Revisiting Monoamine Oxidase Inhibitors

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Monoamine oxidase inhibitors (MAOIs) were among the first class of agents introduced for the treatment of depression. However, they have fallen out of favor among clinicians over the years, due mostly to an unfavorable safety profile, the need for restrictive dietary prohibitions, and the fear of hypertensive crisis. The development of a novel, transdermal MAOI system now offers clinicians an additional option for managing patients with unipolar, bipolar, atypical, and treatment-resistant depression.

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Monoamine oxidase inhibitors (MAOIs) were discovered serendipitously and subsequently became one of the first classes of agents to be introduced for the treatment of depression. Iproniazid, an early MAOI, was originally synthesized in 1951 as an analog of isoniazid, an antitubercular agent. When iproniazid was given as chronic treatment for tuberculosis, patients were noted to exhibit elevated mood.[1] Subsequent clinical trials have corroborated the efficacy of iproniazid as an antidepressant.[2–4] Alongside the clinical evidence for iproniazid as an antidepressant, research data began to elucidate a probable monoamine mechanism of action; iproniazid appeared to produce a rapid and marked increase in brain levels of both serotonin and norepinephrine, presumably due to inhibition of monoamine oxidase. Unfortunately, iproniazid was found to be profoundly hepatotoxic, likely due to isopropylhydrazine, an intermediary metabolite.[5] The clinical usefulness of iproniazid and similar compounds was also severely limited by the "cheese reaction"—elevated blood pressure caused by the inhibition of tyramine deamination in the gut of patients treated with these agents. Despite initial widespread use of iproniazid and other early MAOIs for the treatment of depression, reports of toxicities and acute hypertensive reactions led to a dampening of enthusiasm for actively prescribing MAOIs even though psychiatrists still had confidence in their therapeutic effectiveness.[6] With the continuing increase in the number of available antidepressants, the use of MAOIs relative to other antidepressants declined.[7] Further decline in use was influenced by the 1965 Medical Research Trial, which demonstrated no difference from placebo in patients suitable for electroconvulsive therapy (ECT).[8]

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MECHANISM OF ACTION

The primary role of MAOIs is to inhibit the enzyme monoamine oxidase (MAO). Monoamine oxidase is a mitochondrial enzyme found in the brain and other tissues, such as the gut and liver. It is a flavin-adenosine-dinucleotide (FAD)–containing enzyme that converts biogenic amines to their corresponding aldehydes; subsequently, the aldehyde intermediary is metabolized to the corresponding acid, or in some circumstances, to the alcohol or glycol.[9] In the neuron, MAO functions as a "safety valve" to oxidatively deaminate and inactivate any excess neurotransmitter molecules (norepinephrine, dopamine, and serotonin). The MAOIs inactivate the enzyme, reducing degradation of monoamines and leading to the accumulation of monoamines. This may be responsible for the antidepressant action of these drugs. The classical MAOIs, including the approved MAOIs, form stable complexes with the enzyme, causing irreversible inactivation. The mechanism of action of antidepressants, including the MAOIs, was originally thought to be the result of increased monoamines (serotonin and norepinephrine) at nerve terminals. However, while these increases typically occur within hours after treatment is initiated, the treatment effects are not seen for weeks. More recent hypotheses have focused on receptor-mediated presynaptic and postsynaptic events.[10,11]

Johnston was among the first to observe that MAO enzymes exist as 2 different isomers, MAO-A and MAO-B, which differ on the basis of their substrate affinities and inhibitor sensitivities[6,9,12] (Table 1). MAO-A occurs primarily in the brain and the intestine; in the brain, the primary substrates are epinephrine, norepinephrine, dopamine, and serotonin. Other amines, such as tyramine—a precursor to dopamine—are also catabolized by MAO-A after being absorbed from the gastrointestinal tract or after being generated as the result of bacterial metabolic transformations.[8]

Table 1. Inhibitor Selectivity and Substrate Specificity for MAO-A/MAO-B[a]

Inhibitors	Substrates
MAO-A selective	MAO-A preferred
Clorgiline	Serotonin
Moclobemide	Norepinephrine
MAO-B selective	MAO-B preferred
Selegiline	Phenylethylamine
Nonselective	Histamine
Phenelzine	Common
Tranylcypromine	Dopamine
	Tyramine

[a]Data from Robinson[6] and Holschneider and Shih.[9]
Abbreviation: MAO = monoamine oxidase.

