Identifying Patients With Depression Who Require a Change in Treatment and Implementing That Change

George I. Papakostas, MD

Creating an effective treatment regimen for patients diagnosed with major depressive disorder (MDD) can be a challenge for clinicians. With each treatment trial, only 20% to 30% of patients achieve remission, and many of those who do reach remission experience residual symptoms. Patients with treatment-resistant depression or with residual symptoms are candidates for a change in treatment. Other patients requiring treatment changes are those who experience intolerable adverse effects and those who experience an illness recurrence. Because early detection can lead to improved outcomes, clinicians must be vigilant about assessing patients to identify when one or more of these situations occur. Clinicians must also communicate effectively with their patients to ensure that they understand the treatment strategies, goals, and potential adverse effects; have realistic expectations of treatment; and express their treatment preferences. Timely and appropriate treatment adjustment is necessary to help patients with MDD achieve recovery. *(J Clin Psychiatry 2016;77[suppl 1]:16–21)*

Major depressive disorder (MDD) affects over 350 million people worldwide and is one of the leading causes of disability.[1] Unfortunately, among those who seek treatment, many have unsuccessful treatment trials. Clinicians must recognize the situations in which patients with MDD require a change in treatment. This article addresses how to identify patients who need treatment modifications and provides practical information about implementing those necessary changes.

Three main reasons exist for altering a treatment regimen: inadequate symptom improvement, intolerance to medication, and illness recurrence.[2] Clinicians must be vigilant about comprehensively assessing patients on a frequent basis to identify when one or more of these scenarios occur. The earlier that clinicians can detect a need for a change in treatment, the greater the potential for improved outcomes.[3]

From Massachusetts General Hospital and Harvard Medical School, Boston

This article is derived from the planning teleconference series "Improving the Care and Management of Patients With Inadequate Response to Depression Treatment," which was held in March 2015 and supported by an educational grant from Otsuka Pharmaceutical Development & Commercialization, Inc.

Dr Papakostas has served as a consultant for Abbott, AstraZeneca, Avanir, Axsome,* Brainsway, Bristol-Myers Squibb, Cephalon, Dey, Eli Lilly, Genentech,* GlaxoSmithKline, Evotec, Lundbeck, Inflabloc, Janssen,* Jazz, Johnson & Johnson,* Methylation Sciences, Novartis, One Carbon Therapeutics,* Osmotica,* Otsuka, Pamlab, Pfizer, Pierre Fabre, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Shire, Sunovion, Takeda, Theracos, and Wyeth; has received honoraria from Abbott, AstraZeneca, Avanir, Bristol-Myers Squibb, Brainsway, Cephalon, Dey, Eli Lilly, Evotec, Forest, GlaxoSmithKline, Inflabloc, Jazz, Lundbeck, Medichem, Meiji Seika, Novartis, Otsuka, Pamlab, Pfizer, Pierre Fabre, Ridge Diagnostics, Shire, Sunovion, Takeda, Theracos, Titan, and Wyeth; and has received grant support* from AstraZeneca, Bristol-Myers Squibb, Forest, the National Institute of Mental Health, Neuralstem, Pamlab, Pfizer, Ridge Diagnostics, Sunovion, Tal Medical, and Theracos.

* = activity undertaken on behalf of Massachusetts General Hospital.

Corresponding author: George I. Papakostas, MD, 15 Parkman St WACC#812, Boston, MA 02114 (gpapakostas@partners.org).

dx.doi.org/10.4088/JCP.14077su1c.03

INADEQUATE SYMPTOM IMPROVEMENT

Two situations in which a treatment regimen needs to be changed due to insufficient symptom improvement are cases of treatment-resistant depression (TRD) and cases of response or remission with residual symptoms. Patients in these situations may have a greater risk of relapse and recurrence, more chronic depressive episodes, shorter duration between episodes,[4] impairment in work and relationships,[5] increased morbidity[6] and mortality,[7,8] and an ongoing risk of suicide[9] compared with patients whose MDD remits without residual symptoms.[10]

Inadequate symptom improvement is common among patients diagnosed with MDD. A meta-analysis[11] of 182 randomized, double-blind, placebo-controlled trials of antidepressants for MDD that lasted at least 4 weeks found that almost half of patients did not respond to treatment. The pooled drug response rate was 53.8%, and the pooled placebo response rate in this meta-analysis was 37.3%.

