Please find enclosed the comments from the Department of Mental Health and Substance Use on the Application "The role of classic Monoamine Oxidase Inhibitors in treatment-resistant depression: proposal for the inclusion of Phenelzine in the Complementary List of Essential Medicines" for the addition of phenelzine for the treatment of adults with treatment-resistant depression to the WHO Complementary List of Essential Medicines.

Application number	A32
Name of the application	"The role of classic Monoamine Oxidase Inhibitors in treatment-resistant depression: proposal for the inclusion of Phenelzine in the Complementary List of Essential Medicines"
Submitted by	PsychoTropical Research Institute, Queensland, Australia; International MAOI Expert Group (https://maoiexperts.org)
Date of submission	

Introduction

Major depressive disorder (MDD) is a common mental disorder that affects over 280 million people in the world, with an estimated 3.8% of the population affected, including 5.0% among adults and 5.7% among adults older than 60 years (Global Burden of Disease [GBD] 2019). Depression is the third cause of disability in the global burden of disease (GBD 2019) accounting for 4.3% of the global burden of disease. The estimates for low- and middle-income countries (LMICs) are 3.2% and 5.1%, respectively (WHO 2011). Current predictions indicate that by 2030 depression will be the leading cause of disease burden globally.

Two out of three people suffering from depression do not receive adequate treatment in LMICs (Lancet Commission 2018, Evans-Lacko 2018). In addition to psychosocial interventions, medicines play an important role in the treatment of depression. According to international guidelines, including the Mental Health Gap Action Programme (mhGAP), first-line treatments for depression are psychological and pharmacological interventions, namely antidepressants (ADs). In moderate to severe cases of depression, ADs are recommended as first-line treatment.

However, the response to ADs varies across people with depression (Kennedy 2016). It has been estimated that between one-half and two-thirds of people with depression do not reach a response threshold to pharmacological treatments (Bauer 2002; Trivedi 2006). Such non-response to treatment may vary from partial response to complete 'resistance' to treatment (Bauer 2002; Papakostas 2020). The term treatment-resistant depression (TRD) has been used in clinical and research settings over the years, and it generally refers to a depressive episode that failed to respond or remit to at least two pharmacological treatments (Cosgrove 2021). For TRD, several different options are recommended in the international guidelines, which will be described below.

The proposal

A proposal for the inclusion of phenelzine as a suitable medicine for the forthcoming update of the EML has been submitted to the WHO. Phenelzine is an AD of the class of monoamine oxidase inhibitors (MAOI), which is the oldest class of antidepressants introduced in the 60's on the market. The proposal provides an overview of the evidence on benefits and harms of phenelzine for TRD, also highlighting its safety issues and potential for life-threatening overdose. The following reviews are presented in the proposal:

1. A systematic review and network meta-analysis (NMA) conducted by Suchting et al. in 2021 (Suchting 2021). It included 52 RCTs, comprising 6462 participants, and evaluated the comparative efficacy and acceptability of 13 different ADs and placebo in adults suffering from depression. The review pointed out that all ADs were more effective than placebo in terms of response to treatment (at least 50% reduction of depressive symptoms from baseline to endpoint). No differences in terms of acceptability for phenelzine compared to placebo and to other ADs were found. Notably, this review did not include participants with TRD.
2. A systematic review and pair-wise meta-analysis of RCTs conducted by Henkel and colleagues in 2006, comparing MAOI versus placebo or versus SSRIs and TCAs for the acute treatment of patients with atypical depression (Henkel 2006). It included 8 RCTs and showed superiority of phenelzine compared to placebo in terms of proportion of responders. When compared to SSRIs phenelzine was not superior in terms of response rate. Authors did not perform analysis on acceptability, tolerability or any other safety outcomes. Notably, this review included participants with atypical depression but not with TRD.
3. A review of the literature and meta-analysis of RCTs conducted by Thase et al. in 1995 on the efficacy of MAOI versus TCAs for the treatment of depression (Thase 1995). Such review yielded 54 studies on adults. Phenelzine was more effective than placebo but less effective than TCA in terms of efficacy for depression. Phenelzine was found to be more effective than TCAs in patients with atypical features of depression. This review did not include participants with TRD.

