Phenelzine

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 24. Medicines for mental and behavioural disorders > 24.2. Medicines for mood disorders > 24.2.1. Medicines for depressive disorders

ATC codes: N06AF03

Indication	Other specified depressive disorders ICD11 code: 6A7Y
INN	Phenelzine
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Solid > dosage form:** 15 mg (as sulfate)
EML status history	Application rejected in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Phenelzine
DrugBank	Phenelzine

Expert Committee recommendation

The Expert Committee noted that depressive disorders were highly prevalent and were responsible for a large and increasing global public health burden. The Committee acknowledged that a subgroup of patients with depression did not respond adequately or at all to initial lines of treatment. The Committee noted that the systematic reviews and meta-analyses presented in the application which evaluated the comparative efficacy of phenelzine versus placebo or other antidepressants provided some evidence for the efficacy of phenelzine but did not specifically address the indication of treatment-resistant depression. The Committee considered that there was therefore uncertainty in the applicability of the results to the specific population of patients with treatment-resistant depression. The Committee noted that comparative evidence was lacking for phenelzine versus other treatment approaches for treatment-resistant depression. The Committee noted that phenelzine was associated with potentially serious adverse effects and had a high potential for drug–drug and drug–food interactions. Treatment with phenelzine therefore would require careful and specialized monitoring and management, which may not be available in many low- and middle-income settings. The Committee expressed concern about the feasibility of safe use of phenelzine in settings where specialist monitoring of patients was not available. The Committee noted that phenelzine had limited global availability and was currently more highly priced than other antidepressants in common clinical use. Additionally, the Committee noted that phenelzine was not included in current WHO mhGAP guidelines for treatment of depression. The Expert Committee did not therefore recommend the inclusion of phenelzine on the complementary list of the EML for use in treatment-resistant depression because of uncertain

evidence of benefit in the proposed patient population and increased risk of harms.

Background

Phenelzine is a non-selective and irreversible inhibitor of the enzyme monoamine oxidase. Monoamine oxidase plays a role in the inactivation of several neurotransmitters such as norepinephrine and serotonin. By inhibition of the enzyme, inactivation of these neurotransmitters is prevented, thereby increasing their availability. Phenelzine has not previously been evaluated for addition to the EML. Antidepressant medicines currently included on the EML include the tricyclic antidepressant amitriptyline, and fluoxetine as the representative selective-serotonin reuptake inhibitor, with citalopram, escitalopram, fluvoxamine, paroxetine and sertraline as therapeutic alternatives.

Public health relevance

According to the 2019 Global Burden of Disease study, depressive disorders affected approximately 280 million people worldwide, equivalent to almost 3.8% of the global population and resulted in almost 47 million disability-adjusted life years (DALYs), equivalent to 1.8% of global DALYs (1). In low- and middle-income countries, two out of three individuals suffering from depression do not receive adequate treatment (2,3). Alongside psychosocial interventions, medicines, particularly antidepressants, play an important role in treatment according to international guidelines, including the WHO Mental Health Gap Action Programme (mhGAP) guidelines (4). First-line treatments for depression include both psychological and pharmacological interventions, with antidepressant medicines recommended as the primary treatment option for moderate to severe cases of depression. Estimates suggest that about 30–50% of patients with major depressive disorder do not respond to initial treatment with antidepressants and around 60–70% of patients achieve an incomplete response (5). Estimates for the prevalence of treatment-resistant depression, defined as depressive episodes that fail to respond to or achieve remission with at least two pharmacological treatments (6), vary considerably, from up to 15% (7) to around 30% of treated patients (8,9). Treatment-resistant depression imposes an important personal, societal and economic burden. The effect of depression on well-being has been described as comparable to or worse than that of chronic medical illnesses, such as diabetes and congestive heart failure (10). Patients with treatment-resistant depression experience substantial and lasting impairments in various aspects of functioning and well-being (10). Their quality of life is greatly diminished, leading to reduced work productivity and activity levels (11). Treatment-resistant depression is also associated with a higher risk of psychiatric and somatic comorbidities, including anxiety disorders, hypertensive diseases and central nervous system disorders (12). The condition also increases the risk of suicide and results in greater use of health care resources than treatment-responsive depression (13). Treatment options for treatment-resistant depression include: augmentation or adjunctive therapy with non-antidepressant medications such as lithium, thyroid hormone or second-generation antipsychotics; switching to other antidepressant medicine classes; psychotherapy; electroconvulsive therapy or other forms of brain stimulation; novel therapeutics such as ketamine and esketamine; and compounds targeting the delta opioid receptor. Each approach has advantages and disadvantages, but currently no consensus has been reached on the best treatment pathway for treatment-resistant depression.