Petersen and colleagues[12] described longitudinal naturalistic outcomes in patients with MDD who were treated at 2 academic-based depression specialty clinics, and remission occurred in 50% of patients after 4 adequate or optimal treatment trials. With each treatment trial, only about 20%–30% of patients achieved remission, with nonresponse rates ranging from 15% to 57%. At every treatment point, many patients experienced insufficient symptom improvement.[12]

Treatment-Resistant Depression

The American Psychiatric Association (APA) guidelines[2] for the treatment of MDD recommend that, except for cases of intolerance, patients remain on their treatment at a sufficient dosage and for a sufficient duration (generally 4–6 weeks) before clinicians consider a change. Patients who do not remit (ie, they do not respond at all or they respond only partially) after receiving an adequate dosage and duration of antidepressant therapy can be considered to have

TRD. Nonresponse is commonly defined as less than 25% reduction in depressive symptoms compared to baseline, partial response as 25%–49% improvement from baseline, and response as 50% or greater reduction in symptoms without achieving remission.[13,14]

Clinicians should be diligent in regularly assessing patients to detect symptom improvement, or the lack of it, in a timely manner. When using rating scales, clinicians should use the same scales at each visit to ensure comparable scores. Clinician-rated tools include the Montgomery-Asberg Depression Rating Scale (MADRS)[15] and Hamilton Depression Rating Scale (HDRS),[16] while patient-rated tools, such as the Quick Inventory of Depressive Symptomatology ($QIDS\text{-}SR_{16}$)[17] and the 9-item Patient Health Questionnaire (PHQ-9),[18] are much more user friendly in clinical practice and can save valuable time at visits.

Remission With Residual Symptoms

Remission is defined according to a threshold score on a rating scale. Patients can meet remission criteria without being free of symptoms, and residual symptoms create a need for treatment adjustment. The large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[19] found that, while one-third of patients achieved remission from MDD after the initial treatment trial, more than 90% of these patients had at least 1 residual symptom.

Functioning and Risk of Relapse

The timeliness of identification of cases of TRD or significant residual symptoms is critical because it can affect patients' functioning. In an 8-week trial[20] of 222 patients who had been prescribed fluoxetine for MDD, the early responders displayed superior overall psychosocial functioning at endpoint compared with those who had a later onset of response ($P = .0440$), regardless of functioning at baseline. Overall psychosocial adjustment at endpoint was greater among those who responded than among nonresponders ($P = .0003$), among those who remitted than among responders without remission ($P = .0031$), and among those who had fewer or less severe residual symptoms ($P = .0011$).[20]

Rush and colleagues[21] pointed to a relationship between the degree of treatment resistance and the probability of relapse after wellness had been achieved. Those patients who required more treatment steps to reach remission were found to have a greater rate of relapse.[21] Patients who achieved remission earlier experienced longer durations of remission than patients who took longer to remit.[21] Patients with more residual symptoms after remission were more likely to relapse.[19]

INTOLERANCE TO TREATMENT

Tolerability of treatment is a critical factor in MDD outcomes because it affects adherence as well as the ability to reach or maintain dosing in the clinically therapeutic range. Therefore, intolerance is a situation requiring a treatment change. Hunot and colleagues[22] studied 147 patients who were prescribed an antidepressant for any condition and followed them for 6 months. At endpoint, only 19% of patients were still taking their antidepressants. Half of the overall sample discontinued their antidepressants for part or all of the rest of follow-up (89% of whom did not consult their physician before doing so), and 9% of patients never filled their first prescription. A significant predictor of nonadherence was concern about adverse effects ($P < .001$).[22]

Just as patients consider side effects to be a pivotal factor when assessing whether an antidepressant treatment is successful, so do clinicians. A study by Zimmerman and colleagues[23] reported that, while clinicians consider the presence of a specific symptom or symptom profile as the most critical factor (52.3%) when choosing an antidepressant, the second-most critical factor is the desire to avoid a specific adverse effect (48.7%).