MAO-B is found in the brain, platelets, and other tissues, and its preferred substrates are β-phenylethylamine, dopamine, and tyramine. MAO-B accounts for about 80% of total MAO activity in human basal ganglia. MAO-A is present within the dopaminergic, serotonergic, and noradrenergic nerve terminals. Within the human brain, MAO-A is located in regions with a high density of catecholaminergic neurons and is colocalized with dopamine-β-hydroxylase, the enzyme that converts dopamine to norepinephrine.[13] Inhibition of MAO-A is thought to be the action most directly linked with the antidepressant activity of the MAOIs. However, inhibition of MAO-A also induces tyramine inhibition, with the resultant adverse effects.

While it appears that inhibition of MAO-A activity is required for an antidepressant effect, activity on platelets can be used to assess response for nonspecific MAOIs such as phenelzine. Studies of phenelzine have reported that maximal platelet MAO inhibition occurs within 2 to 4 weeks of starting treatment.[14] Both MAO inhibition and treatment response are dose-dependent, with the best responses in patients who show greater than 80% inhibition. MAO-B activity in platelets correlates poorly with MAO-B and MAO-A activities in cerebral cortex,[15] suggesting that inhibition of MAO in platelets may simply reflect drug absorption or drug compliance. Successful inhibition by itself does not guarantee successful treatment of depression; the best predictors of response remain dose and duration of treatment.

There are currently 5 U.S. Food and Drug Administration (FDA)–approved MAOIs: tranylcypromine, phenelzine, isocarboxazid, selegiline, and selegiline transdermal system. Tranylcypromine, phenelzine, and isocarboxazid are nonselective MAOIs approved for the treatment of refractory depression; selegiline is a selective MAO-B inhibitor that is approved at low doses (10 mg/day) orally for the treatment of Parkinson's disease. Oral doses of 30 to 60 mg/day exhibit antidepressant activity; however, these higher doses of selegiline result in MAO inhibition in the intestinal mucosa and liver. This makes the oral form of the drug similar to the nonselect MAOI at the dose at which antidepressant efficacy is seen. Selegiline transdermal system is approved for the treatment of major depressive disorder (MDD) in adults as an alternative delivery system, which bypasses the gut and the liver while preserving the central nervous system (CNS) effects.[16,17]

Because of the difficulties in balancing inhibition of MAO-A and MAO-B, development of the "perfect" MAOI has been problematic. When selegiline, an oral selective irreversible MAO-B inhibitor, was used at its selective MAO-B dose, the cheese reaction was minimized, but the agent showed no antidepressant action. At higher doses that inhibited MAO-A and initiated an antidepressant response, the drug was similar to other nonselective MAOIs.[18,19] The MAOIs phenelzine, isocarboxazid, and tranylcypromine are considered "irreversible," binding the drug to the MAO enzyme essentially for the "lifetime" of the molecule, so that even a high concentration of substrate cannot displace the inhibition.[20] A minimum period of 7 to 10 days is needed to adequately "wash out" the MAO inhibition caused by the irreversible MAOIs, i.e., for the enzyme to be regenerated.[21] Because the enzyme is inhibited irreversibly, the body must regenerate MAO to resume previous levels of enzymatic activity. Plasma levels of MAOI may not be correlated with the degree of MAO inhibition.[22] However, clinical effects that are dependent on plasma levels—such as orthostasis—may reverse within hours to a few days of drug discontinuation.[23]