In the proposal, the harms of phenelzine are also outlined. Among them toxicity and diet restrictions, drug-drug interactions, common adverse events, and risk of overdose are mentioned.

1. The use of MAOI requires diet restrictions and avoiding certain other medications because of the risk of dangerous hypertensive crisis if associated with certain food and medications. Any food containing high levels of tyramine, such as aged cheeses, sauerkraut, cured meat, drafted beer and fermented products (soy sauce, miso, tofu) should be avoided. Although well-known and manageable through close monitoring and psychoeducation, such dietary restrictions could be hard to be implemented in LMICs and rural areas with scarce resources.
2. Another risk is related to drug-drug interactions, which could lead to serious adverse events (e.g. serotonin syndrome) or inefficacy of other administered medicines. Among drugs that should be avoided include among others some antihistamines, some analgesics, some antihypertensives, and other antidepressants.
3. The most common central nervous system adverse effects of MAOI include dizziness, headache, drowsiness, sleep disturbances (e.g., insomnia, hypersomnia), fatigue, weakness, tremors, twitching, myoclonic movements, and hyperreflexia. Other adverse effects include constipation, dry mouth, gastro-intestinal disturbances, anorexia, nausea, vomiting, arthralgia, increased appetite, and weight gain also have been reported.

4. Contrary to new antidepressants, such as SSRIs, phenelzine overdose can cause severe, life-threatening manifestations, posing questions on the possibility of seeking prompt support in the case of treatment-emergent adverse effects in rural settings, where travelling to the nearest hospital can be challenging.
5. For these reasons, it has been suggested that the prescription of phenelzine should be performed by specialized medical doctors in a secondary care setting, such as psychiatrists.

International guidelines

In the proposal phenelzine is suggested as a treatment for people with depression who did not respond to two pharmacological treatments (i.e. for TRD). International guidelines, however, either do not recommend phenelzine, or recommend it only as a last resort, as follows:

- The 14th edition of The Maudsley Practice Guidelines: recommend after the use of SSRIs, switching to venlafaxine or mirtazapine or bupropion, adding aripiprazole or lithium or quetiapine, combining olanzapine and fluoxetine. MAOI are not recommended (Taylor 2021).
- National Institute for Health and Care Excellence (NICE) guidelines for depression first suggest psychological interventions or switching to another SSRIs or to Serotonin–norepinephrine reuptake inhibitor (SNRIs). MAOI are suggested as an option only in secondary care after the previous attempts failed (NICE2016).
- American Psychiatric Association (APA) Clinical Practice guideline for the treatment of depression recommends psychotherapy and second-generation antidepressants. As second line treatments it recommends switching to other second-generation antidepressants (such as SSRIs and SNRIs) or TCA (APA 2019).
- Canadian Network for Mood and Anxiety Treatments (CANMAT) recommends as first line treatment SSRIs, SNRIs, agomelatine, bupropion, mirtazapine, vortioxetine; and as second line treatments TCAs, quetiapine, trazodone, moclobemide, selegiline, levomilnacipran, vilazodone and as third line option phenelzine, tranylcypromine and reboxetine (Kennedy 2017).
- Phenelzine is not recommended by any of the existing WHO guidelines.

Comment

Currently the WHO Essential List of Medicines (EML) for depressive disorder in adults consists in fluoxetine with a selected square box (including other Selective serotonin reuptake inhibitors [SSRIs]) and amitriptyline as possible pharmacological treatments.

Phenelzine requires proper monitoring and has a less favorable safety profile compared to other ADs, including SSRIs, tricyclics (TCAs) and newer agents. Moreover, as outlined in the proposal, the evidence base for phenelzine lacks randomized controlled trials (RCTs), as MAOIs are old medications and RCTs were not so common when they were introduced on the market.

In TRD phenelzine is not supported by evidence of efficacy.

The risk for serious treatment emergent adverse events, reactions due to drug-drug interaction and overdose, along with the need of specialized facilities and health care professional pose concerns about the usability of such a medication in LMICs.

In conclusion, the lack of high-quality evidence from RCTs, the risk of severe treatment emergent adverse events, the number of drug-drug interactions and the pharmacological profile of toxicity of phenelzine raise concerns about their appropriate and safe use of this medication in LMICs and other settings.

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