Issues in Adherence to Treatment With Monoamine Oxidase Inhibitors and the Rate of Treatment Failure

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In 2000, the economic burden of depression in the United States was estimated to be $83.1 billion. Although many effective treatments are available and treatment rates have increased, response and remission rates for patients with depression remain low and multiple treatment trials are often required. Whether patients are adherent to their medication affects response and remission rates, and nonadherence is common among patients with depression. Increasing adherence improves treatment outcomes and lowers treatment costs. Interventions that increase adherence include educational, behavioral, affective, and provider-targeted strategies; transdermal delivery of drugs also may increase adherence by simplifying the patient's medication regimen. While monoamine oxidase inhibitors (MAOIs) have proven efficacy for depression, particularly for patients with treatment-resistant or atypical depression, they are underprescribed due, in part, to concerns over dietary and drug restrictions that are required to avoid potential serious side effects. However, newer MAOI formulations, including a transdermal delivery system, have improved safety and tolerability profiles and avoid or lessen the need for dietary restrictions, giving clinicians another option for treating patients who may be nonadherent or nonresponsive to their current antidepressant.

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Although many options are available for treating patients with depression, remission rates remain low and recurrent episodes and chronic subsyndromal symptoms are common.[1–3] In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[1] only about a third of patients reached remission after an adequate trial of a first-line antidepressant, and another third still had not reached remission after 4 treatment steps.

Monoamine oxidase inhibitors (MAOIs), developed in the 1950s, have demonstrated efficacy for treating depression, particularly atypical and treatment-resistant depression.[4] MAOIs were once the mainstay of treatment, but their use began to decline in the 1960s after rare but serious hypertensive events were observed. The cause of these events was determined to be an interaction between MAOIs and tyramine, a trace amine found in some foods.[5] Patients taking MAOIs must therefore follow dietary restrictions, and, although these restrictions have been simplified over the years, both patients and clinicians have viewed them as burdensome.[6] By the end of the 1990s, after the introduction of selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants with better tolerability profiles, only 2% of clinicians reported prescribing MAOIs frequently, even though a majority believed they were useful for treating depression.[7]

Due to the need for dietary restrictions and the risk of potentially serious side effects from food and drug interactions, treatment guidelines[8,9] typically recommend older MAOIs as third- or fourth-line treatments, although they do note that they may be considered earlier for patients with atypical or treatment-resistant depression. However, newer MAOI formulations with improved safety profiles have been recommended as first- and second-line treatments and provide another treatment option for patients with treatment-resistant depression.[10]

TREATMENT ADHERENCE AND ILLNESS OUTCOMES

Lack of therapeutic response to an antidepressant may be due to *treatment resistance*, in which, despite taking the medication as prescribed at an adequate dosage for an adequate duration, the patient receives little or no symptomatic improvement. However, nonresponse may also be due to *nonadherence*, in that the patient has not followed the antidepressant regimen, irrespective of initial response to the agent, and, therefore, his or her depression appears to be treatment resistant.

Adherence refers to compliance with day-to-day treatment instructions (eg, timing, dosage, frequency), while *persistence* pertains to continuing to take the medication for the duration prescribed.[11] Treatment adherence and illness outcomes are strongly correlated: response and remission rates are significantly higher and time-to-recurrence rates

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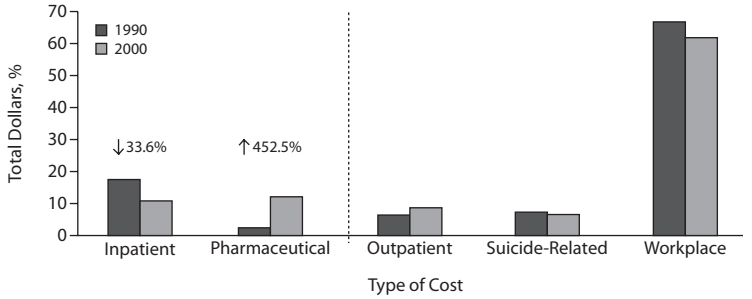
For Clinical Use

- Adherence to an antidepressant affects treatment response and remission rates for patients.
- Patients who appear to be treatment-resistant may be experiencing treatment failure due to nonadherence.
- Multifaceted strategies employing educational, behavioral, affective, and provider-targeted strategies enhance treatment adherence.
- A transdermal MAOI formulation may help to address adherence barriers for patients with treatment-resistant or atypical depression.