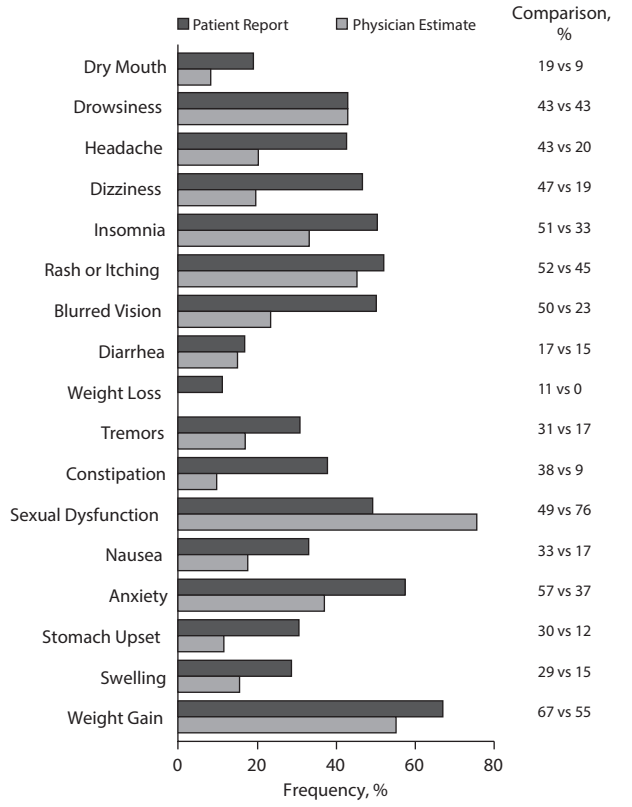
Of the multitude of side effects that patients can experience with antidepressants, clinicians must be able to detect the most common and the most bothersome. Hu and colleagues[24] examined via telephone interviews the incidence and duration of side effects experienced by 401 patients taking selective serotonin reuptake inhibitors (SSRIs). Drowsiness was the most commonly reported side effect (38.4%), followed by sexual dysfunction and dry mouth (33.9% each), and headache (23.4%).[24] However, when patients were asked to rate how bothersome their adverse effects were, different symptoms were highlighted. Sexual dysfunction was ranked first (16.7%), followed by drowsiness (16.5%), weight gain (11.5%), insomnia (11.2%), and anxiety (11.0%).[24] Clinicians should primarily focus on bothersome side effects in order to optimize their ability to identify situations in which patients need a treatment change. Many physicians underestimate the level of discomfort caused by adverse effects. Among the 17 adverse effects clinicians assessed, they underestimated the level of discomfort for all except sexual dysfunction and drowsiness (Figure 1).[24]

Side effects should not be overlooked, as they will most likely persist. Hu and colleagues[24] discovered that the majority of side effects occurred during the first 2 weeks of treatment and persisted until the telephone interview about 3 months later. Several symptoms—such as weight gain, sexual dysfunction, tremors, rash or itching, and swelling—were

Clinical Points

- Use similar rating scales at each patient visit to facilitate comparison of scores and track response and remission.
- Closely monitor patients for residual symptoms and adverse effects to determine if a treatment change is necessary.
- Establish a strong foundation of communication with the patient to encourage understanding about treatment goals, expected efficacy, potential side effects, and reasons for hope.
- Be aware of potential drug interactions when augmenting, combining, or switching medications.

