.<sup>46</sup>
- The Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder lists PLZ as a third line antidepressant treatment option.<sup>47</sup>
- The Royal Australian and New Zealand College of Psychiatrists (RANZCP) indicates in her clinical practice guideline for mood disorders that ‘*It has been proposed that atypical depression responds best to MAOIs*’, including PLZ.<sup>48</sup>

## 8. Review of benefits: summary of evidence of comparative effectiveness

### 8.1. Introductory statements

The evidence base for PLZ use in TRD is discussed in the following subsections, with a focus on randomized controlled trials (RCT) and meta-analyses, as outlined in the WHO application report template. However: given the unique history of the MAOIs as the first antidepressants (ADs) discovered in the 1950s—prior to the dominance of the RCT methodology—there is an important caveat that must be considered when evaluating the evidence base for the efficacy of MAOIs, including PLZ, in the treatment of TRD. This caveat pertains to the shift in research methodologies over the decades since MAOIs were first on the market, which serves to explain the relative paucity of RCTs aimed at comparing the AD effects of PLZ versus other ADs (as RCTs are expensive and often industry-funded and industry-controlled; PLZ is out-of-patent, therefore, the financial incentives for drug companies are minimal). To comprehensively assess the efficacy of PLZ, it is therefore imperative to take into account the earlier literature (albeit reinterpreted from a modern research perspective), and the established use of PLZ and MAOIs in general throughout the decades.

These arguments are further explored in two recent peer-reviewed journal articles, the content of which we present here in an abridged format.

The first article is entitled ‘Causality is the missing key: a comment on the history of MAOIs and RCTs’:

*[...] Whereas RCTs are considered the gold standard today, these trials are expensive and often subject to industry-funding and -control. They are generally used as short-term drug approval trials, and are not designed to address scientific inquiries like the causal and mechanistic relationships between drug pharmacology and treatment response. As MAOIs were in use prior to the dawning of the RCT hegemony, the evidence for their efficacy was and is found in clinical experience predicated on implicit Bayesian logic, i.e., through the application of probabilistic causal reasoning informed by evidence-based inferences from repeated clinical observations and pharmacological research into the presumable cause-effect mechanisms. To further clarify, a brief foray into the history of MAOIs proves instructive.*

*The antidepressant—or ‘psychic energizing’—effect of the MAOIs was serendipitously discovered during 1950s trials with iproniazid, a potent antitubercular drug that was found to elicit ‘Mona Lisa smiles’ in a number of trial subjects, despite their grave somatic illness. Only later, through a process of inferential reasoning, was the presumable pharmacological mechanism behind the mood elevating properties of iproniazid uncovered—it proved a potent inhibitor of MAO, thereby causing substantial increases in intra- and extracellular serotonin, norepinephrine, and dopamine. [...]*

*Thus, in the early days of MAOI use, there was little incentive for organising RCTs to reaffirm what was already known—they are highly effective antidepressants.*

The second article is entitled ‘Requiem or resurrection: Classic monoamine oxidase inhibitors revisited’:

*Recently, the first ever authoritative consensus guideline, detailing the use of MAOIs (phenelzine, tranylcypromine, isocarboxazid) in severe depressive illnesses has been formulated; its recommendations are supported by over 40 international authors—many of them world-leading experts. Problems previously regarded as impediments to MAOI use may now be seen as minimally- or non-existent. Their vanishingly low usage over the recent*

*decades can be accounted for by advertising, fashion, and lack of teaching—not by lack of effectiveness.*

*The historical perspective is important in clarifying th[e] decline in prominence [of the MAOI antidepressants such as PLZ from the 1960s onward]: it is well understood now, but was not then, that MAOIs inhibit the breakdown of tyramine, and that excessive dietary intake can lead to significant blood pressure increases. The cause–effect relationship underlying this ‘cheese reaction’ was soon uncovered but the fear remained; this led to other, less substantiated reactions: knee-jerk policies were enacted, leading to various market withdrawals. This shook the confidence of physicians of that era, many of whom had limited knowledge of psychopharmacology—the field was in its infancy. This, in turn, influenced them to strongly favour the emerging tricyclic drugs for depression. Throughout the subsequent decades, the specific emphasis on the advantages of newer drugs were accentuated, and problems with MAOIs exaggerated.*

*To be clear: the risk of unforeseen and potentially dangerous drug–drug interactions was a legitimate point of concern in the earlier years of MAOI use. Knowledge of serotonin toxicity was incomplete and misunderstood—but is now clear. Such interactions are predictable and straightforward to avoid. The same holds true for interactions with dietary biogenic amines and amino acids. Regrettably, and despite numerous rebuttals, some myths and misgivings are difficult to dispel [...].*

*As randomized control trials (RCTs) became more prevalent, and more industry-funded and -controlled, the number of studies undertaken with the aim of elucidating the working mechanisms and potential benefits of older drugs steadily diminished. Thus, MAOIs had a lower profile when guidelines started being produced, precisely because these were based on RCTs, on which an over-reliance was soon established at the expense of other valid methodologies, including well-founded and reproducible clinical experience. A circular process of reasoning came into existence: low usage, few trials, exclusion from guidelines, lower usage still. Moreover, while there remain many patients with severe affective disorders who respond exclusively to MAOI treatment—after having failed many trials of other classes and combinations of depression drugs—such responses are not easily subject to demonstration by RCTs. We note that the epistemic validity of other methodologies is not*



*inherently inferior to that of RCTs, which have their own limitations and problems. That has been argued by various authors, including Rawlins (2008) , who said ‘the notion that evidence can be reliably placed in hierarchies ... is illusory’, and that ‘the findings of RCTs should be extrapolated with caution.’ Regarding them as the gold standard is misleading.*

## 8.2. Evidence from Meta-analyses

### 8.2.1. Overview

From previous research, we identified 3 key meta-analyses comparing PLZ to other antidepressants. They are:

1. *Revisiting monoamine oxidase inhibitors for the treatment of depressive disorders: A systematic review and network meta-analysis (Suchting et al.)*<sup>49</sup>
2. *Treatment of depression with atypical features: A meta-analytical approach (Henkel et al.)*<sup>50</sup>
3. *MAOIs in the contemporary treatment of depression (Thase et al.)*<sup>51</sup>

These 3 meta-analyses are summarily discussed hereunder; the abstracts are listed for each publication, with additional information provided where necessary. Grade tables are included for each study. An important limitation for all meta-analyses is that the low quality of some RCTs included in the assessment skews the results to a significant extent. Most notably, the low PLZ doses used in some RCTs, as well as an inadequate trial length, may reduce the perceived efficacy of PLZ compared to the response observed in clinical settings.

### 8.2.2. Revisiting monoamine oxidase inhibitors for the treatment of depressive disorders: A systematic review and network meta-analysis (Suchting et al., 2021)

<sup>49</sup>

This is the most recent and most exhaustive meta-analysis comparing PLZ to other antidepressants.