Benefits

A 2021 systematic review and network meta-analysis evaluated the effectiveness and acceptability of monoamine oxidase inhibitors in the treatment of depressive disorders (14). This study was not specific for treatment-resistant depression. The analysis included 52 double-blind, randomized controlled trials (6462 participants) conducted between 1976 and 2012 comparing 14 different antidepressants or placebo. It included nine randomized controlled trials of phenelzine versus placebo or another active comparator. The primary outcomes were efficacy (defined as response rate measured by the proportion of participants demonstrating ≥ 50% reduction on a standardized depression rating scale) and acceptability (all-cause discontinuation rate). The results indicated that, except for fluvoxamine, all antidepressants were more effective than placebo. No significant differences were found in drop-out rates between the antidepressants and placebo. Of all antidepressants evaluated, phenelzine was associated with the highest odds ratio (OR) point estimate for efficacy relative to placebo (OR 4.66, 95%

credible interval (CrI) 2.64 to 8.40). Phenelzine also had the highest surface under the cumulative ranking curve (SUCRA) score (84.3%). In head to head treatment comparisons, phenelzine demonstrated superior evidence for efficacy compared with all other antidepressants investigated. Clomipramine demonstrated superior evidence for acceptability relative to placebo of all treatments investigated (OR 0.66, 95% CrI 0.34 to 1.29; SUCRA 74.4%). For acceptability relative to placebo for phenelzine the OR was 1.00 (95% CrI 0.53 to 1.88; SUCRA 35.4%). The study acknowledged a number of factors limiting the precision of the estimates including the small number of studies that evaluated monoamine oxidase inhibitors, particularly in recent years, and changing standards in diagnosis and reporting over time resulting in heterogeneity in the included studies. Because of the older age of studies investigating monoamine oxidase inhibitors, the authors allowed inclusion of trials with a variety of diagnoses (major depressive disorder, treatment-resistant depression, dysthymic disorder, atypical depression, bipolar depression and depressive disorder not otherwise specified). A 2006 meta-analysis investigated the treatment of major depression with atypical features, comparing monoamine oxidase inhibitors with other antidepressants or placebo (15). The analysis included eight double-blind, randomized controlled trials (670 participants). For each study, effect sizes were determined by calculating the phi coefficient, representing the response-rate difference. Four randomized controlled trials provided data for the comparison of phenelzine and placebo and three randomized controlled trials provided data for the comparison of phenelzine and imipramine. Six of these seven trials showed phenelzine to be superior in terms of the proportion of responders and effect sizes (average effect size versus placebo 0.45, 95% confidence interval (CI) 0.35 to 0.60 and average effect size versus imipramine 0.27, 95% CI 0.16 to 0.42). Three randomized controlled trials provided data for comparison of phenelzine or moclobemide and fluoxetine or sertraline. Phenelzine or moclobemide were not superior to the comparators for response rate or effect size (average effect size 0.02, 95% CI –0.10 to 0.14). A 1995 meta-analysis evaluated controlled trials comparing monoamine oxidase inhibitors approved by the United States Food And Drug Administration for treatment of depression (phenelzine, isocarboxazid and tranylcypromine) with placebo and tricyclic antidepressants in inpatient and outpatient settings (16). For outpatients, isocarboxazid and tranylcypromine had generally comparable overall efficacy. The drug–placebo differences in the percentage of responders were 29.5% (standard deviation (SD) 11.1%; nine studies) for phenelzine, 41.3% (SD 18.0%; three studies) for isocarboxazid and 22.1% (SD 25.4%; three studies) for tranylcypromine. Phenelzine and tranylcypromine were found to be more effective than comparator tricyclics in outpatients with differences in percentage of responders of 8.8% (SD 8.3%; 11 studies) and 16.8% (SD 27.5%; four studies), respectively. For inpatients, the drug–placebo differences in the percentage of responders were 22.3% (SD 30.7%; five studies) for phenelzine and 15.3% (SD 12.6%; four studies) for isocarboxazid. No data were available for tranylcypromine. Both phenelzine and isocarboxazid were less effective than comparator tricyclics in inpatients with differences in percentage of responders of –21.0% (SD 7.7%) and –14.1% (SD 27.5%; two studies), respectively. A 2019 non-randomized retrospective study evaluated the relative effectiveness of tricyclic antidepressant versus monoamine oxidase inhibitor as monotherapy for treatment resistant depression (17). Data from about 2500 treatment charts of patients with treatment-resistant depression attending a university mood disorder clinic between 1983 and 2015 were retrospectively analysed. The study included 147 treatment outcome observations from 94 unipolar, depressed patients who received either tricyclic antidepressant (n = 47) or monoamine oxidase inhibitor (n = 100) monotherapy. Monoamine oxidase therapy was generally more effective than tricyclic antidepressant therapy for patients with treatment-resistant depression. For patients who had failed to respond in at least one prior adequate antidepressant trial, those who received tricyclic therapy showed higher (i.e. worse) end-of-treatment clinical global impressions/severity scores relative to those who received monoamine oxidase therapy. A 2012 prospective study evaluated the longer-term outcome of treatment-resistant depression, including clinical and psychosocial factors that may be associated with outcome, in 150 patients with treatment-resistant depression at a tertiary inpatient service in the United Kingdom (18). The use of monoamine oxidase inhibitors (moclobemide, phenelzine, tranylcypromine and isocarboxazid) among inpatients was associated with remission at time of discharge (OR 6.49, 95% CI 1.63 to 25.91) and remission at the time of final follow-up (OR 4.78, 95% CI 1.15 to 19.85). Among the limitations highlighted by the study authors were that the sample size was small, follow-up duration variable, outcomes for 13% of participants were unaccounted for, and the cohort was taken from a specialist inpatient service and likely to represent patients with more severe illness, and therefore the results may