In an effort to compensate for these drawbacks, several selective and reversible inhibitors of MAO-A (RIMAs) have been developed. RIMAs can be displaced by tyramine from the active site of the enzyme MAO-B, thereby enabling the amine to be metabolized by it. Tyramine is not present in high concentrations in the brain and therefore does not displace the inhibitor from its active site on the enzyme; brain MAO-A will continue to be inhibited, norepinephrine and serotonin levels will be increased, and an antidepressant effect will be achieved.[24,25]

Moclobemide is the most widely studied RIMA and is approved as an antidepressant in Europe but not in the United States. Moclobemide appears to possess some safety advantages due to its diminished sensitivity to the pressor effects of tyramine.[6] Moclobemide treatment is seldom associated with hypertensive crises, even with tyramine ingestion.[26] Brofaromine was first synthesized in the early 1980s, and its potential as an antidepressant was rapidly appreciated. The main pharmacodynamic difference between brofaromine and moclobemide is that the former is also a modest inhibitor of serotonin reuptake, with about 20% of the potency of fluoxetine.[9,20,27] This additional pharmacodynamic effect could, theoretically, enhance therapeutic potency, although it could also convey an increased risk of serotonin syndrome. There are insufficient data concerning either this potential beneficial effect or its risk, and the reversibility of MAO inhibition does provide some degree of protection against development of serotonin syndrome.[28] Recent trials show the RIMAs to be effective in the treatment of patients with endogenous depression.[29,30] Moclobemide has demonstrated efficacy equal to amitriptyline, imipramine, clomipramine, and fluvoxamine.[31,32] Long-term

studies have shown that moclobemide maintains its antidepressant activity for 6 to 12 months and that when given alone or in combination with another antidepressant is effective in elderly patients and in patients with refractory, severe depression.[33–35]

SAFETY AND SIDE EFFECTS

All nonselective MAOIs have some capacity to reduce blood pressure, likely due to enhancement of the central α-adrenergic agonist effects of norepinephrine.[36] As a result, orthostatic hypotension is a common side effect of the irreversible MAOIs and, in particular, of phenelzine. The development of symptoms is gradual and appears generally after 2–3 weeks of treatment. The level of orthostatic hypotension correlates with peak plasma levels of MAOI and can typically be managed with slow titration, divided dosing, or increased fluid intake.[37]

MAOIs fell out of use as first-line antidepressants after many reports of acute episodes of throbbing headache with marked hypertension, sometimes accompanied by intracerebral hemorrhage.[38,39] These events often occurred following ingestion of fermented or dried foods, as well as cheese. Cheese has a high concentration of tyramine, a well-known vasodepressor. Excess tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in headache, tachycardia, nausea, hypertension, cardiac arrhythmias, and stroke. Ordinarily, tyramine is inactivated in the intestine and liver by MAO. However, oral ingestion of MAOIs results in MAO inhibition in the intestinal mucosa and the liver, leading large amounts of tyramine to reach the bloodstream. This causes elevated tyramine levels and the subsequent hypertensive episodes.[40] Prior to the recognition of need for dietary restrictions in patients who were treated with MAOIs, rates of hypertensive reactions were estimated to range from 2.4% to 25%.[41] Serious complications such as stroke or death occurred in as many as 25% of affected patients.[42]

Another potential, but rare, complication of MAOI therapy is the development of serotonin syndrome, which can be precipitated by concomitant administration of opioids or selective serotonin reuptake inhibitors (SSRIs).[43] The serotonin syndrome is characterized by a constellation of at least 3 symptoms that occur after the recent addition or increase in dosage of a serotonergic agent: changes in mental status, agitation, myoclonus, hyperreflexia, fever, shivering, diaphoresis, ataxia, and diarrhea.[44] MAOIs should not be prescribed with tricyclic antidepressants (TCAs), SSRIs, trazodone, nefazodone, venlafaxine, or narcotics.