Figure 1. Percentage of SSRI-Related Side Effects Rated as Bothersome ("a lot" or "extremely") by Patients and Their Physicians (N = 401)[a]



[a]Reprinted with permission from Hu et al.[24]
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

actually more widely experienced later on. Nausea was the exception to the rule, with a dramatic decrease in occurrence from the first 2 weeks (82.9%) to the follow-up interview (32.5%).[24]

Patients may also experience cognitive side effects. Cognitive dysfunction (apathy, inattentiveness, forgetfulness, word-finding difficulty, and mental slowing) was found in more than 30% of patients being treated for MDD.[25]

To manage intolerable side effects, clinicians and patients may be tempted to decrease the doses of antidepressants. However, a meta-analysis[26] found that when patients continued taking the doses used to achieve response or remission, their rates of relapse were lower than for patients whose dosages were reduced (15.1% vs 25.3%, respectively; $P = .001$). Thus, routinely decreasing dosages to resolve side effects is not a practical solution.

While some side effects are simple enough to be elicited with direct questioning, others will require structured scales for detection. Questioning is sufficient for side effects such as nausea, gastrointestinal distress, restlessness, and agitation. Most symptom scales, whether clinician-rated or patient-rated, provide coverage for symptoms of insomnia, and the persistence of high scores on these items can alert the clinician as to whether sleep problems are residual depressive symptoms or side effects. Other adverse effects that, because of their complexity, are better assessed with scales than with simple questioning include fatigue, cognitive symptoms, and sexual dysfunction. Fatigue can be assessed with the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (MGH CPFQ).[25] Cognitive symptoms can also be detected with the MGH CPFQ[25] and with the Perceived Deficits Questionnaire–Depression.[27] Clinician-administered instruments are not feasible in most clinics.[28] Sexual dysfunction can be monitored using the MGH Sexual Functioning Questionnaire[29] or the Arizona Sexual Experience Scale.[30] If scales are not used to assess patients for sexual dysfunction, direct questioning should be used as it is much more effective than relying on patient self-report.[31]

ILLNESS RECURRENCE

Illness recurrences require a minimum symptom duration of 2 weeks; patients must meet diagnostic criteria for a new episode of MDD.[32] Regular assessment during maintenance treatment will allow clinicians to detect signs of recurrence. In a 2-year study[33] of maintenance treatment with venlafaxine or fluoxetine, the rates of recurrence were about 28% and 44%, respectively. When venlafaxine was compared with placebo in 2 successive 1-year maintenance periods, the recurrence rates in year 1 and in year 2 were 23% and 8% for venlafaxine and 42% and 45% for placebo.[34] Mindfulness-based cognitive therapy was not found to be superior to antidepressant medication in time to recurrence of MDD over 2 years.[35]

Early detection of worsening and implementation of a treatment plan to address it can help improve psychosocial functioning. A study by Furukawa and colleagues[36] showed that improvement in psychosocial functioning continues after remission into the recovery period, the post-recovery period, and the sustained recovery period. Remission was defined as 7 or less on the HDRS, recovery as at least 2 consecutive months of remission, and sustained recovery as at least 6 consecutive months of remission.

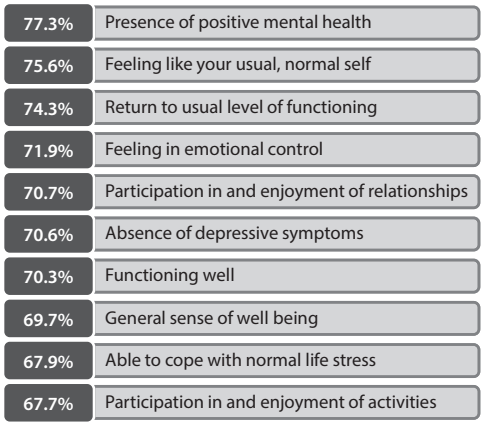
DEVELOPING A SUCCESSFUL TRANSITION PLAN

When clinicians recognize that patients need a change in treatment regimen—whether due to inadequate symptom improvement, intolerance to a medication, or illness recurrence—they must communicate effectively with patients and avoid certain pitfalls to ensure that the transition is successful.