not be generalizable to treatment-resistant depression in other settings.

Harms

The potential adverse effects of monoamine oxidase inhibitors are more diverse and potentially more serious than most other antidepressants. As monoamine oxidase is found throughout the body, its inhibition can lead to various pharmacological effects. While many adverse effects of monoamine oxidase inhibitors are mild to moderate and tend to subside with continued therapy, some reactions can be severe and may necessitate discontinuation of treatment, particularly events involving the cardiovascular, central nervous and hepatic systems. Serious adverse effects, such as hypertensive crisis and serotonin syndrome, have been reported with monoamine oxidase inhibitors, especially when they are taken concomitantly with tyramine-containing foods or certain medicines. These interactions can lead to potentially life-threatening reactions; hence, careful monitoring is required, with close attention paid to potential drug–drug and drug–food interactions. Potential adverse effects of phenelzine include blurred vision, constipation, dry mouth, headache, hypoglycaemia, insomnia, liver enzyme elevation and (rarely) hepatotoxicity, myoclonus, nausea, orthostatic hypotension, paresthesia, pyridoxine-deficiency, oedema, sedation, sexual dysfunction, urinary retention and weight gain (19,20). Phenelzine can cause dose-dependent orthostatic hypotension, especially at the start of treatment and after dose increases. Significant orthostatic hypotension (a drop of ≥ 10–15 mmHg in systolic blood pressure) is a common effect of treatment with monoamine oxidase inhibitors and typically peaks 10–14 days after a dose increase (19). General measures to reduce the chance of orthostatic hypotension include increasing doses slowly and dividing daily doses (21). An important safety concern with the use of phenelzine are drug–drug interactions that can result in serotonin syndrome and hypertensive crisis (20). Concomitant use of phenelzine with other medicines or supplements that have serotonergic activity is contraindicated (19). Phenelzine is also associated with multiple drug–food interactions of concern, in particular, interactions with tyramine, a vasoactive amine found in various foods and beverages including aged cheese, cured meats, soy products, yeast products, fermented foods and tyramine-containing nutritional supplements (20,22). Reduced breakdown of tyramine as a result of monoamine oxidase inhibition may result in hypertensive crisis. Patients receiving phenelzine must follow a tyramine-restricted diet (23).

