The Use of Monoamine Oxidase Inhibitors in Primary Care

Larry Culpepper, MD, MPH

Although primary care clinicians have developed considerable expertise in managing patients with major depressive disorder, and a range of treatment strategies is currently available, some patients still fail to reach remission. Two strategies have fallen out of common use: treating patients with monoamine oxidase inhibitors (MAOIs) and subgrouping patients by diagnosis when selecting antidepressant treatment. Monoamine oxidase inhibitors became less popular because other treatments were perceived to be safer and easier to use. However, a newer transdermal formulation of an MAOI that limits the need for the dietary restrictions of oral MAOIs may make it worthwhile to consider using this class of medication in patients who have failed several treatment trials. Although adverse events due to patients' diets are less likely with the transdermal MAOI, clinicians should still be alert for drug interactions and observe recommended washout periods. Patients who may benefit from MAOI treatment include those with treatment-resistant depression, atypical depression, anxiety, or anergic bipolar depression and those who have experienced intolerable metabolic or sexual side effects with other medications. *(J Clin Psychiatry 2012;73[suppl 1]:37–41)*

The capacity of clinicians to manage major depressive disorder (MDD) in primary care has increased in recent decades, but some patients still do not experience adequate symptomatic improvement and remission, despite the availability of many new treatments. An older class of antidepressants, the monoamine oxidase inhibitors (MAOIs), has been largely abandoned because of perceived safety issues, but a newer formulation may be a useful and safer option for difficult-to-treat depression.

ANTIDEPRESSANT TREATMENT IN PRIMARY CARE

The treatment of patients with MDD in primary care has improved over the past 20 years because of the availability of multiple selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and other newer antidepressants with good efficacy and safety profiles. In addition, the increased emphasis on using evidence-based guidelines, measurement-based care in evaluating treatment response and symptomatic improvement, and collaborative care approaches have helped primary care physicians better manage patients with depression.

Although improvements in depression treatment have occurred, a large proportion of patients still have suboptimal outcomes and many treatment options have considerable potential for serious adverse side effects. The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[1] found that one-third of participants with MDD did not reach remission after 1 year and after receiving up to 4 treatment trials.

Some difficult-to-treat groups of patients with depression include those who have residual symptoms,[2] chronic depression,[3] multiple recurrent episodes,[4] anxious features,[3] or side effects that limit the use of first-line treatment.[2,4–7] Given the continued presence of patients who do not completely respond to first-line therapy, it may be of value to revisit next-step strategies that are used less frequently now than in the past.

MONOAMINE OXIDASE INHIBITORS

Interest in using medications that inhibit monoamine oxidase (MAO) enzymes and in dividing patients with MDD into subgroups that might preferentially respond to particular treatments was high from the 1960s to the early 1990s. One subgroup, those with atypical depression, was recognized as responding better to MAOIs than to tricyclic antidepressants (TCAs).[8] The classification of *atypical depression* has been associated with features of nonendogenous depression, anxiety, panic, reversed vegetative shift, chronic pain, bipolar disorder, and rejection sensitivity.[9]

An understanding of atypical depression can help guide primary care clinicians in recognizing this group of patients and in monitoring their treatment response. Up to 40% of patients with dysthymia or MDD have atypical symptoms, which are usually present during multiple episodes of depression.[10] To meet the criteria for the atypical features specifier with an MDD diagnosis, the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[11] requires mood reactivity (the ability to have an improved mood resulting from actual or potential positive events) plus 2 or more atypical features (significant weight gain or an increase in appetite, hypersomnia, leaden paralysis, or a long-standing pattern of interpersonal rejection sensitivity). However, these criteria have been criticized. For example,

From the Department of Family Medicine, Boston University School of Medicine, Boston Medical Center, Boston, Massachusetts.

This article is derived from the planning teleconference series "A Fresh Look at Monoamine Oxidase Inhibitors for Depression," which was held December 2011 through February 2012 and supported by an educational grant from Mylan Specialty, L.P. (formerly known as Dey Pharmaceuticals, L.P.).