Communicating Effectively

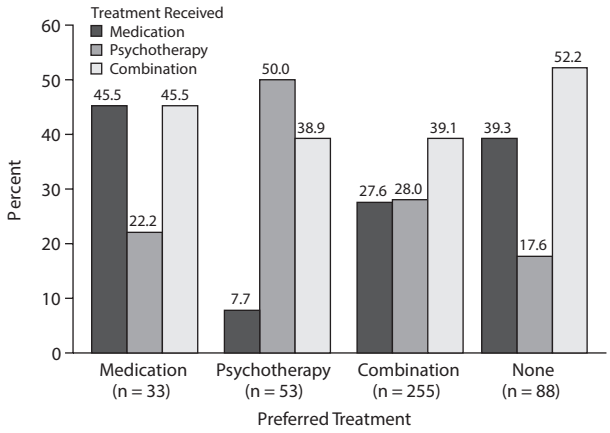
Treatment goals. One of the most important elements for a successful transition in a treatment plan is effective communication between clinicians and patients. Clinicians should communicate realistic goals when a treatment is changed, and patients should be clear about what they consider successful treatment. Zimmerman and colleagues[37]

Figure 2. "Very Important" Remission Factors Identified by Patients With Depression (N = 535)[a]



[a]Data from Zimmerman et al.[37]

Figure 3. Depression Remission Rates by Patient Treatment Preference (N = 429)[a]



[a]Reprinted with permission from Kocsis et al.[38]

interviewed patients to create a questionnaire about remission, which was completed by 535 patients being treated for MDD. The results showed that patients with depression rated these 5 factors as very important when defining remission: presence of positive mental health, feeling like your usual self, returning to a normal level of functioning, feeling in emotional control, and participation in and enjoyment of relationships (Figure 2).[37] Patients understanding clinicians' expectations of improvement and clinicians understanding patients' goals are critical factors in the success of a treatment regimen. While clinicians strive to decrease the number of depressive symptoms to help their patients reach remission, patients are primarily concerned with experiencing positive mental health, not just the elimination of depressive symptoms.

Treatment preference. The APA guidelines recommend that clinicians establish a therapeutic alliance with their patients by actively listening to their preferences and incorporating these concerns into a treatment strategy.[2] A study by Kocsis and colleagues[38] showed that, while antidepressants and psychotherapy were equally effective in treating patients with depression, those who received the treatment that they preferred did much better than those who received an alternate treatment. Patients who preferred antidepressant therapy and received medication had a remission rate of 45.5% compared with a 22.2% remission rate among patients who received psychotherapy instead (Figure 3).[38] A greater difference was displayed with patients who preferred psychotherapy: 50% who received their preferred treatment remitted compared with 7.7% who received antidepressant therapy.[38] This study highlights the importance of making patients feel that their treatment preference is being taken into account by their clinicians. When discussing treatment preferences, clinicians should provide education about any potential adverse effects.

Treatment expectations. Clinicians must ensure that patient expectations of the efficacy of treatment match what is known about the treatment, especially when patients have excessive pessimism. A small study by Krell and colleagues[39] was conducted to determine how patients' pretreatment attitudes modulate response to an antidepressant. Patients who expected their treatment to be "very effective" had a 90% response rate, while only 33% of patients who expected treatment to be "somewhat effective" responded.[39]

Clinicians also need to identify and address negative feelings in patients before and during a treatment change. A study[40] examined the effects of hopelessness about recovery among 312 patients with MDD receiving an 8-week course of fluoxetine. After accounting for depressive severity at baseline, the investigators discovered that patients with higher scores on the Beck Hopelessness Scale at baseline had an increased risk of nonresponse to treatment ($P < .05$).[40]

Avoiding Pitfalls

Augmenting and combining treatments. When polypharmacy is used, such as augmentation and combination, clinicians should be aware of cytochrome P450 interactions with various antidepressant agents. For example, when augmenting aripiprazole[41] with either fluoxetine[42] or paroxetine,[43] because of 2D6 inhibition by the antidepressants, a halving of the aripiprazole dose is recommended. Carbamazepine[44] has been shown to induce 3A4 and therefore requires a doubling of the aripiprazole dose. As for quetiapine,[45] when used with 3A4 inhibitors, a reduction of the dose is necessary; with 3A4 inducers, an increase of the dose is necessary. Olanzapine[46] is sensitive to 1A2 metabolism, so, when it is combined with inhibitors such as fluvoxamine,[47] a lower dose is required; whereas, with inducers such as carbamazepine, a dose increase is necessary. Brexpiprazole, a newly approved atypical antipsychotic as an adjunctive therapy for MDD, requires a halving of the dose when augmented with strong CYP2D6 or CYP3A4 inhibitors and a quartering of the dose if the patient is known to be a poor metabolizer of CYP2D6 or