Cost / cost effectiveness

Comparative cost–effectiveness analyses for monoamine oxidase inhibitors and newer antidepressants for treatment-resistant depression are lacking. The application described the results of a modelled economic analysis of psychological and pharmacological interventions for social anxiety disorder. In this analysis, phenelzine was determined to be the third most cost-effective intervention, after individually delivered cognitive behavioural therapy (using the Clark and Wells model) and general individually delivered cognitive behavioural therapy (24). Notably, the analysis did not take into account the side-effects of pharmacological treatments. The absolute cost of antidepressant medicines in the United Kingdom was compared in 2018 using basic prices within the National Health System The reported cost for 1 year of treatment with phenelzine 60 mg/day was £327.60. In comparison, the reported costs for 1 year of treatment with the antidepressants on the EML were £28.86 for amitriptyline 75 mg/day and £7.04 for fluoxetine 20 mg/day (25). The application reported current and recent internal prices for phenelzine as €45 (60 capsules) in Belgium, Can$ 144.95 (180 tablets) in Canada, £120 (100 tablets) in the United Kingdom and US$ 108.88 (60 tablets) in the United States. No price information was presented from low- and middle-income countries.

WHO guidelines

Phenelzine is not currently recommended in WHO Mental Health Gap Action Programme (mhGAP) guidelines for treatment of treatment-resistant depression (4).

Availability

The application reported that phenelzine is available in Australia, Belgium, Canada, the United Kingdom and the

United States. Shortages of phenelzine have been reported in many of these jurisdictions.

Other considerations

The WHO department of Mental Health and Substance Use reviewed and provided comments on the application. The technical department highlighted the following points. • Phenelzine requires careful monitoring and has a less favourable safety profile compared with other antidepressants, such as selective serotonin reuptake inhibitors and tricyclics (currently included on the EML) and newer agents. • The evidence base for phenelzine is limited as randomized controlled trials on this antidepressant are lacking because it was introduced to the market many years ago when such trials were not commonly performed. • In the context of treatment-resistant depression, phenelzine lacks evidence of efficacy. • The risk of serious treatment emergent adverse events, drug–drug interactions and overdose, as well as the need for specialized facilities and health care professionals, raise concerns about its usability in low- and middle-income countries and other settings.