Dr Culpepper is a consultant for AstraZeneca, Forest, Merck, Pfizer, and Takeda and is a member of the speakers/advisory boards for Merck.

***Corresponding author:** Larry Culpepper, MD, MPH, Dowling 5, 771 Albany St, Boston, MA 02118 (larry.culpepper@bmc.org).*

doi:10.4088/JCP.11096su1c.06

For Clinical Use

- Consider using MAOIs for patients with atypical depression or patients with depression who have not experienced adequate symptomatic improvement with traditional first-line treatments.
- Consider MAOIs for other patient populations that may benefit from MAOI treatment, such as those with anxiety or panic disorders or anergic bipolar depression.
- When prescribing MAOIs, be mindful of drug interactions with the patient's current medications, follow the required washout period, and advise the patient of dietary restrictions, if necessary.
- When prescribing MAOIs, consider the transdermal formulation, which mitigates some concerns about adverse events and dietary restrictions that accompany oral MAOIs.

evidence supporting the primacy of mood reactivity has not been found, and rejection sensitivity may be a better primary symptom.[12] Also, *leaden paralysis* has become an outdated term, rarely described by patients today. Atypical MDD is perhaps better conceptualized as sensitivity to rejection coupled with dysregulated emotional and self-consolatory responses that manifest as hypersomnia and hyperphagia.[12]

Early studies of patients with features of atypical depression consistently demonstrated superior response to MAOIs compared with TCAs. For example, a double-blind, randomized study by Liebowitz and colleagues[13] compared responses to the MAOI phenelzine, the TCA imipramine, and placebo in 119 patients with atypical depression. Response rates at 6 weeks were 71% for phenelzine, 50% for imipramine, and 28% for placebo. A double-blind crossover study[14] also demonstrated preferential responsiveness to MAOIs in 89 chronically depressed outpatients with mood-reactive atypical depression. Among 46 subjects who did not respond to imipramine, 31 completers (67%) responded to phenelzine, whereas, among 22 patients who did not respond to phenelzine, 9 completers (41%) responded to imipramine.

The number of prescriptions of MAOIs declined in the 1990s because newly introduced SSRIs came to be regarded as useful for all patient groups and as having better safety and tolerability profiles.[9] Monoamine oxidase inhibitors were seen as difficult to manage and dangerous because of their potential for serious adverse events, such as hypertensive crisis (caused by either food or drug interactions) and serotonin syndrome (caused by drug interactions with other serotonergic agents).

In the 2000s, however, a considerable side effect burden became apparent for the newer antidepressants (such as sexual dysfunction and weight gain), which are the recommended first-line treatment for depression, as well as for the atypical antipsychotics (like weight gain and metabolic syndrome), which are used as second- and third-line combination pharmacotherapies for depression.[15] Meanwhile, a safer MAOI became available in the form of a transdermal patch. As many primary care physicians are now skilled in managing MDD with second- and third-line medications (including atypical antipsychotics), a re-examination of the use of MAOIs in primary care is warranted. To use MAOIs in this setting, clinicians need an understanding of the mechanism of action, common side effects, and treatment options available within this class of medication.

Mechanism of Action of MAOIs

The MAOIs inhibit the mitochondrial enzyme MAO, which is found in the brain, gut, liver, and other tissues.[16] Monoamine oxidase converts biogenic amines to aldehydes and corresponding acids, some of which are changed into alcohols for elimination. In neurons, MAO normally oxidatively deaminates and inactivates excess neurotransmitters including serotonin, norepinephrine, and dopamine. The inhibition of this conversion increases these neurotransmitters in the brain and other tissues.