*Abstract:*

#### Background

*Monoamine oxidase inhibitors (MAOIs) were the first class of modern antidepressants; however, they are under-utilized as compared to the newer antidepressants.*

#### Methods

*In this systematic review, network meta-analysis was used to investigate the comparative efficacy and acceptability of MAOIs for depressive disorders. Overall, the network meta-analysis included 52 double-blind, randomized controlled trials (RCTs) that compared 14 antidepressants or placebo. Across studies, the mean arm size was  $n = 58$  participants from a total  $N = 6462$  (5309 active drug; 1153 placebo).*

### Results

*Except fluvoxamine, all antidepressants demonstrated superior efficacy to placebo, and none demonstrated substantially better or worse all-cause dropout rates. Phenelzine demonstrated superior evidence for efficacy compared to all other treatments, and clomipramine demonstrated superior evidence for acceptability compared to all other treatments.*

### Limitations

*The study is primarily limited by low estimate precision due to a relative paucity of studies for some of the included treatment conditions. Further evidence is required to study the relative efficacy of MAOIs against newer antidepressants.*

### Conclusions

*The results of this analysis largely support the re-evaluation of the use of MAOIs as antidepressant agents in the treatment algorithm of depression.*

### *Additional excerpts:*

*The findings suggested that phenelzine is one of the most effective of the antidepressants compared in the clinical trials. This may be contrasted with the first large controlled trial of phenelzine by the UK Medical Research Council (Zangwill, 1965), which found that phenelzine was no more effective than placebo. In that study, however, phenelzine was dosed to a maximum of 60mg daily and it was found subsequently that many patients required higher daily doses (75-90mg) to achieve effective MAO inhibition.*

*A re-evaluation of the use of MAOIs as antidepressant agent is necessary for several reasons. First, it is now known that only an unusually high intake of dietary tyramine is liable to cause a significant hypertensive reaction with MAOIs; accordingly, diet can be safely managed in most patients taking MAOI treatment. Second, while MAOIs have proven*

*efficacious in treating atypical depression, they have also been regarded by expert clinicians as helpful in patients with more classic melancholic symptoms who have failed to respond to multiple other therapies, including ECT.*

**Author(s):** Suchting et al.

**Question:** Phenelzine compared to other antidepressants and placebo for depressive disorders

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenelzine	other antidepressants and placebo	Relative (95% CI)	Absolute (95% CI)		
Efficacy (response rate as measured by the proportion of participants that demonstrated 50% or greater reduction on a standardized depression rating scale)												
52	randomised trials	not serious	not serious	not serious	not serious	dose response gradient		2054/6462 (31.8%)	OR 4.66 (2.64 to 8.40)	367 more per 1,000 (from 234 more to 479 more)	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; OR: odds ratio

### 8.2.3. Treatment of depression with atypical features: A meta-analytical approach (Henkel et al.)<sup>50</sup>

#### Abstract:

The present meta-analysis addressed the empirical evidence regarding the treatment of major depression with atypical features. The superiority of monoamine oxidase inhibitors (MAOIs) compared with other antidepressants in the treatment of major depression with atypical features has been frequently reported. According to the CONSORT Statement, studies included in our meta-analysis had to meet several criteria, especially a double-blind, controlled condition and an operational diagnosis according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-III or DSM-IV criteria, respectively. Four databases for research-based evidence were used in a systematic review: Medline, Embase, Psynex and PsycInfo. Only eight publications met inclusion/exclusion criteria, resulting in 11 comparisons. Our results contrast an effect size of 0.45 (95% confidence interval) for a comparison of MAOIs vs. placebo with an effect size of 0.02 (95% confidence interval: - 0.10-0.14) for a comparison of MAOIs vs. selective serotonin reuptake inhibitors. The effect size for MAOIs vs. tricyclic antidepressants was 0.27 (95% confidence interval: 0.16-0.42). MAOIs may be more effective for atypical major depressive disorder than tricyclic antidepressants.

Most clinical research has been conducted on irreversible MAOIs. Additional studies testing more recently developed antidepressants (including reversible MAOIs) with an improved safety profile would be warranted. The available data are insufficient for a direct comparison between MAOIs and selective serotonin reuptake inhibitors.

Author(s): Henkel et al.

Question: Phenelzine compared to other antidepressants or placebo for atypical depression

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenelzine	other antidepressants or placebo	Relative (95% CI)	Absolute (95% CI)		
Response (usually defined as at least 50% reduction in the severity of atypical depression)												
8	randomised trials	not serious	not serious	very serious <sup>a</sup>	not serious	all plausible residual confounding would reduce the demonstrated effect		-/670	not estimable		⊕⊕⊕○ Moderate	IMPORTANT

CI: confidence interval

#### 8.2.4. MAOIs in the contemporary treatment of depression (Thase et al.)<sup>51</sup>

##### Abstract:

We review the literature on the effectiveness of the monoamine oxidase inhibitors (MAOIs) and present metaanalyses of controlled trials comparing the FDA-approved MAOIs with both placebo and comparator tricyclic antidepressants. For outpatients, metaanalyses with intent-to-treat samples revealed generally comparable overall efficacy for phenelzine, isocarboxazid, and tranylcypromine. Drug-placebo differences were 29.5% (+/- 11.1%) (phenelzine; nine studies), 41.3% (+/- 18.0%) (isocarboxazid; three studies), and 22.1% (+/- 25.4%) (tranylcypromine; three studies). For inpatients, phenelzine was 22.3% (+/- 30.7%) (five studies) more effective than placebo, whereas the isocarboxazid-placebo difference was lower (15.3%) (+/- 12.6%). Both phenelzine and isocarboxazid were significantly less effective than comparator tricyclics for inpatients, whereas tranylcypromine has not been adequately studied. Both phenelzine and tranylcypromine appear to be more effective than tricyclics in depressed outpatients with atypical features. Monoamine oxidase inhibitors are also effective treatments for outpatients who have failed to respond to tricyclic antidepressants. Our review also suggests (1) the FDA-approved MAOIs treat a somewhat different group of patients than tricyclics; (2) more severely depressed inpatients may not

respond as well to MAOIs as to tricyclics; and (3) because of preferential MAOI responsivity, atypical or anergic depressions may be biologically different than classical depressions.

Author(s): Thase et al.

Question: Phenelzine compared to tricyclic antidepressants or placebo for depression

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenelzine	tricyclic antidepressants or placebo	Relative (95% CI)	Absolute (95% CI)		
Response												
56	randomised trials	serious	not serious	serious <sup>a</sup>	not serious	none	-799		not estimable		<div>⊕⊕○○</div> <div>Low</div>	NOT IMPORTANT

CI: confidence interval

#### Explanations

a. The limitations of the included RCTs make it difficult to translate the study results to clinical practice.

### 8.3. Other studies of note

#### 8.3.1. Relative effectiveness of tricyclic antidepressant versus monoamine oxidase inhibitor monotherapy for treatment-resistant depression (Kim et al.)<sup>32</sup>

Abstract:

##### Objectives

*Antidepressants may be less effective in treatment-resistant depression (TRD). In this exploratory study, we examined the widely held hypothesis that monoamine oxidase inhibitor (MAOI) therapy may be superior to tricyclic antidepressant (TCA) therapy for TRD. We also examined the influence of the number of prior treatment trials on TCA versus MAOI effectiveness in TRD.*

##### Methods

*Data were retrospectively extracted from approximately 2,500 treatment charts of patients with TRD who were attending a university mood disorder clinic between 1983 and 2015. Hierarchical linear modeling was used to examine the efficacy of drug class on outcome as well as the interaction between drug class and the number of prior antidepressant trials.*

##### Results

*147 treatment outcome observations were made from 94 unipolar, depressed patients who either received TCA (N=47) or MAOI (N=100) monotherapy for TRD. For patients*

*unresponsive to at least one prior trial, drug class significantly predicted end-of-treatment CGI/S scores, with TCAs showing worse (i.e., higher) end-of-treatment CGI/S scores relative to MAOI therapy ( $b=1.04$ ,  $t=4.98$ ,  $p < 0.0001$ ). When examining the interaction between drug class and the number of prior antidepressant trials, the interaction effect was significant ( $b = -0.50$ ,  $t = -2.43$ ,  $p=0.02$ ); however, the advantage for MAOI versus TCA therapy decreases with more prior, failed, antidepressant trials.*

#### Conclusion

*Results suggest that MAOIs may be more effective than TCAs for early stage TRD. This difference in effectiveness between MAOIs and TCAs diminished as the number of prior treatment trials increased. However, the TCA sample size was limited and the analysis was retrospective with non-randomized conditions.*

### 8.3.2. Advances Pertaining to the Pharmacology and Interactions of Irreversible Nonselective Monoamine Oxidase Inhibitors (Gillman)<sup>52</sup>

Excerpt:

*Monoamine oxidase inhibitors are not used to an extent proportionate with their benefits; medical texts and doctors' knowledge require a major update to reflect the evidence of recent advances.*

### 8.3.3. Prediction of longer-term outcome of treatment-resistant depression in tertiary care (Fekadu et al.)<sup>53</sup>

Excerpt:

[There is a] cross-sectional association between certain medication groups (MAOIs and duloxetine) and better outcome. The use of MAOIs is one of the recommended strategies for managing treatment-resistant depression; studies from over two decades ago had indicated the usefulness of MAOIs in nonresponsive depression or depression with specific symptom profiles. However, it occurs only as a third-line option (in combination with a tricyclic antidepressant) in the widely used Maudsley Prescribing Guidelines. We suggest that our findings act as a reminder that MAOIs have a place in the management of treatment-resistant depression, and require more systematic investigation.

