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MAO inhibitors: Risks, benefits, and lore

ABSTRACT

Monoamine oxidase (MAO) inhibitors were the first antidepressants introduced, but their use has dwindled because of their reported side effects, their food and drug interactions, and the introduction of other classes of agents. However, interest in MAO inhibitors is reviving. Here, we discuss their use, risks, and benefits in clinical medicine.

KEY POINTS

Data from multiple studies suggest the efficacy of MAO inhibitors in the management of major depressive disorder and, in particular, major depressive disorder with atypical features and in treatment-resistant depression.

When using oral MAO inhibitors, patients must follow a low-tyramine diet to avoid the "cheese reaction," ie, tyramine-induced hypertensive crisis. However, recent studies suggest that traditional dietary advice may be unnecessarily restrictive.

The selegiline transdermal system (Emsam) is the first approved transdermal patch for treatment of major depression. Unlike oral MAO inhibitors, the patch can be used without the dietary restrictions at its lowest effective dose of 6 mg/24 hours. Because of its transdermal delivery, it has the advantage of not inhibiting the metabolism of dietary tyramine by MAO subtype A in the gut, while providing antidepressant effect in the brain. The patch may be a promising alternative to existing strategies for the management of major depressive disorder.

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Monoamine oxidase (MAO) inhibitors were the first drugs for treating depression. Introduced in the 1950s, they were used extensively for the next two decades. Their use declined substantially since then because of their reported side effects, their food and drug interactions, and the introduction of new classes of antidepressants.

This trend may be changing. These drugs can be effective in major depressive disorder, and particularly in major depressive disorder with atypical features and in treatment-resistant depression.

New, selective MAO inhibitors are being developed. Moreover, the selegiline transdermal system (Emsam),[1,2] introduced in 2006, offers the potential advantage of eliminating the need for burdensome dietary restrictions and has renewed interest in this group of drugs.

In this article, we discuss the history, pharmacology, safety and tolerability of MAO inhibitors, and we summarize recent MAO inhibitor research. Our goal is to familiarize physicians with this class of drugs, including recent updates regarding their safety profile and liberalized dietary recommendations.

DEPRESSION IS COMMON, DIFFICULT

Depression affects 121 million people worldwide.[3] According to a study that compared two surveys of 40,000 people each, the prevalence of major depressive disorder in the United States more than doubled (from 3.3% to 7.0%) from 1992 to 2002.[4] Another survey, in 2002 and 2003, revealed the lifetime prevalence of major depressive disorder to be 16.6%.[5]

Treatments for depression have expanded over the past 20 years, with new classes of drugs

How much cheese is too much?

How much aged cheddar cheese would a person have to eat to experience a pressor response, ie, an increase of more than 30 mm Hg in blood pressure above baseline?

- For an average person not on any medication: 2 pounds (800 g) within 30 minutes
- For a person on tranylcypromine (Parnate), a nonselective irreversible MAO inhibitor): about 0.10 pound (approximately 50 g)[10]
- For a person using the selegiline 6-mg/day transdermal patch: almost 2 pounds.

However, in an all-you-can-eat study, the average quantity of cheese consumed was 1.9 pounds over 2 hours. No one was able to consume 2 pounds in 30 minutes.[1]

such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). However, depression has remained a difficult condition to treat. In the National Institute of Mental Health's Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[6] the remission rate in patients treated with the SSRI citalopram (Celexa) for up to 14 weeks was 28% using one measure and 33% using another. Diversifying and understanding existing and emerging therapeutic options is important to the effective treatment of this disease.

Currently, MAO inhibitors are typically third- or fourth-line drugs, and even psychiatrists have little experience with them

THE RISE AND FALL OF MAO INHIBITORS

The first antidepressant introduced was an MAO inhibitor, iproniazid, followed shortly thereafter by a tricyclic antidepressant, imipramine (Tofranil). When iproniazid, originally an antituberculosis agent, was promoted for its antidepressant properties in the 1950s, very little was known about its side effects. It was later removed from the market because of hepatotoxicity, but several other MAO inhibitors had surfaced for the treatment of depression—eg, phenelzine (Nardil), isocarboxazid (Marplan), and tranylcypromine (Parnate).