Two isomers of MAO with different inhibitor sensitivities and substrate affinities have been identified: MAO-A and MAO-B.[16] Monoamine oxidase-A is located in areas of the brain with a high density of catecholaminergic neurons and the enzyme dopamine β-hydroxylase, which converts dopamine to norepinephrine. Additionally, 80% of MAO in the intestine is MAO-A,[17] which metabolizes dietary tyramine and restricts its uptake into the systemic circulation.[18] Monoamine oxidase-B occurs in the basal ganglia of the brain, platelets, and other tissues.[16]

Serotonin, norepinephrine, and dopamine, neurotransmitters considered to be active in mood regulation and, thus, implicated in major depression, are affected by MAO-A. Therefore, inhibiting MAO-A is thought to induce antidepressant effects.[16] For more information on the mechanism of action of MAOIs at the neurotransmitter level, read the article in this supplement by Chad M. VanDenBerg, MD, "The Transdermal Delivery System of Monoamine Oxidase Inhibitors."[19]

Monoamine oxidase inhibitors are either selective for MAO-A or MAO-B or are nonselective (Table 1). For MAOIs to be effective for depression, MAO-A inhibition needs to take place.[16] At a high dosage (30–60 mg/d), oral selegiline loses its MAO-B selectivity and becomes nonselective, thereby exhibiting antidepressant effects.

The MAOIs are either reversible or irreversible (see Table 1). In the United States, the currently available MAOIs bind to MAO irreversibly, which permanently deactivates MAO, and the enzyme must be regenerated by the body so that it can function again.[16] Seven to 10 days are required for new MAO enzymes to be generated.

MAOI Adverse Effects

Side effects most commonly reported for oral MAOIs include insomnia, sedation, orthostatic hypotension, dizziness, and nausea.[17] Over the longer term, weight gain, edema, muscle pain, myoclonus, paresthesias, and sexual dysfunction have been reported. The literature is lacking about whether weight gain and sexual dysfunction occur to the same extent

Table 1. MAOI Selectivity and Reversibility

Selectivity		Reversibility	
Selective	Nonselective	Reversible	Irreversible
MAO-A	Isocarboxazid	Moclobemide[a]	Clorgiline[a]
Clorgiline[a]	Phenelzine		Isocarboxazid
Moclobemide[a]	Selegiline (at high doses)		Phenelzine
MAO-B	Tranylcypromine		Selegiline
Selegiline (at low doses)			Tranylcypromine

[a]Not available in the United States.
Abbreviations: MAO = monoamine oxidase, MAOI = MAO inhibitor.

Table 2. Medications That Can Cause Hypertensive Crisis and Serotonin Syndrome When Co-Administered With MAOIs and Conditions Contraindicating MAOI Treatment[a]

Medications That Can Cause Hypertensive Crisis With MAOIs
Amphetamines
Antihypertensive agents
Antiparkinsonism agents
Antitussive agents[b]
Dopamine
Epinephrine
Narcotic analgesics
Norepinephrine
Phenylalanine
Stimulants
Tyrosine
Tryptophan
Vasoconstrictors[c]
Medications That Can Cause Serotonin Syndrome With MAOIs
Amphetamines
Anti-obesity drugs (with serotonergic action)
Bupropion
Other MAOIs
Narcotic and opioid analgesics
Serotonin-norepinephrine reuptake inhibitors (SNRIs)
Selective serotonin reuptake inhibitors (SSRIs)
Tetracyclic antidepressants (TeCAs)
Tricyclic antidepressants (TCAs)
Conditions Contraindicating MAOI Treatment
Hypersensitivity to MAOIs
Cerebrovascular disorders
Pheochromocytoma
Liver disease
Renal impairment

[a]Based on the manufacturers' package inserts.[21–25]
[b]Found in cold and cough medications.
[c]Found in cold and hay fever medications and weight-reducing products.
Abbreviation: MAOI = monoamine oxidase inhibitor.

with oral MAOIs as with SSRIs, although reversible MAOIs appear to cause less weight gain than irreversible ones.

More rarely, hepatotoxicity has occurred with MAOI treatment. Other rare side effects that are of particular concern are hypertensive crisis and serotonin syndrome.