Figure 1. Economic Costs of Depression by Type, 1990 Versus 2000[a]



[a]Data from Greenberg et al.[23]

are significantly longer for patients who adhere to their medication regimens than for those who do not.[12]

Nonadherence can negatively affect treatment outcomes, whether the patient takes too much medication or too little. If patients unintentionally miss doses or purposefully take a drug holiday, they may experience discontinuation symptoms or nonresponse. Extra doses may result in increased adverse effects, which may lead patients to discontinue treatment. Adherence is also associated with persistence: patients with lower adherence rates discontinue treatment more frequently than those who adhere day-to-day to their medication.[13]

ADHERENCE RATES IN DEPRESSION

Unfortunately, adherence to treatment is poor among patients with depression. In one 9-week trial,[13] 50% of patients taking antidepressants had at least 1 drug-free interval lasting 2 or more consecutive days, while 19% had at least 1 drug holiday lasting 4 or more consecutive days. Conversely, 67% took too many pills at least once. The risks for overconsumption and underconsumption occurred during specific time courses over the trial, with the risk for taking too many pills decreasing over time and the risk for taking too few increasing over time.

Adherence rates have also been shown to vary for different classes of antidepressants. A large retrospective database analysis[14] (N = 266,665) found that only 12.4% of patients taking an older MAOI or a tricyclic antidepressant (TCA) were adherent to their medication over a 6-month period, compared with 29.3% of patients taking an SSRI and 33.6% of patients taking a serotonin-norepinephrine reuptake inhibitor (SNRI). The transdermal MAOI selegiline was not included in the database, but adherence rates in the published acute clinical studies[15–17] for the drug ranged from 94% to more than 98%, while 84% of patients in a 52-week double-blind trial were adherent.[18] Trials comparing transdermal and oral therapies for illnesses such as Alzheimer's disease and hypertension have shown greater adherence rates among those using the transdermal patch.[19,20]

Persistence rates are also low with antidepressant treatment. Nearly one-third of patients treated for depression discontinue their antidepressant in the first month of treatment,[21] and more than half stop taking prescribed medication by 6 months.[22] Further, more than 60% of those who stop antidepressant treatment do so without consulting their physicians.[22]

ECONOMIC CONSEQUENCES OF NONADHERENCE

In 2000, the economic burden of depression in the United States was estimated to be $83.1 billion, an increase of 7% from 1990 ($77.4 billion in inflation-adjusted dollars).[23] However, in that decade between 1990 and 2000, the treatment rate for depression increased by 56%. One reason that the overall dollar figure increased so little compared with the expansion of the treatment population is that inpatient care decreased from 17.3% of the total costs in 1990 to 10.7% in 2000. During that time, there was a 5-fold increase in dollar sales of antidepressants (Figure 1).[23] Using this lower-cost form of care has made it possible to treat larger numbers of patients without proportionally increasing the economic burden.

The effect of antidepressant treatment on total costs, however, depends on several factors. Stability of treatment is one factor: patients who remain on their initial antidepressant have lower annual per patient costs than patients who discontinue or switch antidepressants, possibly because switching from or discontinuing an antidepressant can be associated with increased outpatient care and hospitalization.[24] Patients taking older MAOIs and TCAs have significantly higher therapy change rates than patients taking newer antidepressants ($P < .001$) and correspondingly higher health care utilization.[14] Therefore, both efficacy and tolerability should be considered when choosing an antidepressant for an individual patient; even the use of a more expensive drug over a less expensive drug may lower overall costs if the patient's adherence/persistence is increased and health care utilization due to unresolved depression is decreased.[25]

Depression is projected to be the second-leading cause of disability by 2020.[26] The World Health Organization (WHO) has recognized the importance of treatment adherence in improving outcomes, enhancing patient safety, and reducing

economic burden and has designated depression as 1 of 9 chronic conditions on which efforts to improve medication adherence should be focused as a means of improving treatment outcomes.[27] Improved treatment response and higher remission rates would lower the burden of depression to society by reducing both direct health care costs and indirect costs, such as decreased work productivity, while increasing quality of life for patients.[28,29]