#### 8.3.4. Cochrane and PubMed search for RCTs and reviews

We performed a systematic search for ‘phenelzine’ on the Cochrane Library archive website on September 12<sup>th</sup> 2022. This search returned 236 publications, consisting of 2 Cochrane Reviews and 234 Trials. Two authors of this application report (VVdE and KG) then filtered out the irrelevant publications, which resulted in 26 remaining publications. The selected publications were then reviewed in-depth, but all were either included in the meta-analyses discussed in section 8.2., or were of insufficient quality to warrant inclusion; therefore: no additional RCTs or reviews were found. This process was then repeated on PubMed, but no additional publications were found.

### 8.4. Assessment of applicability of the available evidence across diverse populations and settings

#### 8.4.1. PLZ in different age groups

There is research indicating the safety of PLZ use in children<sup>54</sup> and adolescents<sup>55</sup>, although this is an uncommon practice that should be discussed on a case-by-case basis with a pediatric psychiatrist. This application report does not therefore advocate on a more general basis for the use of PLZ in children and adolescents, so that more in-depth discussion of this topic is out-of-scope.

#### 8.4.2. PLZ in pregnant or breastfeeding women

Sections 3.2.3 and 3.2.4 of the *Prescriber's Guide* discuss the topics of PLZ use in pregnant or breastfeeding women; these sections are listed hereunder:

#### **3.2. Relative contraindications**

3.2.3 Pregnancy (MAOIs can cross the placental barrier; risk of teratogenic abnormalities cannot be ruled out).

3.2.4 Breastfeeding (MAOIs may be present in breast milk; risk unclear due to lack of literature data).

Therefore: the use of PLZ is not recommended in these populations; exceptions must be made on a case-by-case basis, weighing the potential benefits against the potential risks.

#### 8.4.3. PLZ in the elderly

The use of PLZ in geriatric populations is discussed in sections 4.1.1 and 4.1.2 of the *Prescriber's Guide*. The main consideration is limiting the risk of syncope resulting from severe orthostatic hypotension, which may be achieved by either lowering the initial PLZ dose and/or the rate of dose increases and/or by stabilizing treatment at a lowered maximum dose.

#### **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.



An additional consideration is the management of drug interactions in polypharmacy patients, which are more prevalent in geriatric populations. This requires that attention be given to the previously outlined discussions on drug interactions in the *Prescriber's Guide*.

## 9. Review of harms and toxicity: summary of evidence of comparative safety

### 9.1. Preliminary considerations

The MAOI class of antidepressants, which includes PLZ, is typically well-tolerated (similar to ADs from other classes, such as SSRIs/SNRIs, although more research is required<sup>56</sup>) if the dietary and comedication-related restrictions are adhered to. Both of these topics were comprehensively discussed in previous sections of this report, with supplementary peer-reviewed material offered in the references—most notably the two *Prescriber's Guides*, outlining the general treatment recommendations and the more specific dietary recommendations. These topics are therefore not attended to in this section.

Other considerations of particular note are listed in the sections on selection criteria (provided hereunder) and contraindications of the *Prescriber's Guide* (provided in passage 7.3.2 of this application report):

2.5. The side-effect profiles of phenelzine (a hydrazine derivative) and tranylcypromine (nonhydrazine) differ considerably. The side effects of phenelzine may be experienced as more troublesome:

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.  
(...)

### 9.2. Considerations listed in the American Society of Health-System Pharmacists Drug Information publication from 2022

The American Society of Health-System Pharmacists (AHFS) has published a report on MAOI drug information, which includes in-depth discussions on the safety and harms profile.<sup>57</sup>

This passage 10.2 lists the relevant sections from the AHFS report (in boxes) on topics not previously discussed.

### **Cautions**

The potential adverse effects of monoamine oxidase (MAO) inhibitors are more varied and potentially more serious than those reported for most other classes of antidepressant agents. Because monoamine oxidase is widely distributed throughout the body, MAO inhibitor therapy can be expected to cause diverse pharmacologic effects. Many adverse effects of MAO inhibitors are mild to moderate in severity and often subside as therapy is continued. However, serious reactions requiring discontinuance of therapy can occur and usually involve the cardiovascular, CNS, and hepatic systems. Some of the most serious adverse effects reported with MAO inhibitors (e.g., hypertensive crisis, serotonin syndrome) have occurred when MAO inhibitors were administered concomitantly with certain foods or prescription or nonprescription (OTC) drugs.

### **Nervous System Effects**

The most common adverse CNS effects of MAO inhibitors include dizziness, headache (without increases in blood pressure), drowsiness, sleep disturbances (e.g., insomnia, hypersomnia), fatigue, weakness, tremors, twitching, myoclonic movements, and hyperreflexia. In addition, confusion, disorientation, memory loss, palilalia, euphoria, nystagmus, akinesia, and paresthesias have been reported. Hyperexcitability, increased anxiety, agitation, restlessness, manic symptoms, and precipitation of schizophrenia, have occurred in some patients receiving high dosages of MAO inhibitors. If these symptoms occur, dosage should be reduced or a phenothiazine agent should be administered concomitantly. Worsening of depression and/or emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur with antidepressants.

Rarely, ataxia, shock-like coma, toxic delirium, manic reactions, seizures, and acute anxiety reaction have occurred in patients receiving MAO inhibitors.

### **GI Effects**

Adverse GI effects reported with MAO inhibitors include constipation, dry mouth, and GI disturbances. Anorexia, nausea, vomiting, arthralgia, increased appetite, and weight gain also have been reported.

### **Hepatic Effects**

Although the potential for hepatotoxicity with commercially available MAO inhibitors is lower than with prototypical MAO inhibitors (iproniazid), such toxicities, when they do occur, can be serious because the hydrazine derivatives cause cellular damage to the hepatic parenchyma. A carefully controlled study has shown that patients with impaired liver function may be especially sensitive to tranylcypromine. The manufacturers of commercially available MAO inhibitors report that the most common adverse hepatic effect is elevated plasma transaminase concentrations (without accompanying signs or symptoms of hepatotoxicity). Reversible jaundice and fatal progressive necrotizing hepatocellular damage have been reported rarely.

### **Genitourinary Effects**

Impotence, ejaculatory disturbances, and anorgasmia have been reported in patients receiving phenelzine or tranylcypromine. Urinary frequency, urinary retention, and urinary incontinence also have been reported in patients receiving MAO inhibitors.

### **Dermatologic Effects**

Although a causal relationship to MAO inhibitors has not been established, localized scleroderma, flare-up of cystic acne, rash, pruritus, urticaria, purpura, increased sweating, and photosensitivity have been reported in patients receiving MAO inhibitors.

**Metabolic Effects**

A hypermetabolic syndrome, which may include, but is not limited to, hyperpyrexia, tachycardia, tachypnea, muscular rigidity, elevated creatine kinase (CK, creatine phosphokinase, CPK) concentrations, metabolic acidosis, hypoxia, and coma and may resemble an overdose, has been described in patients receiving MAO inhibitors.