Currently, MAO inhibitors are typically reserved for third- or fourth-line treatment. As a result, even psychiatrists have little experience with these agents. In a 1999 survey of the Michigan Psychiatric Association,[7] 12% of practicing psychiatrists said they had never prescribed an MAO inhibitor, another 27% had not prescribed one in the prior 3 years, and only 2% said they prescribed them frequently. A decade earlier, about 25% had said they prescribed them often.[8]

The prescription rate of MAO inhibitors has remained low during the past 10 years. In a Canadian population-based study[9] conducted among older adults in a large health care database from January 1997 to April 2007, the yearly incidence of MAO inhibitor prescriptions decreased from a rate of 3.1 per 100,000 to 1.4 per 100,000. Drug interactions, side effects, preference for other treatments, and dietary restrictions were the reasons most often cited for not prescribing these drugs.[7]

The side effects of MAO inhibitors were recognized by the mid-1960s, when more than 40 cases of tyramine-induced hypertensive crisis were reported (particularly with tranylcypromine).[10,11] Many of the reported events happened after the patient ate tyramine-rich foods such as aged cheese (hence, "the cheese reaction"—more on this below) or drank draft beer.[10,11] The US Food and Drug Administration (FDA) consequently established dietary restrictions for patients taking MAO inhibitors, but people found the guidelines cumbersome and often switched to newer drugs that did not require a restrictive diet, such as tricyclics and, much later (in the 1980s), SSRIs.

MAO HAS TWO SUBTYPES

MAO is a flavin-containing enzyme critical for regulating neurotransmitter levels by catabolizing endogenous monoamines (eg, norepinephrine, serotonin, and dopamine) and exogenous amines (eg, dietary tyramine). It is found throughout the body but is more highly

concentrated in the liver, kidneys, intestinal wall, and brain.

MAO has two subtypes, isoenzyme A (MAO-A) and isoenzyme B (MAO-B), which vary in their distribution. MAO-A is found primarily in the intestinal tract, liver, and peripheral adrenergic neurons (adrenal glands, arterial vessels, and sympathetic nerves) and preferentially metabolizes serotonin and norepinephrine. MAO-B is found mostly in the brain and liver. However, both isotypes are found in all of the areas mentioned. Since 80% of intestinal MAO is MAO-A, this isoenzyme is primarily responsible for degradation of tyramine, and thus inhibition of MAO-A is associated with the cheese reaction.[10,11]

TYPES OF MAO INHIBITORS

MAO inhibitors can be classified on the basis of whether they are nonselective or selective for either MAO-A or MAO-B, and whether their effect is reversible.

Nonselective MAO inhibitors are phenelzine, isocarboxazid, and tranylcypromine.

Selective MAO inhibitors. Selegiline is selective for MAO-B. Clorgyline is selective for MAO-A, but it is not available in the United States.

A reversible MAO inhibitor is moclobemide (not available in the United States).

Do selectivity and reversibility matter?

Classic MAO inhibitors such as tranylcypromine and phenelzine are neither reversible (binding to the enzyme for the extent of its lifetime of 14–28 days) nor selective for the subtypes. These drugs were used extensively several decades ago to treat atypical depression, anxiety, and phobias. The only selective MAO inhibitor now available in the United States is selegiline, which inhibits MAO-B at low doses but loses its selectivity at dosages greater than 20 mg/day.

Experimental studies suggest that inhibition of more than 70% of MAO-A activity is necessary for the antidepressant effect of selegiline.[12] At oral doses that selectively inhibit MAO-B (5–10 mg/day), selegiline does not seem to have potent antidepressant activity, although it does show success as an adjunctive treatment for Parkinson disease and does not necessitate any dietary restriction. Only at higher oral doses (20–60 mg/day), at which MAO-B selectivity is lost, is the antidepressant effect seen. But the higher doses necessitate dietary restrictions. Therefore, patients who are taking the oral selective MAO inhibitor selegiline have to follow the same dietary restrictions as patients taking the nonselective ones.

Reversible inhibitors of MAO-A have the distinction of being easily displaced by ingested tyramine in the gut and thus do not cause the cheese reaction. However, the only reversible agent available in the world market is moclobemide. It is not available in the United States, and appears to be less effective than older, nonselective MAO inhibitors.[13]

SELEGILINE TRANSDERMAL SYSTEM

The selegiline transdermal system (Emsam) is the first FDA-approved transdermal patch for treatment of major depression. Patients who are using Emsam at its lowest effective dose of 6 mg/24 hours do not need to follow the dietary restrictions that are needed for all oral MAO inhibitors.