Hypertensive crisis. Dietary tyramine is metabolized in the intestine by MAO-A, which restricts the uptake of tyramine into the circulatory system. Inhibition of MAO-A reduces this protective effect and allows large amounts of tyramine into the bloodstream, which triggers the release of norepinephrine from sympathetic nerve synapses. This results in a rapid rise in blood pressure, possibly causing headaches, tachycardia, nausea, hypertension, cardiac arrhythmias, and stroke, perhaps even resulting in death.[16,20] In patients taking an oral MAOI or a transdermal MAOI at dosages greater than 6 mg/24 hours, dietary restrictions are necessary to avoid this so-called "cheese effect."[17,18,20] These restrictions require eliminating tyramine-rich foods such as aged cheese, banana peels, broad bean pods, tap and nonpasteurized beers, Marmite, sauerkraut, soy products, tofu, and dried, aged, smoked, spoiled, or improperly stored meat, poultry, or fish.[20] Dietary modifications are not needed with low doses of a transdermal MAOI or with selective MAO-B inhibitors.

In addition to tyramine-related hypertensive crisis with MAOIs, this condition can also be associated with drug interactions. When prescribing MAOIs, physicians should always be careful to avoid the concurrent use of drugs that can increase the risk of hypertensive crisis, such as agents containing vasoconstrictors (Table 2).[21–25]

Serotonin syndrome. Another rare but serious adverse effect, serotonin syndrome, has been reported as a result of the interaction between MAOIs and other serotonergic agents, such as SSRIs, SNRIs, and TCAs (see Table 2).[21–25] The syndrome is caused by excess serotonergic activity in the central nervous system and results in abdominal pain, diarrhea, flushing, sweating, hyperthermia, rigidity, lethargy, mental status changes, tremor and myoclonus, rhabdomyolysis, renal failure, cardiovascular shock, and possibly death.[15] While the risk of hypertensive crisis is specific to the MAOI class of antidepressants, serotonin syndrome can occur with any serotonin-active antidepressants.

Washout periods. When using MAOIs, a washout period of about 2 weeks is required before switching to or from contraindicated medications.[15] A washout period of 5 weeks is required when switching from fluoxetine, which has a long half-life. Longer washout periods are also required for patients with liver impairment.

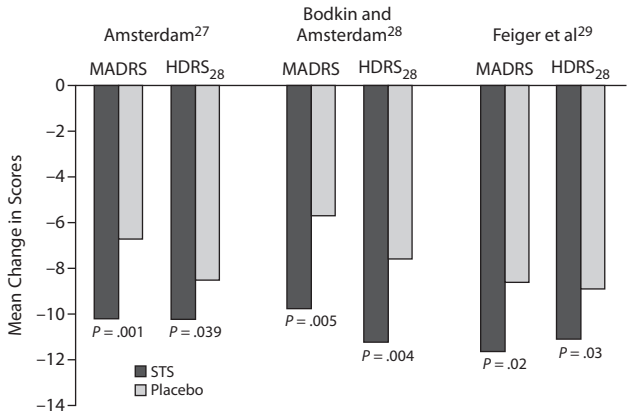
TRANSDERMAL MAOI

A transdermal formulation of the MAOI selegiline, the selegiline transdermal system (STS), was developed to provide a treatment option that mitigates some concerns about adverse events and dietary restrictions that accompany oral MAOI treatment while maintaining the established efficacy of MAOIs. The patches are available in 6-, 9-, and 12-mg dosages.

Drug delivery via an adhesive skin patch allows the MAOI to be directly absorbed into the systemic bloodstream, thereby minimizing the exposure of the gastrointestinal tract (where MAO-A metabolizes dietary tyramine) to the drug.[26] The patch, which is changed every 24 hours, lessens the concentration in the portal circulation, and consequently the need for diet restrictions, and mitigates the risk of hypertensive crisis.

Additionally, transdermal delivery lowers the dosage required to produce an antidepressant effect because of its greater bioavailability: oral selegiline bioavailability is 4% while STS bioavailability is 74%.[27] Bypassing the gut and first-pass metabolism also provides a marked reduction in absorption peaks and valleys for the transdermal formulation versus the oral formulation of selegiline.

Figure 1. Mean Change From Baseline in MADRS and $HDRS_{28}$ Scores for Patients Treated With Transdermal Selegiline Versus Placebo



Abbreviations: $HDRS_{28}$ = 28-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, STS = selegiline transdermal system.