Insomnia is another common side effect, especially with tranylcypromine, and efforts should be made to determine whether the insomnia is the result of the MAOI or the depression itself. MAOIs should not be used in combination with dextromethorphan or with CNS depressants. Meperidine given in conjunction with MAOIs may precipitate tachycardia, hyperactivity, hypertension, hyperpyretic crisis, and severe seizures. Patients on treatment with MAOIs should not undergo elective surgery requiring general anesthesia and should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. MAOIs are contraindicated in patients receiving guanethidine. MAOIs are also contraindicated in patients with pheochromocytoma, congestive heart failure, a history of liver disease, or abnormal liver function. Over-the-counter cold and weight-loss products should also be avoided.[45]

ROLE OF MAOIs IN CLINICAL MEDICINE

MAOIs and Depression

Controlled trials of outpatients with depression who received therapeutic doses of MAOIs demonstrated a response rate of 50% to 70%, an efficacy rate similar to that of TCAs.[11,46,47] In the treatment of severely depressed inpatients, evidence to date supports tranylcypromine, with an efficacy comparable to ECT, imipramine, and amitriptyline.[48] Phenelzine appears efficacious as well, providing it is given at adequate doses. In a meta-analysis of MAOIs in depression, Thase and colleagues[21] report that tranylcypromine, phenelzine, and isocarboxazid appear to be equally effective in treating depression. When compared to placebo in outpatients, isocarboxazid had a larger relative advantage compared to either phenelzine or tranylcypromine in the doses studied; large intragroup variabilities in response rendered these differences nonsignificant. For inpatients, phenelzine was somewhat more effective than placebo, whereas the isocarboxazid-placebo difference was smaller. Thus, the evidence for efficacy in relation to placebo for the treatment of hospitalized patients is not as robust as for TCAs.[18] In patients previously refractory to TCAs, treatment responses of approximately 50% have been reported with MAOI therapy.[49,50]

Using a multiple dose-response design, Robinson et al.[51] found that both phenelzine 45 mg/day and 60 mg/day were efficacious in preventing relapse, with a trend toward favoring the higher dose. Georgotas et al.[52] observed 51 elderly depressed outpatients who had responded to antidepressants and completed continuation therapy under double-blind conditions for 1 year. Twenty-three had been switched to placebo, while 13 and 15 took nortriptyline and phenelzine, respectively. Patients administered phenelzine did significantly better (13.3% recurrences) than patients administered either nortriptyline (53.8% recurrences) or placebo (65.2% recurrences). In addition, patients who had higher Hamilton Rating Scale for Depression (HAM-D) scores and who had an earlier age at onset of the first depressive episode were significantly more likely to have recurrences.[51,52]

Atypical Depression

Atypical depression is said to consist of mood reactivity and 2 of the following: weight gain or increased appetite,

hypersomnia, leaden paralysis, and an enduring pattern of sensitivity to perceived interpersonal rejection.[53,54] This definition was largely modeled after the Columbia Criteria developed by Liebowitz, Quitkin, and others.[55] A number of early studies substantiated the superiority of MAOIs versus TCAs in patients with atypical depression.[56–58] Liebowitz[55] reported that 119 patients who met specific criteria for atypical depression completed 6 weeks of double-blind, randomly assigned treatment with phenelzine sulfate, imipramine hydrochloride, or placebo. The overall response rates were 71% with phenelzine, 50% with imipramine, and 28% with placebo. Phenelzine was widely superior to placebo and also showed superiority to imipramine. Phenelzine superiority appeared even greater after an additional 6-week continuation phase. Imipramine was only moderately effective in this atypical depressive sample. Unexpectedly, the superiority of either phenelzine or imipramine to placebo was largely confined to patients in subsets of the study sample who were prospectively judged to also have a history of spontaneous panic attacks and/or show hysteroid dysphoric features.[59]