Patients on MAO inhibitors should wear a medical alert bracelet

Pharmacokinetics of the selegiline patch

With the transdermal patch, selegiline is extensively absorbed through the skin. Plasma levels are maintained over a 24-hour period, allowing once-daily application. Patches are available that deliver 6, 9, or 12 mg per 24 hours. Steady-state plasma levels are reached after about 5 days.

The bioavailability of selegiline is about 75% with the transdermal delivery system vs 4.4% after oral administration, the lower number being due to first-pass metabolism.[1] About 90% of selegiline is bound to plasma proteins and quickly penetrates the central nervous system.

This drug is metabolized by cytochrome P450 isoenzymes, including CYP2C9, CYP2B6, and CYP3A4. Its metabolites are L-methamphetamine and N-desmethylselegiline.

Clinical research showed that dosage adjustments were not necessary in specific populations studied, including patients with various stages of renal or hepatic failure.[1] Clearance of selegiline was independent of dose, age, sex,

renal function, body weight, or concomitant medications.[1]

Advantages of the patch system

Since selegiline delivered via the patch is not absorbed through the gut, it has little effect on gut MAO-A and therefore is unlikely to lead to tyramine-induced hypertensive crisis. Studies of the selegiline patch show that inhibition of more than 80% of gut MAO-A is necessary to impair metabolism of tyramine in the gut.[1] Therefore, the 6-mg patch will not significantly impair tyramine degradation in the gut. In phase III testing of the selegiline patch, no hypertensive crises were reported among 2,656 outpatients without dietary restrictions. However, it is still recommended that patients on the 9-mg and 12-mg patches follow a tyramine-free diet.[1]

Although there are no data available to suggest that higher dosages are more effective, it is recommended that the dose be titrated in 3-mg increments at intervals of at least 2 weeks until the maximum recommended dosage of 12 mg/24 hours is reached.[2]

Disadvantage of the selegiline patch: Cost

The selegiline patch is expensive: $692.99 for 1 month's supply at a dose of 6 mg/24 hours and $638.99 for 1 month's supply at a dose of 9 or 12 mg/24 hours (verified with a national pharmacy chain at the time of this writing). Insurance coverage for the patch varies, and documentation may be required from the physician. Oral MAO inhibitors are much less expensive.

SAFETY, TOLERABILITY OF MAO INHIBITORS

Side effects of oral agents

Orthostatic hypotension, dizziness, drowsiness, insomnia, and nausea are the most frequently reported side effects of oral MAO inhibitors.[14,15] These side effects can generally be managed symptomatically by slowing the titration, dividing the doses, changing the time it is taken, or, in the case of orthostatic hypotension, increasing fluid intake.[14] Phenelzine has the strongest association with sedation.[14]

Weight gain, edema, muscle pain, myoclonus, paresthesias, sexual dysfunction, and, rarely, hepatotoxicity are late side effects.[15–18] Paresthesias, an infrequent side effect, are often treated with pyridoxine supplementation.[15]

Transient hypertensive episodes within 2 hours after ingestion of MAO inhibitors, which were independent of dietary or drug interactions, have been reported.[19] The hypertensive episodes are usually self-limited but in rare cases result in hypertensive crisis.[19–21]

Serotonin syndrome has been reported with MAO inhibitor monotherapy in rare cases.[22] Serotonin syndrome is characterized by mental status changes, restlessness, myoclonus, hyperreflexia, diaphoresis, or evidence of autonomic hyperactivity.[23] The syndrome is potentially fatal and is treated symptomatically by removing the offending drugs and giving intravenous rehydration.[23]

Side effects of the selegiline patch

The most common adverse events with the selegiline patch include application-site reaction (24% vs 12% with placebo), headache (18% vs 17%), insomnia, diarrhea, dry mouth, and dyspepsia.[24,25] Dose-related orthostatic hypotension was reported (occurring in 9.8% vs 6.7% with placebo) and was most likely to occur in elderly patients.[25] It is suggested that insomnia may be lessened by removing the patch before bedtime. Also, rotating the patch application sites and prompt topical treatment of irritation may lessen local effects.[24]

In an all-you-can-eat study, no one was able to consume 2 pounds of cheese in 30 minutes

Observe a washout period when switching between serotonergic drugs

Most MAO inhibitors irreversibly inhibit MAO for the life of the enzyme, and thus the physiologic effects of phenelzine, isocarboxazid, and tranylcypromine last for up to 2 to 3 weeks.[26] Although the elimination half-life of typical MAO inhibitors is short (1.5–4 hours),[27,28] their physiologic effects are long-lasting.[14]