if they are also taking a drug that is a strong or moderate CYP3A4 inhibitor.[48]

Combination therapy requires clinicians to be aware of the potential interactions around the 2B6 and 2D6 systems between bupropion[49] and other antidepressants, the 3A4 system interactions when prescribing mirtazapine,[50] and the rare but real potential for serotonin syndrome when combining different serotonergic drugs. The situation becomes more complicated when patients possess genotypes associated with ultrarapid metabolism or slow metabolism with one of these enzyme systems. For these cases, genetic testing can be helpful.

Switching treatments. When switching medications, clinicians must be mindful of SSRI withdrawal syndrome, especially when reducing the dosage of serotonin reuptake inhibitor drugs with a short half-life, such as paroxetine and venlafaxine. Withdrawal symptoms include dizziness, insomnia, nervousness, and agitation.[51] Rosenbaum et al[51] conducted a 4-week study of 220 patients who had achieved remission from MDD to observe the effects following temporary (5–8 days) discontinuation of fluoxetine, sertraline, or paroxetine. Following the discontinuation of medication, patients treated with fluoxetine, which has a longer half-life than the other agents, experienced fewer bothersome withdrawal symptoms than patients treated with sertraline and paroxetine ($P < .001$).[51] During a switch, withdrawal symptoms should be distinguished from adverse events of the oncoming drug and from symptom worsening. The Discontinuation-Emergent Signs and Symptoms scale[51] can assist clinicians in correctly identifying withdrawal symptoms.

Serotonin syndrome, or hypertensive reaction or crisis, is also important to identify. Patients with serotonin syndrome typically have at least 3 of the following symptoms: mental status changes, agitation, myoclonus, hyperreflexia, fever, shivering, diaphoresis, ataxia, and diarrhea, with or without hypertension.[52] The majority of reports surrounding serotonin syndrome have been found in patients who have combined over-the-counter medications, tricyclic antidepressants, or an SSRI with a monoamine oxidase inhibitor (MAOI).[52] Fluoxetine, specifically, is known to increase a patient's risk of developing serotonin syndrome during a medication switch because its active metabolite has a long half-life, lasting up to 14 days in some patients.[52] Clinicians should be especially vigilant when using agents that have "hidden" serotonin-norepinephrine reuptake inhibitor effects, such as MAOIs, ziprasidone[53,54] and quetiapine.[55]

CONCLUSION

Like all medical interventions, antidepressant therapies may not succeed in some patients. Three of the main reasons to alter the treatment regimen are insufficient symptom improvement, intolerance to treatment, and illness recurrence. By focusing on early detection and timely treatment changes, clinicians may be able to increase their patients' chances of achieving and maintaining remission. Clinician vigilance, the regular use of standardized scales, frequent follow-up visits, and expansive patient-clinician communication are key factors to the success of any treatment regimen. If a treatment regimen is not reaching clinical expectations, careful consideration of the patient's history, and possibly genetics, may lead clinicians to consider strategies such as augmenting, combining, or switching therapies.

Drug names: aripiprazole (Abilify and others), brexpiprazole (Rexulti), bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Tegretol, Equetro, and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), mirtazapine (Remeron and others), olanzapine (Zyprexa and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), ziprasidone (Geodon and others).