Quitkin et al.[60] reported that in an initial study with 120 patients with reactive mood and associated atypical symptoms, phenelzine was superior to both imipramine and placebo. Unexpectedly, the benefit of antidepressants was limited to patients who also had spontaneous panic attacks. To help establish the validity of this syndrome, a new sample of 90 atypical depressives was studied.[61] The clinical and demographic characteristics of the original and replication sample were virtually identical at baseline. In addition, the treatment response with placebo, imipramine, or phenelzine was also indistinguishable in the 2 patient groups, supporting the idea that this may be a distinct unipolar depressive subgroup.[61] McGrath et al.[62] reported that of 46 patients who were previously unresponsive to imipramine and who completed phenelzine treatment, 31 (67%) responded to phenelzine. Of 22 patients previously unresponsive to phenelzine who completed imipramine treatment, 9 (41%) responded to imipramine. The difference in response rates was statistically significant. Even after they had shown no response to 7 weeks of placebo and 6 weeks of imipramine treatment, 10 (83%) of 12 patients who then completed treatment with phenelzine responded, suggesting that among chronically ill, mood-reactive depressed patients with many symptoms of atypical depression, phenelzine was strikingly effective in those who had been nonresponders to imipramine.

Treatment-Resistant Depression

The MAOIs have been used as a second- or third-line strategy for treatment-resistant depression (TRD) for more than 30 years.[63] While comparative studies of treatment options for treatment-refractory depression are limited, switching to an MAOI remains an overlooked option. In fact, a number of studies have demonstrated the effectiveness of MAOIs in treatment-refractory depression. Review of both controlled and uncontrolled studies demonstrates that approximately 50% of TCA-resistant patients respond to MAOIs; response rates increase to approximately 70% in patients with subforms of atypical depression.[21,64,65] The poorest response rate noted to date in a study of TCA-resistant depression was noted by Nolen et al.[66] in 5 of 17 inpatients. However, improvement in this study was based on HAM-D scores; when the Clinical Global Impressions scale (CGI) was used as the improvement measure, 59% of patients responded.[66] It is unclear whether the MAOIs are particularly useful in TRD because of distinctly different mechanisms of action.[63] Certain subgroups of patients with TRD may be more responsive to MAOIs (atypical, anergic bipolar, and anxious/phobic); Thase et al.[64] found that only 33% of TRD patients with typical major depression responded to MAOIs versus the almost 80% of patients with reversed vegetative features who responded to MAOIs. The effectiveness of MAOIs has not been confirmed in patients who have failed therapy with an SSRI; however, MAOIs are probably the treatment of choice for later-stage TRD—patients who are resistant to both SSRIs and TCAs individually—and as augmentation strategies.[63] To avoid possible incidence of serotonin syndrome, SSRIs should not be used in combination with MAOIs.

Anxiety Disorders

Studies have demonstrated the efficacy of MAOIs in panic disorder with and without agoraphobia, as well as other phobias. Open trials and placebo-controlled studies have revealed a high efficacy for phenelzine in the treatment of panic symptoms, although anxiety and avoidance may still be present in 25% to 40% of patients, necessitating additional behavior therapy.[67,68] There is some evidence that MAOIs may be of more benefit than TCAs in patients with panic attacks, particularly if the panic attacks occur in association with a depressive syndrome.[69,70] The response of social anxiety disorders to phenelzine is estimated to be within the range of 60% to 70%.[32,64] Liebowitz et al.[71] found that the phenelzine response was superior to that of atenolol or placebo at 8 and 16 weeks. The biological mechanism of the antipanic and antiphobic action noted with the use of MAOIs remains unclear.[72,73]