Switching from a MAO inhibitor to another serotonergic agent. Concomitant use of MAO inhibitors and other serotonergic drugs is associated with the risk of serotonin syndrome. After stopping an MAO inhibitor, a 14-day washout period is recommended before starting another serotonergic agent.[29] Patients should continue to be monitored closely after the washout period, as cases of serotonin syndrome have been reported later.[30] A 14-day

TABLE 1

Monoamine oxidase (MAO) inhibitors: Contraindications and concerns

Foods to avoid
Aged cheeses and meats
Banana peels
Concentrated yeast extracts (Marmite)
Draft beer (including alcohol-free beer)
Fava beans, broad bean pods
Improperly stored meat, fish, or poultry
Sauerkraut, kimchee
Soybean products
Tyramine-containing nutritional supplements
Wine (not to exceed two drinks a day)

Drugs to avoid
Amphetamines
Bupropion (Wellbutrin)
Cyclobenzaprine (Flexeril)
Dextromethorphan (contained in many cough-and-cold remedies)
Linezolid (Zyvox)
Meperidine (Demerol)
Methadone
Mirtazapine (Remeron)
Other MAO inhibitors
Pentazocine (Talwin)
Propoxyphene (Darvon)
Selective serotonin reuptake inhibitors
Serotonin-norepinephrine reuptake inhibitors
Noncutaneous sumatriptans
Tricyclic antidepressants
Tramadol (Ultram)
St. John's wort
Weight-reducing preparations that contain vasoconstrictors (eg, pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine)

Electroconvulsive therapy, elective surgery
Avoid because of anesthesia

Local anesthesia
Avoid because of sympathomimetic vasoconstrictors

Pheochromocytoma
People with this condition should avoid MAO inhibitors due to risk of hypertensive crisis

Caution with pregnancy
Category C; no data available regarding lactation

washout period is also recommended when switching between MAO inhibitors, although more rapid switches have been made safely.[31]

Switching from another serotonergic agent to an oral MAO inhibitor. Similarly, a 14-day washout period (or five half-lives) is necessary after stopping most of the serotonergic agents mentioned above before beginning treatment with an oral MAO inhibitor. Fluoxetine (Prozac) has a longer half-life and therefore requires a longer washout period, ie, 5 weeks.

Switching from another serotonergic agent to the selegiline patch. When switching to the selegiline patch from another serotonergic drug, the washout period is 1 week after stopping most drugs or 5 weeks after stopping fluoxetine. One must wait 2 weeks after stopping the selegiline patch before starting therapy with any of the other serotonergic drugs.

Drugs to avoid due to interactions

In view of the risk of severe of drug-drug interactions, particularly the risk of serotonin syndrome, the following serotonin-enhancing compounds are contraindicated in patients taking a MAO inhibitor: SSRIs, SNRIs, tricyclic antidepressants, other MAO inhibitors, mirtazapine, and St. John's wort. Other pharmaceuticals to be avoided include bupropion, meperidine, tramadol, methadone, propoxyphene, pentazocine, dextromethorphan, and cyclobenzaprine (TABLE 1). Also, there have been numerous reports of serotonin syndrome with the use of the broad-spectrum, MAO-based antibiotic linezolid (Zyvox), by itself or in conjunction with other serotonergic agents.[32–35]

Several studies suggested a hazardous combination of nonsubcutaneous sumatriptans (5-HT1B/1D agonists) and MAO-B inhibitors, while subcutaneous sumatriptan migraine-abortive treatment and MAO-B inhibitors appear to be safe.[36,37]

Also, amphetamines, cough-and-cold preparations, and weight-reducing preparations that contain vasoconstrictors (eg, pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine) should be avoided, as the risk of hypertensive crisis increases with these products.

Patients on MAO inhibitors should wear a medical alert bracelet in case they need to undergo emergency surgery and are unable to verbally communicate their drug history. They should be instructed to alert all health care providers about their MAO inhibitor use.[14]

Beware of worsening depression

Physicians, patients, and family members should be advised to observe for worsening depression or "suicidality" during the course of treatment with MAO inhibitors, as with all antidepressants.