Efficacy, Safety, and Tolerability of STS

The efficacy, safety, and side effect profile of STS have been reported in several randomized controlled trials[27–29] and in one long-term study.[30] In the first large-scale study[28] of STS for major depression, 177 adults were randomly assigned to treatment with STS at 6 mg/24 hours or to placebo for 6 weeks. Subjects were required to follow a tyramine-restricted diet and avoid sympathomimetic agents. As early as week 1, a robust treatment response emerged with STS, which was maintained throughout the study. Using the Hamilton Depression Rating Scale (HDRS) and the Montgomery-Asberg Depression Rating Scale (MADRS) as endpoint measures, STS demonstrated significantly superior efficacy compared with placebo (Figure 1)[28]: 46% greater improvement on the $HDRS_{17}$ ($P = .01$), 52% on the $HDRS_{28}$ ($P = .004$), and 79% on the MADRS ($P = .005$). No clinically meaningful orthostatic changes were observed, and no hypertensive episodes were reported. Application-site reactions (itching, redness, or irritation) were the most commonly reported adverse effect (36% STS vs 17% placebo, $P = .006$).

An 8-week randomized controlled study[27] examined 289 outpatients taking STS at 6 mg/24 hours or placebo; dietary restrictions were not required, but contraindicated treatments were not allowed. At endpoint, significantly more subjects had responded to STS than to placebo ($P = .031$). Additionally, significant differences favoring STS were seen in MADRS scores ($P = .001$) and $HDRS_{28}$ scores ($P = .039$; see Figure 1), but not in $HDRS_{17}$ scores.[27] Regarding adverse events, no clinically meaningful blood pressure changes occurred and no differences in sexual symptoms were noted between the 2 groups at week 8. However, application-site reactions were observed more frequently in the STS group than in the placebo group (31.5% vs 15.1%, $P = 001$).

Another 8-week randomized controlled study[29] assessed the safety and benefit of the selegiline patch in flexible doses ranging from 6 mg/24 hours to 12 mg/24 hours. The 265 subjects with MDD were not advised to follow a tyramine-restricted diet. More patients responded to STS (40%) than to placebo (30%), and the STS group had significantly greater improvement in $HDRS_{28}$ scores ($P = .03$) and MADRS scores ($P = .02$) compared with the placebo group (see Figure 1).[29] Greater improvement in $HDRS_{17}$ scores favored the STS group, but was not significant. Hypertensive crisis did not occur with any of the dosages, and the most commonly reported side effects were application-site reaction and insomnia. Sexual dysfunction was low and comparable for both groups.

In a maintenance study,[30] 322 patients who responded to the STS patch at 6 mg/24 hours over 10 weeks were randomized to continue STS or switch to placebo; no dietary restrictions were required. During the 52-week follow-up, significantly fewer participants in the STS continuation group relapsed versus the placebo switch group (16.8% vs 30.7%, respectively; $P = .0025$). No hypertensive crises occurred, and the only common adverse event that did not have comparable occurrence rates to placebo was application-site reaction.

Of particular note in these studies is the lack of occurrences of hypertensive crisis with the selegiline patch, regardless of whether diets were restricted or not. Dietary restrictions are not required for patients who are prescribed the lowest dosage (6 mg/24 h), but because the total number of patients in these studies was small, the US Food and Drug Administration (FDA) still requires dietary restrictions at higher dosages.[24]

PATIENTS FOR WHOM MAOIs COULD BE CONSIDERED

Primary care physicians who have developed expertise in measurement-based care for depression beyond first-line therapy may need to reconsider MAOIs, particularly STS, as a potential treatment option. Patient populations who may benefit from MAOI treatment include those with atypical depression, those who have not adequately responded to first-line treatments, those with other psychiatric conditions, or those who have experienced intolerable side effects with other antidepressants.