**Ocular Effects**

Rarely, therapy with MAO inhibitors has been associated with adverse ocular effects (e.g., amblyopia, visual disturbances, blurred vision). Aggravation of glaucoma has also occurred. Retinal degradation, retinal scarring, cataracts, and loss of photoreceptor cells have been observed in animal toxicity studies with safinamide.

**Hematologic Effects**

A normocytic, normochromic anemia has reportedly developed in some patients receiving MAO inhibitors. Leukopenia, agranulocytosis, and thrombocytopenia also have been reported.

**Other Effects**

Other adverse effects of MAO inhibitors include arthralgia, lupus-like syndrome, edema of the glottis, fissuring in the corner of the mouth, and impaired water excretion resembling syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

**Precautions and Contraindications**

MAO inhibitors can cause potentially serious adverse effects, and should only be used in carefully selected patients who can be closely supervised and only by clinicians who are completely familiar with the proper use, potential adverse effects, and associated precautions and contraindications of the drugs. MAO inhibitors generally are not used as initial therapy in the management of depression, but are reserved for patients who do not respond adequately to other antidepressant agents.

(e.g., selective serotonin-reuptake inhibitors [SSRIs], tricyclic antidepressants) or in whom other therapies are contraindicated.

#### **Other Precautions and Contraindications**

Since MAO inhibitors may suppress anginal pain that would otherwise serve as a warning sign of myocardial ischemia, patients with angina pectoris or coronary artery disease should be warned against overexertion.

MAO inhibitors should be used with caution in patients with impaired renal function, since the drugs may accumulate in plasma in these patients.

Since MAO inhibitors have a variable effect on the seizure threshold, the drugs should be used with caution in patients with a history of seizures.

Since hepatic damage (e.g., progressive necrotizing hepatocellular damage) has occurred in some patients receiving MAO inhibitors (e.g., isocarboxazid [no longer commercially available in the US], phenelzine), periodic evaluation of liver function (i.e., bilirubin, serum alkaline phosphatase, serum aminotransferases [transaminases]) is recommended in patients receiving high dosages and in those receiving prolonged therapy with the drugs. MAO inhibitors are contraindicated in patients with a history of liver disease or abnormal liver function tests.

MAO inhibitors should be used with caution in patients with hyperthyroidism, since these patients have an increased sensitivity to pressor amines.

### 9.3. Additional considerations and information relating to patient exposure data and the frequency of adverse events

#### 9.3.1 Introduction: MAOI toxicity data

This passage 10.3 addresses relevant topics on toxicity data not previously discussed. By way of general introduction to MAOI toxicity data, it is prudent to refer to Gillman, who summarizes the findings from the seminal 2002 study on AD toxicity by Buckley and McManus as follows: ‘The toxicity of MAOIs in overdose is approximately the same as typical TCAs, such as amitriptyline, at around 50 deaths per million scripts.’<sup>52</sup> The data relating specifically to PLZ indicate a greater safety margin still, with around 15 deaths per million scripts.<sup>58</sup>

### 9.3.2. Exposure data

López-Muñoz et al. (2007) describe the exposure data in the first year following the market availability of iproniazid, the first serendipitously discovered MAOI:<sup>59</sup>

One year after the Syracuse meeting [1957], and despite the fact that iproniazid was marketed only as an antitubercular agent, under the trade name Marsilid, more than 400,000 patients affected by depression had been treated with the drug, which opened the way for the first group of specifically antidepressant drugs, later known as MAOIs.

Despite the success of iproniazid at treating depressive illnesses in the 1950s, this drug was soon discontinued in favour of MAOIs with better 'hepatic safety profile[s]';<sup>60</sup> this includes PLZ, which was introduced to the pharmacopoeia in 1960 (along with tranylcypromine in 1961 and preceded by isocarboxazid in 1959).<sup>60</sup> Collectively, these three MAOIs have been used in many hundreds of thousands or even millions of patients over the decades.<sup>61</sup> Current PLZ usage is estimated by ChemEurope to range from 75000 to 85000 patients worldwide.<sup>62</sup>

### 9.3.3. PLZ overdose

Lott (2021) describes the potentially fatal PLZ dose and the symptoms associated with it in the recently published 'MAOI Toolkit for clinical use'<sup>63</sup>:

Drug overdose is always a potential risk in the treatment of depression. Overdose with an irreversible MAOI (especially tranylcypromine, phenelzine, or isocarboxazid) causes severe, life-threatening manifestations. It is estimated that 5mg/kg or more may lead to a potentially fatal outcome. After overdose, patients may be asymptomatic for up to 24 hours. When symptoms develop they occur in a biphasic pattern. There is initial peripheral sympathetic stimulation with hypertension and CNS excitation; later hypotension occurs. Over a period of days there is a potential end result of coma and death.

### 9.3.4. PLZ addiction and abuse

Although the overall risk of addiction and/or abuse is low with PLZ, there are a number of case reports documenting this infrequent occurrence.<sup>64-67</sup> Detailed prevalence estimates are not available.

## 10. Summary of available data on comparative cost and cost-effectiveness

### 10.1 Introduction – PLZ: an inexpensive though neglected drug

The comparative underuse of PLZ and other MAOIs for the treatment of depressive disorders is attributable to profit incentives inherent to the industry-dominated model of (mental) healthcare; the newer drugs are patentable and lucrative, whereas the patent for MAOIs like PLZ has expired, rendering them unprofitable and therefore obsolete in the minds of many pharmaceutical company directors—despite their superior effectiveness. This is an uncomfortable truth, but a truth nonetheless. This argument was further explored in a peer-reviewed publication called ‘Requiem or resurrection: Classic monoamine oxidase inhibitors revisited’<sup>68</sup>; see excerpts below.

#### **Excerpts:**

*No science is immune to the infection of politics and the corruption of power ~ J. Bronowski*

Medical research has become steadily more commercialised, with inevitable profit motives driving attention to expensive newer drugs which are fabricated (much like some of the accompanying research studies) with the hopes of advancing the field and the market influence of the parties involved. In the psychopharmacology of depression, hopes of the first kind are yet to materialise: the classic, irreversible and nonselective monoamine oxidase inhibitors (MAOIs)—a drug class serendipitously proven to possess potent psychic energizing potential throughout the 1950s’ tuberculosis trials with iproniazid—remain to this day the most effective drugs for the treatment of depression.

[...]

Is it any wonder, then, that MAOIs have fallen from grace? If the evidence base is continually eroded, the passage of time alone will wither what remains. The

perceived diminution of value further catalyses the culling: out with the old, the outmoded, the obsolete... and in with the novel and newly marketed drugs. It would be convenient for some pharmaceutical stakeholders if the collective clinical memory of classic MAOIs could be effaced—that way, production of these out-of-patent (and therefore unprofitable) relics of early psychopharmacology could finally cease. And what of the patients? Yes—what? They may be glad to receive a heartfelt notice, preferably as late as possible—for a timely unveiling of ‘trade secrets’ such as supply shortages or market withdrawals of these vitally important, late-line depression drugs does not do; that would shatter the illusion of it all being one big and unfortunate and utterly unavoidable accident.

And what of their lives, the starkly diminished, the lost lives? Yes—what? There are collateral calamities, always, in the march of progress and profit. That is the status of the goings-on. But these truths typically go untold—they do not very well fit the mould of academic orthodoxy. Only a maverick or eccentric would speak the words, and would do well to utter an accompanying *moraturi te salutant*—their scholarly identity is unlikely to survive the speaking. In summary conclusion: despite the advent of modern depression drugs—including the comparatively ineffective reversible and selective MAO-A inhibitor moclobemide—classic MAOIs remain essential for the treatment of severe ‘difficult-to-treat’ depressive illnesses. This is well understood in specialized academic sub-circles. But the abstract knowledge alone does not suffice. Prescribing rates must increase. Thousands of patients are not given the option of a proper MAOI trial. Thousands more live in fear of having this effective treatment taken away. This is disgraceful. Access to affordable drugs for depression, including MAOIs, is an inviolable human right—at least it should be. The addition of classic MAOIs to the WHO list of Essential Medicines is the next logical step. We are preparing application reports with the aim of achieving this.