Bipolar Depression

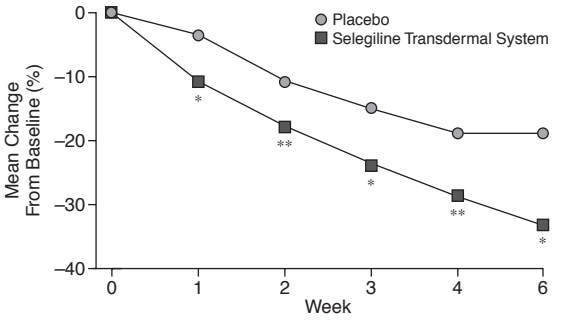
MAOIs have not been as extensively studied in bipolar depression as they have in unipolar depression, with or without atypical features. Himmelhoch et al.[74] reported on the utility of tranylcypromine in an open-label study of TCA-resistant bipolar depressed patients, most of whom were receiving lithium concurrently. Sixteen of the 212 patients responded to treatment with tranylcypromine. Other studies have extended this finding, with tranylcypromine consistently performing well. Himmelhoch et al.[75] later compared the efficacy of tranylcypromine with imipramine in the treatment of anergic bipolar depressive illness. A controlled,

double-blind comparison was used to study 56 outpatients with bipolar disorder who met operationalized criteria for anergic bipolar depression (N = 28 tranylcypromine, N = 28 imipramine). Tranylcypromine produced statistically significant superior outcome on a number of clinical measures in terms of lower attrition, greater symptomatic improvement, and higher global response without increased risk of treatment-emergent hypomania or mania. Thase et al.[76] studied 16 outpatients with anergic bipolar depression. Fourteen had not responded to 4 weeks of treatment with at least 30 mg/day of tranylcypromine or 150 mg/day of imipramine, and 2 patients were crossed over because of intolerable side effects from the initial drug. Twelve patients were crossed over from imipramine to tranylcypromine; 9 of them responded to tranylcypromine. Highly significant improvements were documented on the HAM-D, Beck Depression Inventory, and Pittsburgh Reversed Vegetative Symptom Scales. Four patients were switched from tranylcypromine to imipramine, but only 1 responded. Larsen and Rafaelsen[77] reported on favorable long-term treatment of TCA-resistant bipolar depression with isocarboxazid; Quitkin et al.[78] described a series of 5 patients with bipolar depression with endogenous features who responded to treatment with phenelzine following unsuccessful treatment with TCAs.

FUTURE DIRECTIONS

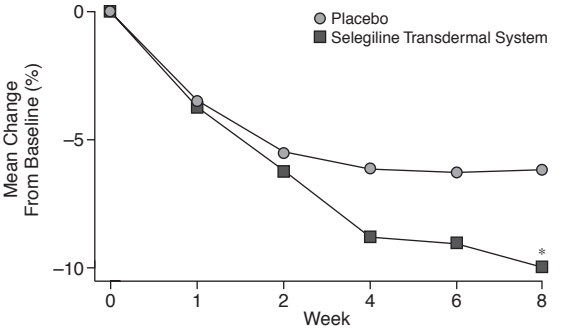
One survey of psychiatrists reported that the leading concerns about prescribing MAOIs were the restrictive dietary prohibitions and the fear of hypertensive crisis following ingestion of foods containing tyramine.[79] Transdermal delivery of an MAOI may alleviate the inhibition of tyramine from the intestinal mucosa without compromising the CNS effects,[16,17] and the results from 2 clinical trials have demonstrated that transdermal selegiline provided a statistically significant antidepressant benefit when compared with placebo. The first trial[80] evaluated the safety and efficacy of transdermal selegiline in adult outpatients with major depression. Following a 1-week placebo lead-in, 177 adult outpatients with major depressive disorder were randomly assigned to receive selegiline transdermal system (STS) (6 mg/24 hour [20 mg] patch) applied once daily (N = 89) or placebo (N = 88) for 6 weeks. The patients followed a tyramine-restricted diet during the medication trial and for 2 weeks after completion of treatment. Response to medication or placebo was measured by using the 17-item and 28-item versions of the HAM-D, the Montgomery-Asberg Depression Rating Scale (MADRS), and the CGI-Severity of Illness and -Improvement measures. Greater improvement was observed after 6 weeks in patients treated with transdermal selegiline than in those given placebo according to all measures. A statistically significant difference between drug and placebo was seen in the HAM-D and MADRS scores as early as week 1 of treatment (Figure 1). With the exception of application-site reactions, which were more common with transdermal selegiline, there were no differences noted in the adverse event profile. No orthostatic hypotensive or hypertensive reactions were observed.[80]