Evidence-based treatment guidelines, such as the American Psychiatric Association (APA) practice guidelines[15] and the British Association for Psychopharmacology guidelines,[31] acknowledge the effectiveness of MAOIs for atypical depression as well as treatment-resistant depression. For recommendations using MAOIs as given in treatment guidelines, read the article in this supplement by Michael E. Thase, MD, "The Role of Monoamine Oxidase Inhibitors in Depression Treatment Guidelines."[32]

Besides efficacy in atypical depression and treatment-resistant depression,[8] MAOIs may be useful for patients with other psychiatric disorders, as well. For example, MAOIs have been shown to be effective for anxiety disorders, including panic disorder (with and without agoraphobia) and social anxiety.[33,34] Patients with bipolar depression may also preferentially respond to MAOIs, particularly TCA-resistant patients or those with anergic bipolar disorder.[35–37]

Because MAOIs can be effective for patient subpopulations, patients with treatment-resistant depression should be evaluated for features of atypical depression, anxiety and phobias, and anergic bipolar depression. Additionally, the transdermal formulation may provide a valuable alternative to other second- or third-step treatment options and should also be considered for patients who have experienced intolerable adverse effects, particularly weight gain or sexual side effects, with other antidepressants.

CONCLUSION

Over the past decade, primary care physicians have become more experienced and skilled in treating MDD, but they continue to have patients who do not experience adequate response and symptomatic improvement with newer antidepressants. Additionally, some patients may experience intolerable adverse events, limiting the usefulness of first-line antidepressants. Monoamine oxidase inhibitors have proven efficacy for treating depression, particularly for patients with atypical depression and treatment-resistant depression and possibly for patients with anxiety or panic disorders or anergic bipolar depression, although this antidepressant class has declined in use because of the potential for severe side effects and drug interactions. However, newer formulations can lessen the need for dietary restrictions, and fewer side effects may occur with transdermal MAOIs than with some newer antidepressants. Due to its ease of administration and good safety and tolerability profile, a transdermal MAOI may be a viable treatment option for primary care physicians who have become experienced in treating depression beyond the first-line stage.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), isocarboxazid (Marplan), phenelzine (Nardil), selegiline oral formulation (Eldepryl, Zelapar, and others), selegiline transdermal system (EMSAM), tranylcypromine (Parnate and others).
Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