*[Note: this publication is where our intent to submit this application report was formalised, which was received with great enthusiasm by numerous experts in the field.]*



To summarise: PLZ's infrequent use<sup>69-73</sup> does not align with the evidence garnered from clinical experience and the evidence expressed in the literature; gross misappraisals of the side-effect burden associated with MAOIs,<sup>74</sup> along with misevaluations of the personal, societal, and economic costs of TRD have led to insufficient MAOI use in patient populations who are in dire need of these drugs and for whom many/all other ADs have failed. This application report hopes to remedy this misalignment of PLZ's well-established effectiveness in otherwise intractable cases of depression and its scarce and ever-diminishing use, which is significantly influenced by the industry-controlled propaganda for newer ADs and the existing profit disincentives for repopularising MAOI use.

## 10.2. PLZ cost-effectiveness

### 10.2.1. Introduction

Comparative cost-effectiveness analyses which include MAOI ADs like PLZ and newer ADs are scant—nevertheless, several authors write of the favourable cost-effectiveness of PLZ (which is further explored in the subsequent sections); these authors include Dwight-Johnson et al. (2003), who write: *'Medication costs are lower for tricyclic antidepressants and MAOIs than for the newer agents'*<sup>75</sup>, as well as Woods and Baker (2002), who similarly attest that PLZ is more cost-effective than newer ADs.<sup>76</sup>

### 10.2.2. Study on cost-effectiveness of interventions for Social Anxiety Disorder (Mavranouzouli et al.)<sup>77</sup>

In a recent study on 'the cost-effectiveness of psychological and pharmacological interventions for social anxiety disorder', Mavranouzouli et al. (2015) performed a model-based economic analysis to compare and contrast different treatment modalities, including various psychotherapeutic interventions (e.g., cognitive behavioral therapy, psychodynamic therapy) and various drug interventions (e.g., SSRI ADs like citalopram and sertraline, the SNRI AD venlafaxine, and the MAOI PLZ).<sup>77</sup> This study is strikingly relevant to the present application report because many drugs used to treat social anxiety disorder are primarily used as ADs, providing an instructive head-to-head comparison of the effectiveness and cost-effectiveness of these different AD classes.

With regard to absolute effectiveness, the authors found that PLZ was most effective among the drug-based interventions, attesting to PLZ's potent anxiolytic action, and ranked second overall behind only individually delivered cognitive behavioral therapy (ICBT); see 'Table 4' below.

**Table 4. Results of network meta-analysis that were utilised in the economic model: probability of recovery at end of treatment.** Interventions ranked according to probability of recovery (highest to lowest).

Intervention	Probability of recovery		
	mean	median	95% credible intervals
ICBT, C&W	0.62	0.65	0.16 to 0.95
Phenelzine	0.51	0.51	0.09 to 0.91
ICBT, general	0.47	0.46	0.08 to 0.90
ICBT, Hope	0.41	0.38	0.06 to 0.86
Paroxetine	0.40	0.37	0.06 to 0.85
ICBT, short	0.39	0.36	0.05 to 0.84
Venlafaxine	0.38	0.35	0.05 to 0.84
Fluvoxamine	0.37	0.34	0.05 to 0.84
Sertraline	0.37	0.33	0.04 to 0.83
Escitalopram	0.35	0.31	0.04 to 0.82
SHWS, internet	0.35	0.31	0.05 to 0.80
Fluoxetine	0.35	0.31	0.04 to 0.81
SHWS, book	0.34	0.30	0.04 to 0.81
GCBT, general	0.34	0.30	0.04 to 0.80
SHNS, book	0.34	0.30	0.04 to 0.80
Citalopram	0.34	0.29	0.04 to 0.82
Exposure	0.33	0.29	0.04 to 0.79
Mirtazapine	0.33	0.28	0.03 to 0.83
GCBT, Heimberg	0.32	0.28	0.04 to 0.78
Moclobemide	0.30	0.25	0.03 to 0.76
Pregabalin	0.29	0.25	0.03 to 0.77
SHWS, book	0.27	0.22	0.03 to 0.73
PDPT	0.26	0.21	0.03 to 0.72
Pill placebo	0.21	0.16	0.02 to 0.64
IPT	0.20	0.15	0.02 to 0.64
Mindfulness	0.19	0.14	0.02 to 0.63
Supportive therapy	0.16	0.11	0.01 to 0.57
Wait list	0.10	0.07	0.01 to 0.39

*Table from Mavranouzouli et al. (2015)<sup>77</sup>*

With regard to cost-effectiveness, the authors found, similarly, that PLZ ranked first among drug-based interventions, and ranked second overall behind only integrative cognitive behavioral therapy-based interventions; see 'Table 5' below.

**Table 5. Cost effectiveness of interventions for adults with social anxiety disorder: results of probabilistic analysis.** Mean values per person 5 years after end of treatment.

Intervention	% without SA at 5 years	Mean QALYs	Mean total costs (£)	Incremental analysis & ICERs (£/QALY)	Mean NMB (£)	Ranking by highest NMB
ICBT, C&W	50.25	3.75	6,178	9,179 versus phenelzine	68,810	1
ICBT, general	41.40	3.64	5,714	Extendendly dominated <sup>a</sup>	67,040	2
ICBT, Hope	37.52	3.59	5,853	Dominated	65,916	6
ICBT, short	36.25	3.57	5,970	Dominated	65,479	9
Phenelzine	34.80	3.57	4,557	1,472 versus SHNS book	66,899	3
SHWS, internet	34.02	3.54	5,186	Dominated	65,699	7
SHWS, book	33.59	3.54	4,741	Dominated	66,037	5
GCBT, general	33.54	3.54	5,436	Dominated	65,327	11
SHNS, book	33.28	3.53	4,501		66,197	4
Exposure	33.00	3.53	5,448	Dominated	65,179	14
GCBT, Heimberg	32.40	3.52	5,463	Dominated	65,013	17
Paroxetine	30.01	3.51	4,561	Dominated	65,603	8
Venlafaxine	29.46	3.50	4,633	Dominated	65,380	10
Fluvoxamine	29.08	3.50	4,666	Dominated	65,245	12
Sertraline	28.75	3.49	4,583	Dominated	65,239	13
SHNS, internet	29.55	3.49	5,042	Dominated	64,714	20
Escitalopram	28.12	3.48	4,591	Dominated	65,058	15
Fluoxetine	27.98	3.48	4,597	Dominated	65,016	16
PDPT	28.80	3.48	6,509	Dominated	63,055	25
Citalopram	27.53	3.47	4,602	Dominated	64,890	18
Mirtazapine	27.18	3.47	4,611	Dominated	64,786	19
Moclobemide	25.95	3.45	4,740	Dominated	64,323	21
Pregabalin	25.78	3.45	4,898	Dominated	64,118	22
IPT	25.44	3.44	5,987	Dominated	62,728	27
Mindfulness	24.86	3.43	5,041	Dominated	63,527	23
Pill placebo	22.29	3.40	4,713	Dominated	63,360	24
Supportive therapy	22.89	3.40	5,934	Dominated	62,136	28
Wait list	20.43	3.37	4,593	Dominated	62,810	26

<sup>a</sup>Extended dominance occurs when an option is less effective and more costly than a linear combination of two alternative options.

Interventions have been ranked from the most to least effective according to the number of QALYs gained.

C&W: Clark and Wells model; GCBT: group cognitive behavioural therapy; ICBT: individually delivered cognitive behavioural therapy; ICER: Incremental Cost Effectiveness Ratio; IPT: interpersonal therapy; NMB: Net Monetary Benefit, estimated using a willingness to pay £20,000/QALY; PDPT: psychodynamic psychotherapy; SA: Social Anxiety disorder; SHNS: self-help no support; SHWS: self-help with support.