Diet can be more lenient than in the past

The dietary restrictions classically advised for patients taking oral MAO inhibitors were established to prevent hypertensive crises associated with tyramine ingestion. However, some of these restrictions were unsubstantiated,[38] and evidence from more recent studies suggests that they are unnecessarily strict[39] and may lead to resistance by the physician, the patient, or both to using this potentially beneficial therapy.[14] There is also a risk that patients will inadvertently discover that a food that was in the "restricted" list caused them no harm upon ingestion and thus will become cavalier about dietary adherence.[39]

To prevent dietary noncompliance, physicians should conduct ongoing diet surveys and encourage adherence to evidence-based dietary recommendations.[40]

The FDA and drug-package inserts for oral MAO inhibitors continue to recommend stringent dietary restrictions, including no aged cheeses or meats, soy sauce, soy beans, soy paste, miso soup, Italian green beans (fava beans), snow peas, broad bean pods, sauerkraut, kimchee, concentrated yeast extracts (Marmite), wine, beer (including alcohol-free beer), and many other foods. However, several studies have measured the tyramine content of food and determined that less than 6 mg per serving is generally safe.[39,41] The results of these investigations have led to more lenient dietary guidelines.[39]

Absolute dietary restrictions include[39]:

- Aged cheeses and meats
- Banana peels
- Broad bean (fava) pods
- Spoiled meats
- Marmite
- Sauerkraut
- Soybean products
- Draft beers.

Among the many foods determined to be unnecessarily restricted are avocados; bananas; beef or chicken bouillon; chocolate; fresh and mild cheeses, eg, ricotta, cottage cheese, cream cheese, processed cheese slices; fresh meat, poultry, or fish; meat gravy (fresh); monosodium glutamate; peanuts; properly stored pickled or smoked fish (eg, herring); raspberries; and yeast extracts (except Marmite).[39]

Dietary restrictions should continue for 2 weeks after stopping an MAO inhibitor.

Dietary restrictions for the selegiline patch

Tyramine-containing foods pose less risk with the selegiline patch than with oral MAO inhibitors, and studies[42] show that the 6-mg patch does not necessitate dietary restrictions. The accumulating data suggest that the risk of a tyramine-induced event is extremely low with the patch even in doses above 6 mg. But in the meantime, the recommendations for the 9-mg and 12-mg patches remain the same as for the classic oral MAO inhibitors, and tyramine-containing food should be restricted.

EFFICACY OF MAO INHIBITORS IN CLINICAL PRACTICE

Data from numerous studies suggest MAO inhibitors are effective in managing major depressive disorder, and specifically atypical depression,[43–48] treatment-resistant major depressive disorder,[49,50] and bipolar depression.[51,52] Guidelines from the American Psychiatric Association and the British Association for Psychopharmacology suggest that MAO inhibitors be recommended for treatment of major depressive disorder in patients with atypical features and when other antidepressants have failed.[53]

The use of MAO inhibitors for atypical and treatment-resistant depression is supported by a number of studies

MAO inhibitors have also been used in the treatment of Parkinson disease, bulimia, anxiety disorders, anorexia nervosa, and body dysmorphic disorder.[54]

Major depressive disorder

In controlled trials in outpatients with depression who were treated with therapeutic doses of MAO inhibitors, the response rate was 50% to 70%.[55] When tranylcypromine was used in severely depressed inpatients, its efficacy was comparable to that of electroconvulsive therapy, imipramine, and amitriptyline.[56] Thase et al,[57] in a meta-analysis, found that the MAO inhibitors tranylcypromine, phenelzine, and isocarboxazid were equally effective in treating depression.

Atypical depression

Atypical depression is one of the most common subtypes of major depressive disorder. Diagnostic criteria for major depressive disorder with atypical features include mood reactivity and two of the following: weight gain or hyperphagia, hypersomnolence, leaden paralysis, or an enduring pattern of rejection sensitivity.[58] An estimated 30% of outpatients with unipolar depression meet these criteria.[59]

Multiple randomized controlled trials showed that MAO inhibitors were superior to tricyclic antidepressants in treating atypical depression. One study, involving more than 400 patients, determined that atypical depression responded better to phenelzine than to imipramine.[43] Another study evaluating 153 critically depressed patients showed significantly greater response with phenelzine than with imipramine or placebo.[49] Furthermore, in another double-blind controlled crossover study, 89 mood-reactive, nonmelancholic, chronically depressed outpatients were found to have a striking response to phenelzine after being unresponsive to imipramine.[50] Another report[48] indicated that in a double-blind, randomized, placebo-controlled trial among 119 patients with atypical depression treated for 6 weeks, the overall response rates were 78% with phenelzine, 50% with imipramine, and 28% with placebo.