ENHANCING TREATMENT ADHERENCE

Data indicate that the primary predictors of nonadherence to antidepressants include unpleasant adverse effects, a lack of patient education about the illness and treatment, and a poor relationship between the physician and the patient.[30] Systematic reviews[31,32] conducted to identify interventions that improve adherence have generally been inconclusive, signifying a need for carefully designed clinical trials on the effects of single and combined interventions. A trend toward greater adherence rates was found in treatment groups who received more interventions,[31] suggesting that multifaceted strategies best enhance adherence. An analysis[32] of 23 narrative reviews that recommended interventions to improve adherence found that only 23% of the recommendations were supported by evidence from randomized controlled trials or meta-analyses. The most commonly recommended interventions were patient education, a strong patient-physician alliance, family education, clinical management strategies (eg, routinely see patients often during initial treatment), proactive management of side effects, and a simplified treatment regimen. The best evidence-supported interventions were side effect management and preference for SSRIs; the preference for SSRIs was supported by meta-analyses that indicated that the fewer side effects experienced with SSRIs than with other antidepressants allowed for fewer dropouts from treatment.

In a review of randomized controlled trials, Vergouwen and colleagues[33] classified interventions to improve adherence into 2 broad categories: patient education and collaborative care. Forms of patient education varied among the studies and consisted of verbal information about side effects, leaflets handed to the patient and explained at the visit, personalized mailed literature, or a combination of these methods. Collaborative care interventions entailed physicians and other mental health or primary care professionals employing multimodal methods to improve adherence (eg, increased visits, increased education, monitoring of medication use, and patient support provided by nurses). The review of the effectiveness of these interventions found no clear benefit in the aggregate for patient education alone on adherence or treatment outcomes. However, 9 of 11 collaborative care studies demonstrated improvements in adherence and better depression outcomes.

Chong et al[34] reviewed 26 studies to determine the effectiveness of educational, behavioral, and multifaceted interventions in improving antidepressant adherence and treatment outcomes (Figure 2). The majority of the 5 education studies employed mailed materials; none reported an increase in adherence or persistence among participants. The single behavioral study employed a psychosocial intervention to identify and address barriers to adherence, and improvements in both adherence and outcomes were reported. The 20 studies of multifaceted interventions employed a variety of educational, behavioral, affective, and provider-targeted components. Most multifaceted strategies focused on care management and patient follow-up, which involved collaboration among allied health professionals, psychiatrists, primary care physicians, and pharmacists. Of the 22 multifaceted interventions used in the 20 studies, 15 interventions produced positive effects versus usual care for adherence outcomes or for both adherence and depression outcomes. Each intervention that included pharmacy refill monitoring demonstrated increased adherence to antidepressants. However, pinpointing the specific components of multifaceted interventions that most effectively contribute to improved adherence and outcome will require more research.