*Table from Mavranetzouli et al. (2015)<sup>77</sup>*

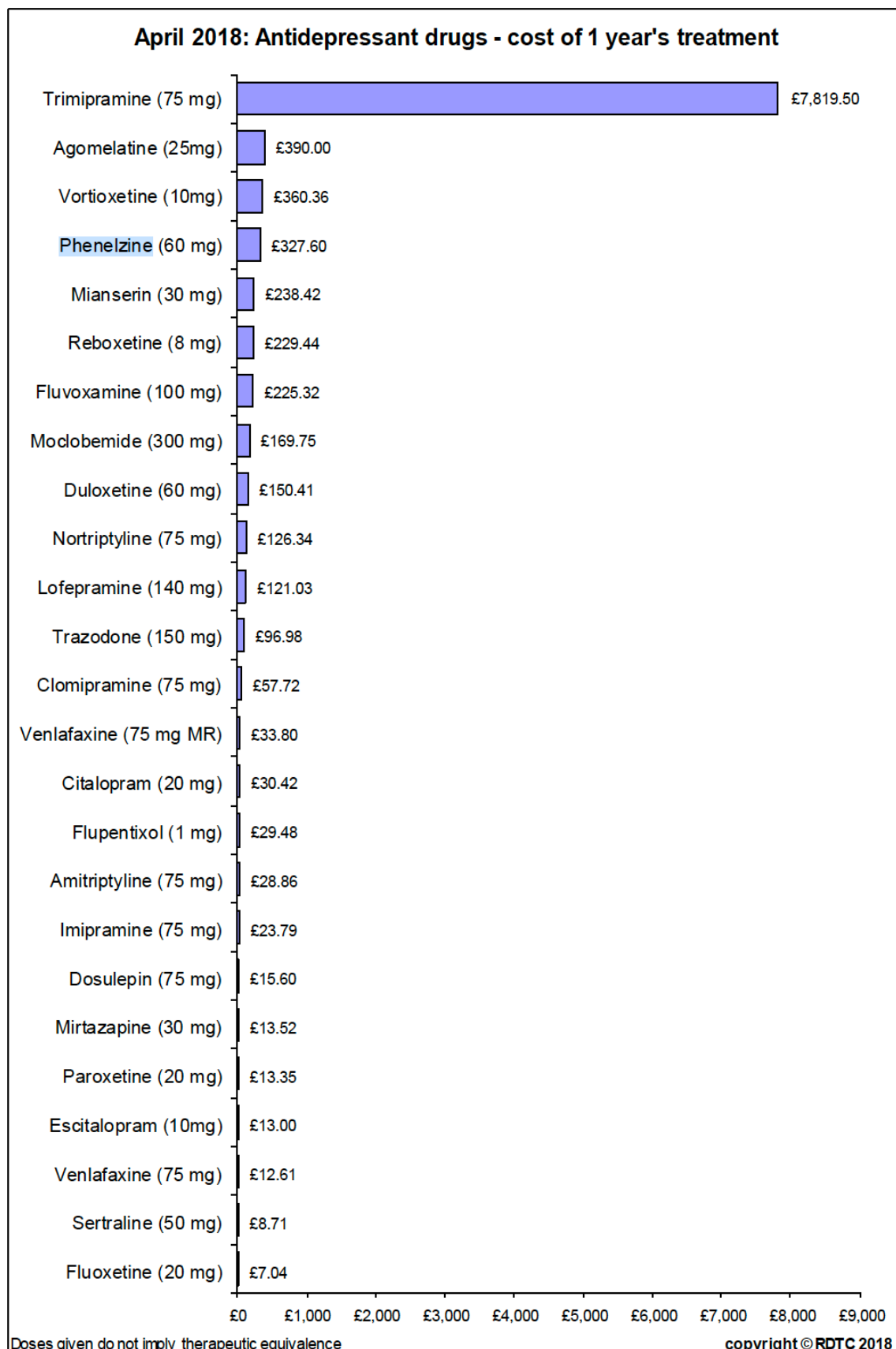
Given the considerable overlap in neurobiological correlates between anxiety disorders and depressive disorders, and the clear superiority of PLZ in terms of both absolute and cost-effectiveness compared to other ADs and AD classes, it may be plausibly inferred that similarly convincing divergences apply to PLZ's superiority over other ADs in the treatment of the various major depressive disorders.

### 10.2.3. The April 2018 study on absolute cost of various drugs by the National Health Service (United Kingdom)<sup>78</sup>

The Newcastle Regional Drug and Therapeutic Centre, a subsidiary to the National Health Service (NHS) of the United Kingdom, conducted a study on the absolute cost of various

drugs for the treatment of various conditions, including a comparison of AD costs; see 'Table' below (next page).

Whereas this study does not take into account the variable effectiveness of the different ADs and AD classes—which would significantly favour PLZ—the study does confirm the viability of PLZ use in comparison to the other ADs, many of which will have been tried and failed prior to resorting to MAOI treatment; therefore, the conclusion may be drawn that PLZ is acceptable cost-wise for use in treatment-resistant depressive illnesses.



*Table from Regional Drug and Therapeutics Centre (Newcastle)<sup>79</sup>*

#### 10.2.4. The NHS absolute cost study on the 'Guidance on the use of antidepressants'

In a publication on 'Guidance on the use of antidepressants' from the United Kingdom's National Health Service (NHS), Sussex Partnership, the costs of various AD combination/augmentation strategies are compared against the cost of PLZ use (image):<sup>80</sup>

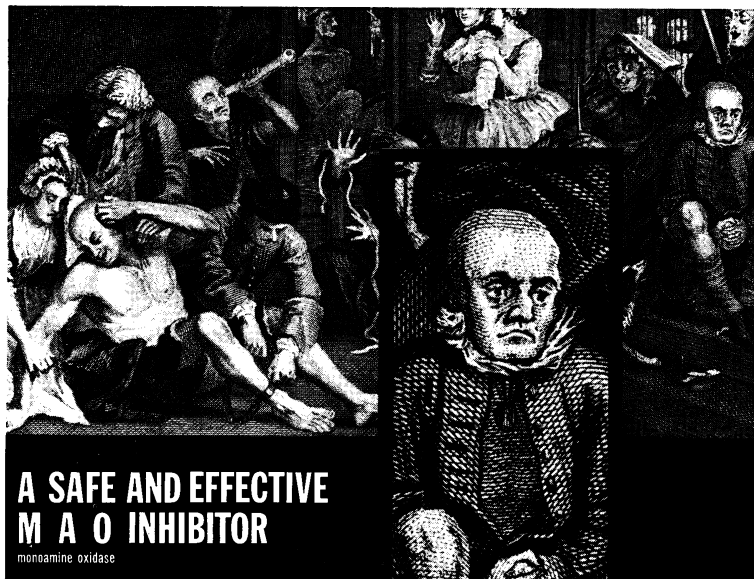
Name	Dose range	Cost/30 days*	Comments
Add lithium to existing therapy	Aim for plasma level of 0.4-1.0mmol/l	800mg per day £2.25	ECG before initiating. Needs baseline tests and continued monitoring.
Venlafaxine	High dose >200mg/day	225mg/day IR - £2.80 M/R – £6.50 (using 150mg +75mg M/R tablets)	Consider risk of cardiotoxicity. BP monitoring. Discontinuation reactions common.
Combination of SSRI or venlafaxine with mirtazapine	Up to maximum dose of each.	30mg mirtazapine added £1.17	Increased risk of serotonin syndrome, so patient should be informed. (See appendix 4).
MAOIs (Phenelzine is drug of choice)	See latest BNF for doses	15mg TDS £18.90	Dietary restrictions and risk of hypertensive crisis. Postural hypotension, dizziness, insomnia, headaches.
Combination of SSRI or venlafaxine with atypical antipsychotic	Mostly studied with fluoxetine and venlafaxine	Addition of quetiapine 300mg/day IR - £36.72 XL - £85	Evidence for combination with quetiapine, olanzapine, risperidone and aripiprazole. Quetiapine is now licensed for treatment of major depressive episodes in bipolar disorder and for add-on treatment in MDD in those who have had suboptimal response to antidepressant therapy.
Liothyronine Tri-iodothyronine (T3)	20-50 micrograms per day	40 micrograms <b>£516.40</b>	TFT monitoring required. <b>HIGH COST</b>
*Drug Tariff – December 2017			

Thus: even in the current market, where MAOI prices are inflated due to reasons outlined in the previous section 11.1, which are further expanded on in the upcoming section 11.3.1, PLZ is deemed more cost-friendly than two commonly used augmentation strategies in the treatment of depressive disorders, namely quetiapine and T3.