A recent meta-analysis of treatment trials in atypical depression revealed a large mean effect size of 0.45 for the superiority of MAO inhibitors over placebo and a medium mean effect size of 0.27 for the superiority of MAO inhibitors over tricyclic antidepressants.[60] Additionally, in a randomized, double-blind placebo-controlled trial, patients with comorbid atypical depression and bulimia showed significant improvement in both bulimic and depressive symptoms when given phenelzine vs imipramine or placebo.[61]

The current data comparing SSRIs and MAO inhibitors in the treatment of atypical depression are limited. The above-mentioned meta-analysis of three such trials (when moclobemide was used in two out of three trials) revealed no significant difference in efficacy.[60] However, the authors themselves warned about the limitations of the studies, including low power to detect differences. Parker and Crawford[59] compared self-rating of effectiveness of the various previous treatments in patients with depression with and without atypical features using an online survey. The analysis of the responses of 1,934 patients showed no overall difference in treatment response to both drug and nondrug therapies between respondents with and without atypical features, except with SSRIs. The "atypical" group had a significantly lower mean effectiveness score for SSRIs overall, and a lower mean effectiveness rating for two of six SSRIs examined. The authors speculated that even though there was no differential outcome detected in individuals with atypical depression treated with MAO inhibitors, this negative finding may simply have reflected the low prevalence of sample respondents who received MAO inhibitors (which was 4% in the "atypical depression" group of 338).[59]

Treatment-resistant depression

The ultimate goal in treating major depressive disorder is to achieve complete remission. If complete remission is not achieved, the risk of relapse is high,[62,63] as is the risk of more severe future depressive episodes[63] and death from any cause.[64] Therefore, the ability of clinicians to make appropriate and evidence-based changes in treatment strategy is of high importance.

The use of MAO inhibitors as a third-line or fourth-line choice for treatment-resistant depression is supported by a number of studies.[49,50,65–67] MAO inhibitors appear to be especially effective in the subgroup of patients who have treatment-resistant depression with atypical or anergic bipolar features.

The selegiline patch, when used at a dosage of 6 mg/24 hours, is the only MAO inhibitor in the US that requires no diet restrictions

Bipolar depression

Anergic bipolar depression is defined as a condition associated with fatigue, psychomotor retardation, and at least one reversed neurovegetative symptom in a patient with bipolar disorder meeting the criteria for a major depressive episode. According to several trials,[51,52,68] MAO inhibitors may be more effective than a tricyclic antidepressant in the treatment of anergic bipolar depression. However, more studies are required to determine the role of antidepressants in general and MAO inhibitors in particular in the management of bipolar depression.

Efficacy of the selegiline patch

The efficacy of the selegiline patch in the treatment of depression was examined in four double-blind placebo-controlled studies.[69–72] There were three short-term studies (a 6-week study of 177 patients,[69] an 8-week study of 265 patients,[72] and an 8-week study of 289 patients[70]) and a fixed-dose 1-year relapse prevention study of 322 patients.[71] The inclusion criterion for the short-term studies was diagnosis of a first or a recurrent episode of major depressive disorder in patients with a Hamilton Depression Rating Scale (HDRS) score higher than 20. The HDRS score was used to assess improvement in depressive symptoms. In all studies, patients on active patch had significant improvement in depressive symptoms on the HDRS compared with placebo. In the relapse prevention study,[71] patients with major depressive disorder that responded to transdermal selegiline 6 mg within the first 10 weeks were stratified either to continue receiving the selegiline 6-mg patch or to receive placebo. Those continually receiving selegiline experienced a significantly longer time to relapse. At 12 months, the relapse rate was 16.8% with the selegiline patch vs 30.7% with placebo. The patch was reported to be well tolerated, with the most common side effect being application site reaction. The adherence to the treatment was high—84.2% in the active-patch group and 89.6% in the placebo group.[71]

DO MAO INHIBITORS HAVE A PLACE IN PRIMARY CARE?

MAO inhibitors have secured their place in the history of psychiatry as the first antidepressants. Overall, MAO inhibitors remain underused. However, with the introduction of new and selective MAO inhibitors including the selegiline patch, and with data suggesting efficacy in the management of certain subtypes of depression, we expect that interest in this class of drugs will grow among psychiatrists. Based on the current guidelines for MAO inhibitors to be used as a third- or fourth-line treatment, as well as on research data, it is premature to recommend their more extensive use in a primary care setting. Whether this will change in the future depends on both the research advances and new, safer formulations of MAO inhibitors.

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