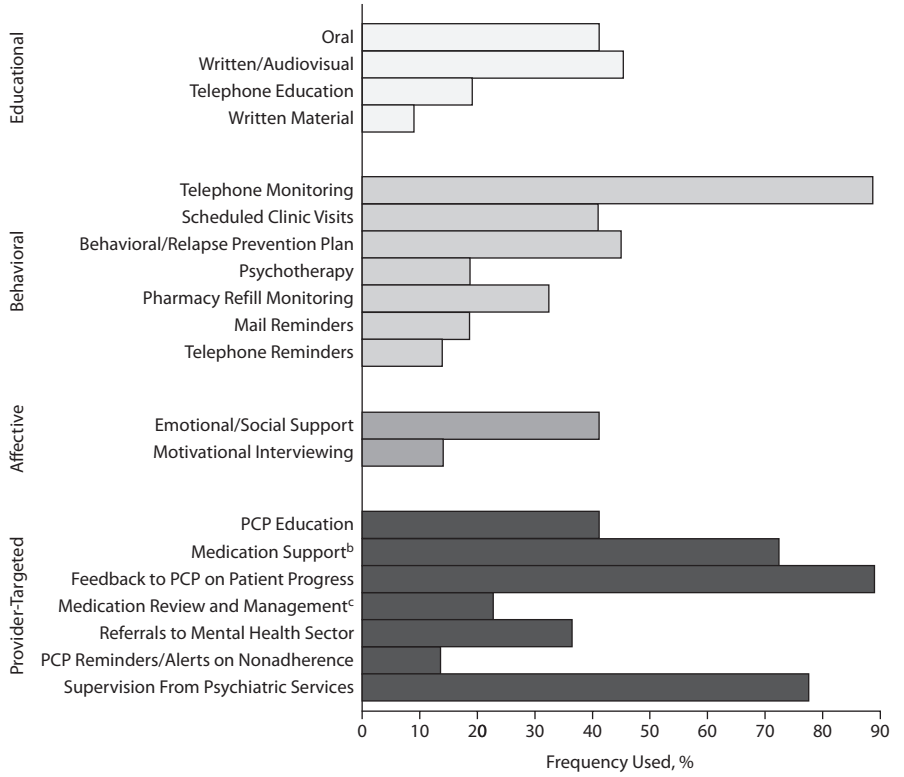
Lin and colleagues[21] looked at predictors of adherence to antidepressant therapy and determined that patients were more likely to adhere to medication during the first month of treatment when they received 5 specific educational messages: (1) to take the medication every day, (2) to not expect efficacy before 2 to 4 weeks, (3) to keep taking the antidepressant even when feeling better, (4) to check with the physician before stopping the medication, and (5) to ask questions regarding the medication using a provided contact. Subsequently, Lin et al[35] determined that significantly increasing a patient's favorable attitude toward antidepressant medication and their self-confidence in managing medication side effects was associated with greater adherence to long-term pharmacotherapy.

Finally, a comprehensive review[36] of the literature on psychiatric medication adherence noted that evidence supports cognitive-behavioral strategies and motivational interviewing as approaches to improve adherence. Other interventions also recommended included strengthening the therapeutic alliance, specifically addressing medication adherence during treatment visits, assessing the patient's motivation to take the prescribed medication, and identifying and addressing his or her potential barriers to adherence.

TRANSDERMAL DELIVERY AND TREATMENT ADHERENCE

Transdermal formulations of drugs are delivered directly into the circulatory system, thereby avoiding the gastrointestinal system and the hepatic first-pass effect. Transdermal delivery systems have been developed for a variety of drugs that treat neurologic conditions, including rivastigmine for Alzheimer's disease and dementia due to Parkinson's disease, rotigotine for Parkinson's disease and restless legs syndrome, the selegiline transdermal system for major depressive disorder, and the lidocaine 5% patch for pain from postherpetic neuralgia.[37] Delivering medication transdermally has both practical and pharmacokinetic advantages over oral delivery that may increase treatment adherence.

Figure 2. Educational, Behavioral, Affective, and Provider-Targeted Strategies Used in Multifaceted Interventions to Improve Treatment Adherence, by Frequency[a]



[a]Data from Chong et al.[34]
[b]Medication support provided by treatment algorithm or expert advice.
[c]Medication review and management provided by a pharmacist.
Abbreviation: PCP = primary care physician.

While oral medications produce a rapid peak in plasma levels that then rapidly declines, skin patches provide a smooth and continuous delivery of the medication.[37] Keeping drug levels within the therapeutic range may increase efficacy while decreasing adverse events owing to fluctuations in plasma levels. Additionally, transdermal formulations are generally applied once a day, which can simplify dosing regimens for patients who need to take more than one medication per day. Transdermal patches can be used by incapacitated patients or by patients with swallowing problems. Another advantage is that the patch is a visual reminder for patients to take the medication, and caregivers can also see that the medication is being used. Transdermal delivery is rated highly in patient satisfaction, and caregivers prefer patches to capsules, in part due to their ease of use.[38,39]

One disadvantage of the transdermal patch is that 20% to 50% of patients will have a skin reaction at the application site.[40] Most commonly, these reactions consist of a localized redness or itching, sometimes with edema; symptoms are typically mild to moderate, temporary in duration, and disappear spontaneously within several days following patch removal. Application site reactions are usually a form of irritant contact dermatitis and can be minimized by rotation of the application site, careful removal of the patch, and the use of moisturizers and topical corticosteroids.