1. Global Burden of Disease database [internet]. Washington, DC: Institute for Health Metrics and Evaluation; 2019 (https://vizhub.healthdata.org/gbd-results/, accessed 6 October 2023).
2. Patel V, Saxena S, Lund C, Thornicroft G, Baingana F, Bolton P, et al. The Lancet Commission on global mental he alth and sustainable development. Lancet. 2018;392(10157):1553–98.
3. Evans-Lacko S, Aguilar-Gaxiola S, Al-Hamzawi A, Alonso J, Benjet C, Bruffaerts R, et al. Socio-economic variations in the mental health treatment gap for people with anxiety, mood, and substance use disorders: results from the W HO World Mental Health (WMH) surveys. Psychol Med. 2018;48(9):1560–71.
4. Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders. T hird edition. Geneva: World Health Organization; 2023 (https://iris.who.int/handle/10665/374250, accessed 21 Nove mber 2023).
5. Trevino K, McClintock SM, McDonald Fischer N, Vora A, Husain MM. Defining treatment-resistant depression: a co mprehensive review of the literature. Ann Clin Psychiatry. 2014;26(3):222–32.
6. Cosgrove L, Naudet F, Högberg G, Shaughnessy AF, Cristea IA. Reconceptualising treatment-resistant depression as difficult-to-treat depression. Lancet Psychiatry. 2021;8(1):11–3.
7. Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a r eview of current concepts and methods. Can J Psychiatry. 2007;52(1):46–54.
8. Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient Prefer Adherence. 2012;6:369–88.
9. Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P, et al. The prevalence and national burden of treat ment-resistant depression and major depressive disorder in the United States. J Clin Psychiatry. 2021;82(2):20m136 99.
10. Hays RD, Wells KB, Sherbourne CD, Rogers W, Spritzer K. Functioning and well-being outcomes of patients with depression compared with chronic general medical illnesses. Arch Gen Psychiatry. 1995;52(1):11–9.
11. Jaffe DH, Rive B, Denee TR. The humanistic and economic burden of treatment-resistant depression in Europe: a cross-sectional study. BMC Psychiatry. 2019;19(1):247.
12. Steffen A, Nübel J, Jacobi F, Bätzing J, Holstiege J. Mental and somatic comorbidity of depression: a comprehensi ve cross-sectional analysis of 202 diagnosis groups using German nationwide ambulatory claims data. BMC Psychiat ry. 2020;20(1):142.
13. Soares B, Kanevsky G, Teng CT, Pérez-Esparza R, Bonetto GG, Lacerda ALT, et al. Prevalence and Impact of trea tment-resistant depression in Latin America: a prospective, observational study. Psychiatr Q. 2021;92(4):1797–815.
14. Suchting R, Tirumalaraju V, Gareeb R, Bockmann T, de Dios C, Aickareth J, et al. Revisiting monoamine oxidase i nhibitors for the treatment of depressive disorders: a systematic review and network meta-analysis. J Affect Disord. 2021;282:1153–60.
15. Henkel V, Mergl R, Allgaier AK, Kohnen R, Möller HJ, Hegerl U. Treatment of depression with atypical features: a meta-analytic approach. Psychiatry Res. 2006;141(1):89–101.
16. Thase ME, Trivedi MH, Rush AJ. MAOIs in the contemporary treatment of depression. Neuropsychopharmacology . 1995;12(3):185–219.
17. Kim T, Xu C, Amsterdam JD. Relative effectiveness of tricyclic antidepressant versus monoamine oxidase inhibit or monotherapy for treatment-resistant depression. J Affect Disord. 2019;250:199–203.
18. Fekadu A, Rane LJ, Wooderson SC, Markopoulou K, Poon L, Cleare AJ. Prediction of longer-term outcome of treat ment-resistant depression in tertiary care. Br J Psychiatry. 2012;201(5):369–75.
19. Van den Eynde V, Abdelmoemin WR, Abraham MM, Amsterdam JD, Anderson IM, Andrade C, et al. The prescribe r's guide to classic MAO-inhibitors (phenelzine, tranylcypromine, isocarboxazid) for treatment-resistant depression. CNS Spectrums. 2023:28(4):427–40.
20. Hirsch M, Birnbaum RJ. Monoamine oxidase inhibitors (MAOIs): pharmacology, administration, safety, and side e ffects [internet]. Alphen aan den Rijn: Wolters Kluwer; 2023 (https://www.uptodate.com/contents/monoamine-oxida se-inhibitors-maois-pharmacology-administration-safety-and-side-effects, accessed 6 October 2023).
21. Wimbiscus M, Kostenko O, Malone D. MAO inhibitors: risks, benefits, and lore. Cleve Clin J Med. 2010;77(12):859 –82.
22. Flockhart DA. Dietary restrictions and drug interactions with monoamine oxidase inhibitors: an update. J Clin Psy chiatry. 2012;73(Suppl 1):17–24.
23. Van den Eynde V, Gillman PK, Blackwell BB. The prescriber's guide to the MAOI diet – thinking through tyramine troubles. Psychopharmacol Bull. 2022;52(2):73–116.

24. Mavranezouli I, Mayo-Wilson E, Dias S, Kew K, Clark DM, Ades AE, et al. The cost effectiveness of psychological a nd pharmacological interventions for social anxiety disorder: a model-based economic analysis. PLoS One. 2015;10(10):e0140704.
25. Cost comparison charts (internet). Newcastle-upon-Tyne: Regional Drug and Therapeutics Centre; 2018 (https:// rdtc.nhs.uk/prescribing-support-document/cost-comparison-charts/, accessed 6 October 2023).