Disclosure of off-label usage: Dr Papakostas 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. World Health Organization. Depression: Fact Sheet No. 369. Published October 2012. http://www.who.int/mediacentre/factsheets/fs369/en/. Accessed November 10, 2015.
2. Gelenberg AJ, Freeman MP, Markowitz JC, et al. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder.* Arlington, VA: American Psychiatric Association; 2010.
3. Papakostas GI, Fava M. *Pharmacotherapy for Depression and Treatment-Resistant Depression.* 1st ed. Singapore: World Scientific Publishing; 2010.
4. Judd LL, Paulus MJ, Schettler PJ, et al. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? *Am J Psychiatry.* 2000;157(9):1501–1504.
5. Miller IW, Keitner GI, Schatzberg AF, et al. The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. *J Clin Psychiatry.* 1998;59(11):608–619.
6. Asarnow JR, Porta G, Spirito A, et al. Suicide attempts and nonsuicidal self-injury in the treatment of resistant depression in adolescents: findings from the TORDIA study. *J Am Acad Child Adolesc Psychiatry.* 2011;50(8):772–781.
7. Scherrer JF, Chrusciel T, Garfield LD, et al. Treatment-resistant and insufficiently treated depression and all-cause mortality following myocardial infarction. *Br J Psychiatry.* 2012;200(2):137–142.
8. Banankhah SK, Friedmann E, Thomas S. Effective treatment of depression improves post-myocardial infarction survival. *World J Cardiol.* 2015;7(4):215–223.
9. Judd LL, Akiskal HS, Paulus MP. The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder. *J Affect Disord.* 1997;45(1-2):5–17.
10. Olin B, Jayewardene AK, Bunker M, et al. Mortality and suicide risk in treatment-resistant depression: an observational study of the long-term impact of intervention. *PLoS ONE.* 2012;7(10):e48002.
11. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? a meta-regression of double-blind, randomized clinical trials in MDD. *Eur Neuropsychopharmacol.* 2009;19(1):34–40.
12. Petersen T, Papakostas GI, Posternak MA, et al. Empirical testing of two models for staging antidepressant treatment resistance. *J Clin Psychopharmacol.* 2005;25(4):336–341.
13. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry.* 2003;53(8):649–659.
14. Nierenberg AA, DeCecco LM. Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. *J Clin Psychiatry.* 2001;62(suppl 16):5–9.
15. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134(4):382–389.
16. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23(1):56–62.
17. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry.* 2003;54(5):573–583.
18. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief

depression severity measure. *J Gen Intern Med.* 2001;16(9):606–613.
19. Nierenberg AA, Husain MM, Trivedi MH, et al. Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report. *Psychol Med.* 2010;40(1):41–50.
20. Papakostas GI, Petersen T, Denninger JW, et al. Psychosocial functioning during the treatment of major depressive disorder with fluoxetine. *J Clin Psychopharmacol.* 2004;24(5):507–511.
21. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006;163(11):1905–1917.
22. Hunot VM, Horne R, Leese MN, et al. A cohort study of adherence to antidepressants in primary care: the influence of antidepressant concerns and treatment preferences. *Prim Care Companion J Clin Psychiatry.* 2007;9(2):91–99.
23. Zimmerman M, Posternak M, Friedman M, et al. Which factors influence psychiatrists' selection of antidepressants? *Am J Psychiatry.* 2004;161(7):1285–1289.
24. Hu XH, Bull SA, Hunkeler EM, et al. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. *J Clin Psychiatry.* 2004;65(7):959–965.
25. Fava M, Graves LM, Benazzi F, et al. A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment. *J Clin Psychiatry.* 2006;67(11):1754–1759.
26. Papakostas GI, Perlis RH, Seifert C, et al. Antidepressant dose reduction and the risk of relapse in major depressive disorder. *Psychother Psychosom.* 2007;76(5):266–270.
27. Lam RW, Saragoussi D, Danchenko N, et al. Psychometric validation of Perceived Deficits Questionnaire–Depression (PDQ-D) in patients with major depressive disorder (MDD). *Value Health.* 2013;16(7):A330.
28. Papakostas GI, Culpepper L. Understanding and managing cognition in the depressed patient. *J Clin Psychiatry.* 2015;76(4):418–425.
29. Labbate LA, Lare SB. Sexual dysfunction in male psychiatric outpatients: validity of the Massachusetts General Hospital Sexual Functioning Questionnaire. *Psychother Psychosom.* 2001;70(4):221–225.
30. McGahuey CA, Gelenberg AJ, Laukes CA, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. *J Sex Marital Ther.* 2000;26(1):25–40.
31. Montejo-González AL, Llorca G, Izquierdo JA, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther.* 1997;23(3):176–194.
32. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
33. Thase ME, Gelenberg A, Kornstein SG, et al. Comparing venlafaxine extended release and fluoxetine for preventing the recurrence of major depression: results from the PREVENT study. *J Psychiatr Res.* 2011;45(3):412–420.
34. Kornstein SG. Maintenance therapy to prevent recurrence of depression: summary and implications of the PREVENT study. *Expert Rev Neurother.* 2008;8(5):737–742.
35. Kuyken W, Hayes R, Barrett B, et al. The effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse/recurrence: results of a randomised controlled trial (the PREVENT study). *Health Technol Assess.* 2015;19(73):1–124.
36. Furukawa TA, Takeuchi H, Hiroe T, et al. Symptomatic recovery and social functioning in major depression. *Acta Psychiatr Scand.* 2001;103(4):257–261.
37. Zimmerman M, McGlinchey JB, Posternak MA, et al. How should remission from depression be defined? The depressed patient's perspective. *Am J Psychiatry.* 2006;163(1):148–150.
38. Kocsis JH, Leon AC, Markowitz JC, et al. Patient preference as a moderator of outcome for chronic forms of major depressive disorder treated with nefazodone, cognitive behavioral analysis system of psychotherapy, or their combination. *J Clin Psychiatry.* 2009;70(3):354–361.
39. Krell HV, Leuchter AF, Morgan M, et al. Subject expectations of treatment effectiveness and outcome of treatment with an experimental antidepressant. *J Clin Psychiatry.* 2004;65(9):1174–1179.
40. Papakostas GI, Petersen T, Homberger CH, et al. Hopelessness as a predictor of non-response to fluoxetine in major depressive disorder. *Ann Clin Psychiatry.* 2007;19(1):5–8.
41. Abilify (aripiprazole) [package insert]. Tokyo, Japan: Otsuka Pharmaceutical Company; November 2009.
42. Fluoxetine (fluoxetine hydrochloride) capsule [package insert]. Sellersville, PA: Teva Pharmaceuticals, USA Inc; April 2012.
43. Paroxetine [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2007.
44. Tegretol (carbamazepine) [package insert]. East Hanover, NJ: Novartis; February 2009.
45. Seroquel (quetiapine) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2009.
46. Zyprexa (olanzapine) [package insert]. Indianapolis, IN: Eli Lilly and Company; January 2010.
47. Luvox (fluvoxamine) [package insert]. Baltimore, MD: Jazz Pharmaceuticals, Inc; July 2014.
48. Rexulti (brexpiprazole) [package insert]. Rockville, MD: Otsuka America Pharmaceutical, Inc; July 2015.
49. Bupropion [package insert]. Greenville, NC: GlaxoSmithKline; 2009.
50. Remeron (mirtazapine) [package Insert]. Kenilworth, NJ: Schering Corp; 2009.
51. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biol Psychiatry.* 1998;44(2):77–87.
52. Rapaport MH. Dietary restrictions and drug interactions with monoamine oxidase inhibitors: the state of the art. *J Clin Psychiatry.* 2007;68(suppl 8):42–46.
53. Geodon (ziprasidone) [package insert]. New York, NY: Pfizer Inc; November 2009.
54. Stahl SM, Shayegan DK. The psychopharmacology of ziprasidone: receptor-binding properties and real-world psychiatric practice. *J Clin Psychiatry.* 2003;64(suppl 19):6–12.
55. Jensen NH, Rodriguiz RM, Caron MG, et al. *N*-desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-HT_{1A} agonist, as a putative mediator of quetiapine's antidepressant activity. *Neuropsychopharmacology.* 2008;33(10):2303–2312.