Figure 1. Change in MADRS Scores in Major Depression Patients Treated With Selegiline Transdermal System: Results of a 6-Week Trial[a]



[a]Data from Bodkin and Amsterdam.[80]
*p < .05.
**p < .005.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 2. Change in MADRS Scores in Major Depression Patients Treated With Selegiline Transdermal System: Results of an 8-Week Trial (ITT, LOCF)[a]



[a]Data from Amsterdam.[81]
*p = .001 for between-group comparison at week 8.
Abbreviations: ITT = intent to treat, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

The second trial[81] also evaluated the safety and efficacy of transdermal selegiline in 365 patients with major depressive disorder. Patients were 18 to 65 years old with a DSM-IV diagnosis of major depressive disorder and a 17-item HAM-D score ≥ 20. Patients were randomly assigned to receive either STS 6 mg/24 hour (20 mg) patch daily (N = 145) or placebo patch (N = 144) for up to 8 weeks. A tyramine-restricted diet was neither required nor advised. At endpoint, transdermal selegiline was statistically superior to placebo on the MADRS (p = .001) and HAM-D-28 (p = .039) ratings and was superior, though nonsignificant, on the HAM-D (p = .069) and CGI-Severity of Illness ratings (p < .055, Figure 2). Side effect profiles

were similar for STS and placebo with the exception of application-site reaction, which was observed in 31.5% of STS patients and 15.1% of placebo-treated patients (p = .001). No significant differences were observed in blood pressure measures between treatment groups.[81]

The selegiline transdermal system appears to offer an advantage over oral selegiline because it does not inhibit MAO-A in the periphery and does not inhibit tyramine metabolism. The results of this trial have led to FDA approval of the transdermal dosage form of the MAOI selegiline. Oral selegiline is currently approved at a dose of 10 mg/day and without dietary restrictions as a selective MAOI for the treatment of Parkinson's disease. The STS appears to offer an advantage over oral selegiline because it does not inhibit MAO-A in the periphery and does not inhibit tyramine metabolism. The STS 6 mg/24 hour patch allows for levels of medicine to inhibit MAO in the brain thought to be necessary for antidepressant effect while sufficiently preserving MAO-A in the digestive tract to break down tyramine. In their entirety, the data for STS 6 mg/24 hour (20 mg) support the recommendation that tyramine dietary modifications are not needed; however, dietary modifications are required with the STS 9 mg/24 hour (30 mg) patch and the 12 mg/24 hour (40 mg) patch.[81]

CONCLUSIONS

Since their introduction, MAOIs have lost favor among clinicians, due mostly to the unfavorable safety profile. However, reviews, meta-analyses, and controlled studies show that these agents are effective in the management of depression.[82] MAOIs are effective for a range of clinical presentations in both inpatients and outpatients, including unipolar, bipolar, atypical, and treatment-resistant depression. With the recent development of a novel, transdermal MAOI system, psychiatrists now have an additional option for treating their more challenging patients.

Drug names: atenolol (Tenormin and others), clomipramine (Anafranil and others), imipramine (Tofranil and others), isocarboxazid (Marplan), isoniazid (Nydrazid, Laniazid, and others), meperidine (Demerol and others), nortriptyline (Pamelor and others), phenelzine (Nardil), selegiline (Eldepryl and others), selegiline transdermal system (EMSAM), tranylcypromine (Parnate and others), venlafaxine (Effexor and others).

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