### 10.3 PLZ: recent prices in different markets

#### 10.3.1. Introduction

PLZ is relatively inexpensive to produce, and was long considered 'economical in use', as attested to by early advertisements; see 'Nardil' image below.



## A SAFE AND EFFECTIVE MAO INHIBITOR

monoamine oxidase

*From "Bedlam" by Hogarth*

a new advance in the  
treatment of **depression**

- Nardil is a new kind of anti-depressant which acts selectively on the brain.
- Nardil acts rapidly, improvement is seen within the first week and often in the first few days.
- Nardil is safe—toxic effects on blood or liver are extremely rare.
- Nardil has a simple and convenient dosage schedule (one tablet three times a day) which helps patient co-operation.
- Nardil is economical in use. Basic N.H.S. cost only 4/11 (excl. p.t.) for 25 tablets.

Nardil is available in bottles of 100 and 500 sugar-coated tablets each containing 15 mg. phenelzine.

# NARDIL

BRAND OF PHENELZINE

TRADE MARK



NAR 445

Full technical information may be obtained from

WILLIAM R. WARNER & CO. LTD., EASTLEIGH, HAMPSHIRE



As time went on, the misunderstood safety- and effectiveness profile of PLZ, along with the introduction of newer and more profitable (i.e., patentable) ADs which were and are aggressively marketed by pharmaceutical stakeholders, the market share of PLZ and the other MAOIs was greatly reduced as a result of several confluent factors, including dwindling prescription rates, diminished research interest in MAOI ADs, insufficient awareness of updates in their pharmacological mechanisms of action, declining consumer demand, etc.

As the demand for PLZ went down, so too did the supply, resulting in a higher price point for PLZ at present. In essence, these market-governed developments are reversible, as there are no prohibitive production costs inherent to the synthesis process of PLZ.

### 10.3.2. PLZ: current prices

For a long time, up to the turn of the millennium, the cost of MAOIs was very low; presumably due to industry- and profit-driven incentives (and to promote the use of newer ADs), the cost of MAOIs has increased substantially—as outlined in previous passages.

For an overview of current (and recent) prices of PLZ in various countries:

(A) A search on [pharmachecker.com](https://pharmachecker.com) on 30 October 2022 yielded the following price for PLZ ('Nardil') from Canada (produced by ERFA): \$144.95 for 180 tablets.

(B) In Belgium, up until the cessation of commercialization in 2019 by Pfizer, the market authorization holder of Nardelzine (PLZ),<sup>3</sup> the price was as follows: *tablets 100 x 15 mg R/ €33,48*.<sup>81</sup> At present (and since September 2019) PLZ is available in Belgium as a magistral preparation from pharmacies who process the pharmaceutical material of PLZ in capsules (price: approx. €45 per 60 capsules).

(C) In the United Kingdom, PLZ is available<sup>82</sup> ('Nardil') from Neon Healthcare for £120 per 100 tablets (source: <https://www.nice.org.uk/bnf>, consulted on 30 October 2022).

(D) In the United States of America, PLZ is available from Greenstone for \$108.88 per 60 tablets (source: <https://www.singlecare.com/prescription/phenelzine-sulfate>, consulted on 30 October 2022).

## 11. Regulatory status, market availability, and pharmacopoeial standards

### 11.1. Regulatory status of PLZ

PLZ is FDA-approved since June 9<sup>th</sup>, 1961.<sup>83</sup>

Below is an excerpt from the section on indications from the Neon Healthcare leaflet (2022), entitled 'Package leaflet: Information for the user Nardil 15 mg film-coated tablets phenelzine'<sup>84</sup>:



### **1. What Nardil is and what it is used for**

Nardil contains the active ingredient phenelzine, which belongs to a group of medicines called monoamine oxidase inhibitors, or MAOIs.

Nardil is used to treat certain types of depression. It works by changing the way messages are sent from one nerve to another in the brain. Nardil is especially helpful when:

- depression does not follow the typical pattern
- anxiety or fear is a main symptom
- treatment with other antidepressants has failed.

Below is an excerpt from the section on indication from Pfizer's leaflet (2008), entitled 'NARDIL® (Phenelzine Sulfate Tablets USP)'<sup>85</sup>:

#### **INDICATIONS AND USAGE**

NARDIL has been found to be effective in depressed patients clinically characterized as "atypical," "nonendogenous," or "neurotic." These patients often have mixed anxiety and depression and phobic or hypochondriacal features. There is less conclusive evidence of its usefulness with severely depressed patients with endogenous features.

NARDIL should rarely be the first antidepressant drug used. Rather, it is more suitable for use with patients who have failed to respond to the drugs more commonly used for these conditions.

*[Note: the statement on PLZ's effectiveness in endogenous depressions is outdated; see supra.]*

#### 11.2. Market availability of PLZ

PLZ is available in the national drug markets of the United Kingdom, Belgium, Canada, the United States of America, and Australia<sup>86</sup>.

#### 11.3. Pharmacopoeial standards for PLZ

PLZ is listed in the British pharmacopoeia<sup>1</sup>, and the United States of America pharmacopoeia<sup>19</sup>.

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## Addenda

### Addendum A



## International MAOI Expert Group

*Tempus perficit circulum, vetus renovatur*

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Dear WHO Expert Committee,

The Presiding Council of the International MAOI Expert Group endorse this application to the WHO for the inclusion of phenelzine and tranylcypromine on the Essential Medicines List in the 'mood disorders' section.

We deem these drugs as essential for the treatment of severe affective disorders of various types—most notably 'treatment-resistant unipolar depression'.

We recognise that there is not an extensive number of Randomised Controlled Trials to support their use, particularly when compared with modern antidepressants; nevertheless, the substantive experiences, over six decades, of many senior clinicians and psychopharmacology specialists worldwide (as represented by our group) strongly support their uniquely effective and life-saving properties.

Signed on behalf of the Presiding Council,

Ken Gillman  
Presiding Council Chairman

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[secretariat@maoiexperts.org](mailto:secretariat@maoiexperts.org) • [www.maoiexperts.org](http://www.maoiexperts.org)



Utrecht, 2 August 2022

To whom it may concern,

As the president of the European College of Neuropsychopharmacology ([www.ecnp.eu](http://www.ecnp.eu)) and on behalf of the College, I write in support of having the Monoamine Oxidase Inhibitor (MAOI) antidepressants phenelzine and tranylcypromine included in the WHO List of Essential Medicines.

ECNP is Europe's largest non-institutional supporter of applied and translational research and education in Europe and supports innovative research in the convergent disciplines of neuropsychopharmacology and facilitate the communication of ideas, discoveries and best practices. The college also encourages the scientific activities of countries in Europe and co-ordinate the development of common European standards. We also facilitate dialogue with regulators, government bodies, international agencies and industry. To achieve its aims, ECNP organises a wide range of activities, programmes and events across Europe; every year we bring together more than 6000 scientists and clinicians.

MAOI are essential when narrow action antidepressants (such as SSRIs) and the broad action tricyclics have failed and accordingly, we recommend that the compounds obtain formal listing.