Selegiline Transdermal Delivery System

In addition to metabolizing excess neurotransmitters in the brain, monoamine oxidase (MAO) metabolizes dietary tyramine during digestion. Inhibiting MAO in the gut can allow excess tyramine to enter the circulatory system, where it triggers norepinephrine release. An excess accumulation of norepinephrine then causes a rapid increase in blood pressure, which can lead to hypertensive crisis. Therefore, patients taking older oral MAOI formulations must follow dietary restrictions to avoid excessive intake of tyramine, and these restrictions are one of the most frequent reasons clinicians cite for not prescribing MAOIs.[7]

The transdermal formulation of the MAOI selegiline is delivered directly into the circulatory system and thus leaves MAO-A in the gut largely unaffected (Table 1).[41] Due to the avoidance of the first-pass metabolism, transdermal selegiline has much greater bioavailability than an oral formulation and can achieve an antidepressant effect with a lower dosage.[42] Dietary restrictions are not necessary with the lowest dosage of transdermal selegiline (6 mg/24 h), improving the likelihood of adherence; however, a low-tyramine diet must still be followed with higher doses due to a lack of safety data. Precautions against drug interactions must also be taken with the transdermal selegiline at all doses, as with other MAOIs.

Table 1. Potential Advantages for Adherence With Transdermal Versus Oral MAOIs[a]

Tissue specificity in drug targeting: targeted specific inhibition on MAO in the brain versus the intestine
Increased bioavailability (increased drug delivery to brain): no first-pass metabolism
Easy administration route: skin patch
Convenience and simplicity: single daily dose, easily removed when adverse side effects are experienced
Good alternative use according to the patient's medical condition (eg, swallowing difficulties)
Decreased gastrointestinal side effects: skin absorption and no first-pass metabolism
Minimizing serious adverse effects: reduced risk of hypertensive crisis
Less restriction in food consumption: no food restriction on a recommended and target dose at 6 mg/24 h
Improved quality of life: no exposure to others when taking medication
Improved medication adherence/compliance: possibly by complex factors (eg, easy accountability, difficult to miss a dose, and a more acceptable form for long-term treatment)

[a]Reprinted with permission from Pae et al.[41]
Abbreviations: MAO = monoamine oxidase, MAOI = MAO inhibitor.

Not only does the transdermal formulation of selegiline lessen the risk for serious potential food interactions that accompanies other irreversible MAOIs, but its side effect profile is superior to that of other types of agents that are used in patients with treatment-resistant depression. Except for application site reactions, transdermal selegiline has a tolerability profile similar to that of placebo.[16] Therefore, patients who have been nonadherent to their earlier antidepressants due to intolerable side effects, including weight gain[43] and sexual dysfunction,[44] might benefit from the use of transdermal selegiline.

CONCLUSION

Treatment rates for depression have increased dramatically in recent years, but treatment resistance is common and remission and response rates remain low. Nonadherence to antidepressants can adversely affect treatment outcomes and contribute to the economic burden of depression through higher utilization of health care services and greater loss of productivity. Multifaceted interventions employing a variety of educational, behavioral, affective, and provider-targeted components can increase adherence rates. To increase the likelihood of adherence, persistence, and stability of treatment, tolerability and efficacy should be considered when choosing among antidepressants. For some patients with resistant depression or problems with adherence to oral medication, a transdermal MAOI formulation may be a suitable option.

Going forward, additional research can help to illuminate the position of transdermal selegiline in depression treatment algorithms. For instance, should treatment guidelines move the formulation up in the treatment process, and, if so, under what circumstances? If a patient has benefited from an oral MAOI but has also experienced adverse side effects, is there an equivalency between the amount of oral agent needed to attain symptomatic relief and the dosages of the selegiline patch? Additionally, what is the economic profile of transdermal selegiline compared with oral agents? Does the patch enhance adherence, and does that translate to a reduced overall cost profile? And, finally, what is the best way to educate practitioners about classic MAOIs and the newer MAOI formulations, so that prescribers feel more comfortable in prescribing them to patients who might benefit from them? For a more in-depth look at these questions, see "Discussion: A Fresh Look at Monoamine Oxidase Inhibitors for Depression" in this Supplement.[45]

Answering these questions will help to guide clinicians and, particularly, primary care physicians, who now provide the majority of outpatient treatment for depression. The advent of SSRIs and other newer antidepressants that were easier to administer than earlier treatments helped prescribers to feel more comfortable prescribing psychotropic medications to their patients with depression.[46] The transdermal formulation of selegiline now provides an easier-to-manage MAOI option and offers physicians another alternative for patients with atypical or treatment-resistant depression.

