Received: 22 August 2024 | Accepted: 23 August 2024

DOI: 10.1111/acps.13753

INVITED EDITORIAL

Acta Psychiatrica Scandinavica WILEY

Monoamine oxidase inhibitors: Seriously underused in the treatment of major depression

Monoamine oxidase inhibitors (MAOIs) were the first licensed antidepressants, they were discovered serendipitously, during a trial of iproniazid in patients with tuberculosis in the 1950s. Iproniazid appeared to have a "psychic energizing effect," which resulted in the improvement of depressive symptoms in some tuberculosis patients,[1] around that time, iproniazid was shown to inhibit the MAO enzyme. Iproniazid was approved as an antidepressant, and this led to the development of several other MAOIs. Brain neurotransmitter levels are inactivated by MAO-A (serotonin, norepinephrine, dopamine) and MAO-B (dopamine) isoenzymes. Inhibition of the MAO enzyme leads to an increasing synaptic availability of these monoamines. In addition, tranylcypromine is similar in chemical structure to amphetamine and shares its dopamine-releasing and stimulant-like effects. Tranylcypromine and phenelzine are the most frequently used non-selective MAOIs, which bind the MAO enzyme irreversibly, and deactivate it permanently. Moclobemide is a selective MAO-A inhibitor, and enters into a reversible binding to the enzyme. Tranylcypromine and Phenelzine were widely prescribed until the late 1960s. The use of MAOIs has declined dramatically, as stated in their network meta-analysis by Gimenez-Palomo et al.[2] The historical perspective is important in understanding this decline.

In the 1960s it was not well understood that MAOIs inhibit the breakdown of tyramine, and that excessive tyramine intake when using an MAOI, can lead to a hypertensive crisis. A series of initially unexplained hypertensive crises actually occurred, some even resulting in stroke. The cause of this "cheese reaction" was uncovered in the late 1960s, but the fear for the hypertensive reaction remained. Furthermore, in one of the first large randomized clinical trials in psychiatry,[3] which included 260 depressed patients, both ECT and imipramine appeared to be effective, whereas phenelzine and placebo were not. In hindsight, one may well argue, that both the duration of treatment with phenelzine (4 weeks) and its dose (maximum 60 mg daily) were insufficient, therefore, phenelzine fell short of its full efficacy potential. Subsequently, MAOIs were regarded as not very effective and dangerous antidepressant drugs. This perception influenced physicians to strongly favor tricyclic antidepressants (TCAs) over MAOIs. Usage of MAOIs further declined, following the development of newer antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs). Concerns about the safety profile of MAOIs, including potentially dangerous drug–drug interactions, which could result in serotonin syndrome, and the risk of a hypertensive crisis restricted their use. Furthermore, the use of MAOIs was not promoted by any pharmaceutical company.

In several countries the number of prescriptions of MAOIs is extremely low: about 500 patients treated in a population of 16 million.[4]

A consequence of this low prescription rate is that psychiatrists in training are rarely educated about MAOIs. Residents in psychiatry may graduate from excellent training programs with hardly any knowledge about MAOIs, not knowing specific indications for treatment with MAOIs, and how to avoid safety issues with these drugs.

Education within psychiatric training usually focuses on recent literature and systematic reviews.[5] Since the large majority of studies on MAOIs are dated, they tend to be strongly underrepresented in recent literature.

Therefore, the comprehensive systematic review by Gimenez-Palomo et al.[2] is a valuable contribution emphasizing the role of MAOIs in the treatment of major depression.

The authors concluded that the antidepressant efficacy of MAOIs and other antidepressants was similar. However, as pointed out by Lee and Wei[6] in a letter to the editor in response to the systematic review, MAOIs have shown to be superior to other antidepressants in several subtypes of major depression. At Columbia University New York, a series of six studies were performed in patients with atypical depression. In patients with atypical depression, defined as major depression with preserved mood reactivity and two secondary atypical symptoms, phenelzine consequently proved to be more effective than both imipramine and placebo.[7] These six studies comprised 409 patients with an overall response rate of 26% for placebo versus 44% for imipramine versus 72% for phenelzine.