Sincerely yours,

Gitte Moos Knudsen



## Addendum C



36 Cambridge Place  
Hills Road  
Cambridge  
CB2 1NS  
01223 358 395

**Administrative Officer**  
Mrs Lynne Harmer  
01223 358 421  
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Miss Sarah Channing-Wright  
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Essential Medicines

World Health Organisation

Dear Colleague

### **Monoamine oxidase inhibitors as treatment for people with depressive, anxiety, or stress-related disorders**

As President of the British Association for Psychopharmacology (BAP), and on behalf of its Council ([www.bap.org.uk](http://www.bap.org.uk)) I am writing in support of the proposal of having the monoamine oxidase Inhibitor (MAOI) medicines phenelzine and tranylcypromine included within the WHO List of Essential Medicines.

The BAP is a learned society and registered charity. It promotes research and education in psychopharmacology, neuroscience and related areas, and brings together people in academia, health services, and industry. Formed in 1974, it is the largest such national association in Europe, and the second largest in the world. The BAP remit comprises two interlinked broad areas: the neuropsychobiological foundation of brain function and behaviour, and its alterations in psychological distress and mental disorders; and the study of treatments for mental disorders (including substance use disorders), focusing on targets, mechanisms of action, effectiveness, and tolerability of current and novel treatments.

Council members from the BAP were crucial in the development of the Royal College of Psychiatrists Position Statement on use of MAOIs in psychiatric practice, published in July 2020 (attached), which has helped to inform clinical practice and to ensure continuing supplies of MAOIs for patients within the United Kingdom.

MAOIs can be beneficial in a group of patients with depressive or anxiety disorders who might not respond to other pharmacological and psychological treatments. In particular, they can be effective in patients with otherwise treatment-resistant depression, and in patients with social anxiety disorder or post-traumatic stress disorder. They have a different tolerability profile to 'first-line' drugs such as selective serotonin reuptake inhibitors (SSRIs) and some patients who are intolerant of SSRIs do tolerate MAOI treatment rather better. The exclusion of MAOIs from the WHO list of Essential Medicines restricts treatment choice for patients and clinicians and compromises clinical outcomes for conditions which are common, distressing, impairing and associated with increased morbidity and mortality.

Yours faithfully

A handwritten signature in black ink, appearing to read 'David Baldwin'.

Prof. David S. Baldwin MA DM FRCPsych FHEA FRSA  
President of British Association for Psychopharmacology [www.bap.org.uk](http://www.bap.org.uk)

Professor of Psychiatry and Section Head, Clinical Neuroscience, Medicine, University of Southampton  
Honorary Consultant Psychiatrist, Mood Disorders Service, Southern Health NHS Foundation Trust  
Honorary Professor of Psychiatry, University of Cape Town, South Africa  
Councillor, European College of Neuropsychopharmacology [www.ecnp.eu](http://www.ecnp.eu)  
Medical Patron, Anxiety UK [www.anxietyuk.org.uk](http://www.anxietyuk.org.uk)

## Addendum D



FACULTY OF MEDICINE & DENTISTRY  
DEPARTMENT OF PSYCHIATRY

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Tel: 780.407-6503  
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[www.psychiatry.med.ualberta.ca](http://www.psychiatry.med.ualberta.ca)

December 14, 2022

World Health Organization  
Geneva, Switzerland

Dear WHO Officials:

We understand that the International Monoamine Oxidase Inhibitor (MAOI) Expert Group is applying for inclusion of the MAOIs phenelzine and tranylcypromine in the WHO List of Essential Medicines in the "Medicines used in depressive disorders" category (section 24.2.1). The members of the Department of Psychiatry, University of Alberta listed below have indicated electronically their support for the inclusion of these two drugs in that category since they are an important part of the pharmacotherapy armamentarium used to treat depressive disorders, which are a major public health concern worldwide.

The University of Alberta is in the top 5 of research universities in Canada, and the Department of Psychiatry has very active teaching and research programs, with approximately 50 psychiatry residents and over 30 MSc/PhD students.

Thank you for your consideration of this important matter.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'Glen Baker'.

Glen Baker, PhD, DSc  
Professor Emeritus

List of supporting departmental members (in alphabetical order):

Adam Abba-Aji, MD, MBA, MSc, FRCPC, FRCPsych, Associate Clinical Professor  
Katherine J. Aitchison, BM BCh, PhD, FRCPsych, Professor  
Samer Aldandashi, MD, FRCPC, Assistant Clinical Professor  
Glen Baker, PhD, DSc, Professor Emeritus  
Jan Banasch, MD, FRCPC, Clinical Professor  
(continued)

Lisa Burback, MD, FRCPC, Associate Clinical Professor  
Carson Chrenek, MD, FRCPC, Assistant Clinical Professor  
Serdar Dursun, MD, PhD, FRCPC, Professor  
Peter Florence, MD, FRCPC, Assistant Clinical Professor  
Klaus Gendemann, MD, FRCPC, Clinical Professor  
Andrew Greenshaw, PhD, Professor  
Andrew Holt, PhD, Associate Professor  
Gordon Kelly, MD, FRCPC, Assistant Clinical Professor  
Atul Khullar, MD, MSc, FRCPC, Associate Clinical Professor  
Maryana Kravtsenyuk, MD, MSc, FRCPC, Assistant Clinical Professor  
Jean-Michel Le Melleo, MD, Professor  
Daniel Li, MD, MSc, FRCPC, Associate Clinical Professor  
Xinmin Li, MD, PhD, FRCPC, Professor  
Jason Long, MD, FRCPC, Assistant Clinical Professor  
Nicholas Mitchell, MD, MSc, FRCPC, Assistant Clinical Professor  
Chantal Moreau, MD, FRCPC, Associate Clinical Professor  
Jorge Perez-Parada, MD, MSc, FRCPC, Assistant Clinical Professor  
David Ross, MD, PhD, Professor  
Mahnaz Salsali, MD, PhD, FRCPC, Assistant Clinical Professor  
Laura Stovel, MD, FRCPC, Associate Professor  
Jennifer Swainson, MD, FRCPC, Associate Clinical Professor  
Rejish Thomas, MD, MSc, FRCPC, Assistant Clinical Professor  
Patrick White, MB BCh, MRCPsych, Clinical Professor  
Yanbo Zhang, MD, PhD, FRCPC, Associate Professor

## Addendum E

**PROF. GORDON PARKER AO** FAAHMS, FASSA, MB. BS., MD., PhD., DSc., FRANZCP  
Provider No. 0095673F

Faculty of Medicine & Health, Discipline of Psychiatry  
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UNSW 2052  
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[g.parker@unsw.edu.au](mailto:g.parker@unsw.edu.au)



23rd June 2022

Dear Sir/Madam,

I write in support of having the Monoamine Oxidase Inhibitor (MAOI) antidepressants phenelzine and tranylcypromine included in the WHO List of Essential Medicines.

In terms of my credentials, I was department head of the School of Psychiatry at the UNSW for 20 years, head of the Prince of Wales Department of Psychiatry for 15 years and was the founder and initial Executive Director of the Black Dog Institute – and initiated its focus on research into and management of the mood disorders. As an academic I have published 23 books and over one thousand papers, with a strong focus on mood disorders.

My focus as a clinician weights managing those with mood disorders (especially treatment-resistant conditions) and I currently see about forty patients/week, and with telepsychiatry undertake assessment and management of several patients each month who live overseas and are referred to me by psychiatrists in other countries.

I have prescribed MAOIs for over forty years and remain impressed by their distinctive cost-benefit ratio, including and perhaps especially in melancholic depressions. In practice I find that most patients find the food limitations minimal while the MAOIs not uncommonly bring depression to an end when antidepressants of all other classes have failed. I do not view them as first-line or even second-line agents, but they are essential when narrow action antidepressants (such as SSRIs) and the broad action tricyclics have failed.

Thus, they can be invaluable and so deserve such formal listing.

Sincerely,

A handwritten signature in black ink, appearing to read 'Gordon Parker'.

Gordon Parker, Scientia Professor, UNSW.