Drug names: lidocaine (Lidoderm and others), rivastigmine (Exelon and others), rotigotine (Neupro), selegiline transdermal system (EMSAM).
Disclosure of off-label usage: Dr Cohen 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 activity.

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. 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.
3. Judd LL, Akiskal HS, Maser JD, et al. A prospective 12-year study of subsyndromal and syndromal depressive symptoms in unipolar major depressive disorders. *Arch Gen Psychiatry.* 1998;55(8):694–700.
4. Krishnan KR. Revisiting monoamine oxidase inhibitors. *J Clin Psychiatry.* 2007;68(suppl 8):35–41.
5. 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.
6. Gardner DM, Shulman KI, Walker SE, et al. The making of a user friendly MAOI diet. *J Clin Psychiatry.* 1996;57(3):99–104.
7. Balon R, Mufti R, Arfken CL. A survey of prescribing practices for monoamine oxidase inhibitors. *Psychiatr Serv.* 1999;50(7):945–947.
8. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition*. Washington, DC: American Psychiatric Association; 2010. http://psychiatryonline.org/content.aspx?bookid=28&sectionid=1667485. Accessed April 17, 2012.
9. 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. http://www.bap.org.uk/pdfs/antidepressants.pdf. Accessed March 23, 2012.
10. Lam RW, Kennedy SH, Grigoriadis S, et al, for the Canadian Network for Mood and Anxiety Treatments (CANMAT). Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults, pt 3: pharmacotherapy. *J Affect Disord.* 2009;117(suppl 1):S26–S43.
11. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value Health.* 2008;11(1):44–47.
12. Akerblad AC, Bengtsson F, von Knorring L, et al. Response, remission and relapse in relation to adherence in primary care treatment of depression: a 2-year outcome study. *Int Clin Psychopharmacol.* 2006;21(2):117–124.
13. Demyttenaere K, Mesters P, Boulanger B, et al. Adherence to treatment