REFERENCES

1. Gaynes BN, Warden D, Trivedi MH, et al. What did STAR*D teach us? results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr Serv.* 2009;60(11):1439–1445.
2. Judd LL, Akiskal HS, Maser JD, et al. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. *J Affect Disord.* 1998;50(2–3):97–108.
3. Rush AJ, Warden D, Wisniewski SR, et al. STAR*D: revising conventional wisdom. *CNS Drugs.* 2009;23(8):627–647.
4. Mueller TI, Leon AC, Keller MB, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *Am J Psychiatry.* 1999;156(7):1000–1006.
5. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry.* 2002;63(4):357–366.
6. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. *J Clin Psychiatry.* 2010; 71(10):1259–1272.
7. Keller MB, Lavori PW, Rice J, et al. The persistent risk of chronicity in recurrent episodes of nonbipolar major depressive disorder: a prospective follow-up. *Am J Psychiatry.* 1986;143(1):24–28.
8. Thase ME, Trivedi MH, Rush AJ. MAOIs in the contemporary treatment of depression. *Neuropsychopharmacology.* 1995;12(3):185–219.
9. Davidson JR. A history of the concept of atypical depression. *J Clin Psychiatry.* 2007;68(suppl 3):10–15.
10. Quitkin FM. Depression with atypical features: diagnostic validity, prevalence, and treatment. *Prim Care Companion J Clin Psychiatry.* 2002;4(3):94–99.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
12. Parker GB. Atypical depression: a valid subtype? *J Clin Psychiatry.* 2007;68(suppl 3):18–22.
13. Liebowitz MR, Quitkin FM, Stewart JW, et al. Antidepressant specificity in atypical depression. *Arch Gen Psychiatry.* 1988;45(2):129–137.
14. McGrath PJ, Stewart JW, Nunes EV, et al. A double-blind crossover trial of imipramine and phenelzine for outpatients with treatment-refractory depression. *Am J Psychiatry.* 1993;150(1):118–123.
15. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder,* Third Edition. Washington, DC: American Psychiatric Association; 2010.
16. Krishnan KR. Revisiting monoamine oxidase inhibitors. *J Clin Psychiatry.* 2007;68(suppl 8):35–41.
17. Wimbiscus M, Kostenko O, Malone D. MAO inhibitors: risks, benefits, and lore. *Cleve Clin J Med.* 2010;77(12):859–882.
18. Culpepper L, Kovalick LJ. A review of the literature on the selegiline transdermal system: an effective and well-tolerated monoamine oxidase inhibitor for the treatment of depression. *Prim Care Companion J Clin Psychiatry.* 2008;10(1):25–30.
19. VanDenBerg CM. The transdermal delivery system of monoamine oxidase inhibitors. *J Clin Psychiatry.* 2012;73(suppl 1):25–30.
20. Stahl SM, Felker A. Monoamine oxidase inhibitors: a modern guide to an unrequited class of antidepressants. *CNS Spectr.* 2008;13(10): 855–870.
21. Marplan (isocarboxazid) [package insert]. Validus Pharmaceuticals, Inc; 2007.
22. Nardil (phenelzine sulfate) [package insert]. New York, NY: Pfizer, Inc; 2011.
23. Eldepryl (selegiline) [package insert]. Napa, CA: Dey Pharma LP; 2011.
24. EMSAM. (selegiline patch) [package insert]. Napa, CA: Dey Pharma LP; 2010.
25. Parnate (tranylcypromine) [package insert]. Research Triangle Park, NC: GlaxoSmithKline LLC; 2011.
26. Wecker L, James S, Copeland N, et al. Transdermal selegiline: targeted effects on monoamine oxidases in the brain. *Biol Psychiatry.* 2003; 54(10):1099–1104.
27. Amsterdam JD. A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. *J Clin Psychiatry.* 2003;64(2): 208–214.
28. Bodkin JA, Amsterdam JD. Transdermal selegiline in major depression: a double-blind, placebo-controlled, parallel-group study in outpatients. *Am J Psychiatry.* 2002;159(11):1869–1875.
29. Feiger AD, Rickels K, Rynn MA, et al. Selegiline transdermal system for the treatment of major depressive disorder: an 8-week, double-blind, placebo-controlled, flexible-dose titration trial. *J Clin Psychiatry.* 2006; 67(9):1354–1361.
30. Amsterdam JD, Bodkin JA. Selegiline transdermal system in the prevention of relapse of major depressive disorder: a 52-week, double-blind, placebo-substitution, parallel-group clinical trial. *J Clin Psychopharmacol.* 2006;26(6):579–586.
31. Anderson IM, Ferrier IN, Baldwin RC, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *J Psychopharmacol.* 2008;22(4):343–396.
32. Thase ME. The role of monoamine oxidase inhibitors in depression treatment guidelines. *J Clin Psychiatry.* 2012;73(suppl 1):10–16.
33. Buigues J, Vallejo J. Therapeutic response to phenelzine in patients with panic disorder and agoraphobia with panic attacks. *J Clin Psychiatry.* 1987;48(2):55–59.
34. Ravindran LN, Stein MB. The pharmacologic treatment of anxiety disorders: a review of progress. *J Clin Psychiatry.* 2010;71(7):839–854.
35. Thase ME, Frank E, Mallinger AG, et al. Treatment of imipramine-resistant recurrent depression, III: efficacy of monoamine oxidase inhibitors. *J Clin Psychiatry.* 1992;53(1):5–11.
36. Quitkin FM, McGrath P, Liebowitz MR, et al. Monoamine oxidase inhibitors in bipolar endogenous depressives. *J Clin Psychopharmacol.* 1981;1(2):70–74.
37. Himmelhoch JM, Thase ME, Mallinger AG, et al. Tranylcypromine versus imipramine in anergic bipolar depression. *Am J Psychiatry.* 1991;148(7):910–916.