The second subtype of major depression, in which MAOIs probably are superior in efficacy is bipolar depression. In a systematic review, Heijnen et al.[8] found an overall response rate of 74% for tranylcypromine (40–60 mg) compared with 28% in control conditions in bipolar depression. Their results emphasize the statement by Thase and Sachs[9] in a previous review: "All other things equal, the MAOI tranylcypromine could be considered a treatment of first choice for bipolar depression. The track record of this drug spanning open-label, placebo-controlled, and imipramine-comparator clinical trials."

In an open study in patients with bipolar depression,[10] who already received a mood stabilizer, the antidepressant effect of tranylcypromine appeared to be superior to that of paroxetine, as demonstrated by a recovery rate of 53% on tranylcypromine versus 27% on paroxetine.

Furthermore, current evidence suggests tranylcypromine and other MAOIs may have a low risk of inducing a switch into mania.[8]

Therapeutic experience and non-controlled open studies suggest a clear therapeutic benefit from tranylcypromine in patients resistant to adequate antidepressant treatment. Unfortunately, there are only relatively few randomized controlled trials with MAOIs in patients with treatment-resistant depression (TRD), even though this is a major indication for their use.

However, a previous meta-analysis comprising a number of controlled studies, reported an overall response rate of 58% to tranylcypromine in patients with TRD.[11] Some authors consider tranylcypromine as a first choice in stage-3 TRD according to the Thase and Rush classification.[12,13]

In summary regarding the efficacy of non-selective MAOIs (especially tranylcypromine): they appear to be effective in two forms of major depression, which are notoriously difficult to treat: bipolar depression and treatment-resistant depression. MAOIs, specifically phenelzine, are also very effective in atypical depression, which may be less of a clinical challenge.

Moclobemide, a selective MAO-A inhibitor, has less side-effects than the non-selective MAOIs. Selective MAOI-A inhibitors, such as moclobemide, were developed as alternatives lacking the "cheese effect" and vigorously promoted in the late 1980s and early 1990s, with industry sponsored research, leading to substantial prescription of this drug. However, many clinicians believe that moclobemide is not as effective as nonselective MAOIs such as tranylcypromine or phenelzine. Consistent with these clinical impressions, is the result of a meta-analysis showing a clinically significant advantage for the older MAOIs compared with moclobemide.[14]

When using a non-selective, irreversible MAOI (tranylcypromine, phenelzine) it is necessary to follow a tyramine-restricted diet. Many of the traditional MAOI diets, which remain standard at numerous hospitals, are unnecessarily restrictive. Reports of food interactions with MAOIs published in the early 1960s led to the development of stringent dietary restrictions. Consumption of numerous foods, principally cheese, by patients on MAOIs was associated with potentially fatal hypertensive crises.

However, many of the foods once thought to be dangerous for patients on MAOIs are now considered to be safe. Although the clinician's initial response may be to choose the more conservative diet, an excessively stringent diet may actually be unfavorable, since psychiatrists and patients may refrain from considering a potentially effective treatment with an MAOI. Furthermore, patients may become lax with their diet after accidentally discovering that certain diet items are actually not harmful.

Numerous studies have attempted to quantify the tyramine content of food. A tyramine content of less than 6 mg per portion is generally considered safe. Concurrent administration of an MAOI with drugs increasing the availability of serotonin might lead to the serotonin syndrome. Excessive stimulation of the 5-HT1a and 5-HT2 receptors may result in symptoms of serotonin syndrome. Most cases of serotonin syndrome have been reported when an MAOI was combined with meperidine, L-tryptophan, dextromethorphan, an SSRI, or a TCA that inhibits the reuptake of serotonin (clomipramine, imipramine).[15]

Irreversible MAOIs (tranylcypromine, phenelzine) are very effective drugs in the treatment of both resistant and bipolar major depression. They can induce full remission when other antidepressants, combinations, and augmentation strategies, and even electroconvulsive therapy (ECT), have failed. Despite this, they are infrequently prescribed, in part because of substantial overestimation of their risk profile. Thus, it is essential to have MAOIs available in the psychiatrist's therapeutic arsenal and to have clinicians who are knowledgeable about their usage.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/acps.13753.

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How to cite this article: Birkenhager TK, Heijnen WT. Monoamine oxidase inhibitors: Seriously underused in the treatment of major depression. *Acta Psychiatr Scand*. 2024;1-3. doi:10.1111/acps.13753