regimen in depressed patients treated with amitriptyline or fluoxetine. *J Affect Disord.* 2001;65(3):243–252.
14. Sheehan DV, Keene MS, Eaddy M, et al. Differences in medication adherence and healthcare resource utilization patterns: older versus newer antidepressant agents in patients with depression and/or anxiety disorders. *CNS Drugs.* 2008;22(11):963–973.
15. 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.
16. 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.
17. 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.
18. 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.
19. Molinuevo JL, Arranz FJ. Impact of transdermal drug delivery on treatment adherence in patients with Alzheimer's disease. *Expert Rev Neurother.* 2012;12(1):31–37.
20. Burris JF, Papademetriou V, Wallin JD, et al. Therapeutic adherence in the elderly: transdermal clonidine compared to oral verapamil for hypertension. *Am J Med.* 1991;91(1A):S22–S28.
21. Lin EH, Von Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. *Med Care.* 1995;33(1):67–74.
22. Sawada N, Uchida H, Suzuki T, et al. Persistence and compliance to antidepressant treatment in patients with depression: a chart review. *BMC Psychiatry.* 2009;9(1):38.
23. Greenberg PE, Kessler RC, Birnbaum HG, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? *J Clin Psychiatry.* 2003;64(12):1465–1475.
24. Birnbaum HG, Ben-Hamadi R, Greenberg PE, et al. Determinants of direct cost differences among US employees with major depressive disorders using antidepressants. *Pharmacoeconomics.* 2009;27(6):507–517.
25. Wu EQ, Ben-Hamadi R, Lu M, et al. Treatment persistence and health care costs of adult MDD patients treated with escitalopram vs citalopram in a Medicaid population. *Manag Care.* 2012;21(1):49–58.
26. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet.* 1997;349(9064):1498–1504.
27. World Health Organization. *Adherence to Long-Term Therapies: Evidence for Action*. Geneva, Switzerland: World Health Organization; 2003. http://www.who.int/chp/knowledge/publications/adherence_report/en. Accessed April 18, 2012.
28. von Knorring L, Akerblad AC, Bengtsson F, et al. Cost of depression: effect of adherence and treatment response. *Eur Psychiatry.* 2006;21(6):349–354.
29. Wade AG, Häring J. A review of the costs associated with depression and treatment noncompliance: the potential benefits of online support. *Int Clin Psychopharmacol.* 2010;25(5):288–296.
30. Nemeroff CB. Improving antidepressant adherence. *J Clin Psychiatry.* 2003;64(suppl 18):25–30.
31. Pampallona S, Bollini P, Tibaldi G, et al. Patient adherence in the treatment of depression. *Br J Psychiatry.* 2002;180(2):104–109.
32. Bollini P, Pampallona S, Kupelnick B, et al. Improving compliance in depression: a systematic review of narrative reviews. *J Clin Pharm Ther.* 2006;31(3):253–260.
33. Vergouwen ACM, Bakker A, Katon WJ, et al. Improving adherence to antidepressants: a systematic review of interventions. *J Clin Psychiatry.* 2003;64(12):1415–1420.
34. Chong WW, Aslani P, Chen TF. Effectiveness of interventions to improve antidepressant medication adherence: a systematic review. *Int J Clin Pract.* 2011;65(9):954–975.
35. Lin EH, Von Korff M, Ludman EJ, et al. Enhancing adherence to prevent depression relapse in primary care. *Gen Hosp Psychiatry.* 2003;25(5):303–310.
36. Julius RJ, Novitsky MA Jr, Dubin WR. Medication adherence: a review of the literature and implications for clinical practice. *J Psychiatr Pract.* 2009;15(1):34–44.
37. Farlow MR, Somogyi M. Transdermal patches for the treatment of neurologic conditions in elderly patients: a review. *Prim Care Companion CNS Disord.* 2011;13(6):doi:10.4088/PCC.11r01149.
38. Shahiwala A. Formulation approaches in enhancement of patient compliance to oral drug therapy. *Expert Opin Drug Deliv.* 2011;8(11):1521–1529.
39. Winblad B, Kawata AK, Beusterien KM, et al. Caregiver preference for rivastigmine patch relative to capsules for treatment of probable Alzheimer's disease. *Int J Geriatr Psychiatry.* 2007;22(5):485–491.
40. Ale I, Lachapelle JM, Maibach HI. Skin tolerability associated with transdermal drug delivery systems: an overview. *Adv Ther.* 2009;26(10):920–935.
41. Pae CU, Lim HK, Han C, et al. Selegiline transdermal system: current awareness and promise. *Prog Neuropsychopharmacol Biol Psychiatry.* 2007;31(6):1153–1163.
42. Azzaro AJ, Ziemniak J, Kemper E, et al. Pharmacokinetics and absolute bioavailability of selegiline following treatment of healthy subjects with the selegiline transdermal system (6 mg/24 h): a comparison with oral selegiline capsules. *J Clin Pharmacol.* 2007;47(10):1256–1267.
43. Robinson DS, Amsterdam JD. The selegiline transdermal system in major depressive disorder: a systematic review of safety and tolerability. *J Affect Disord.* 2008;105(1–3):15–23.
44. Clayton AH, Campbell BJ, Favit A, et al. Symptoms of sexual dysfunction in patients treated for major depressive disorder: a meta-analysis comparing selegiline transdermal system and placebo using a patient-rated scale. *J Clin Psychiatry.* 2007;68(12):1860–1866.
45. Cohen LJ, Sclar DA, Culpepper L, et al. Discussion: a fresh look at monoamine oxidase inhibitors for depression. *J Clin Psychiatry* 2012;73(suppl 1):42–45.
46. Olfson M, Marcus SC, Druss B, et al. National trends in the outpatient treatment of depression. *JAMA.* 2002;287(2):203–209.