Identifying Difficult-to-Treat Depression: Differential Diagnosis, Subtypes, and Comorbidities

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Treatment-resistant depression (TRD) is a common clinical presentation responsible for much of the burden of major depressive disorder worldwide. For this reason, TRD requires aggressive identification and management. Although several models have been proposed to describe TRD, consensus is still needed on the criteria (ie, dose, duration, compliance, number of trials required) used to define treatment response and resistance. When diagnosing patients with depression, clinicians should identify risk factors associated with treatment resistance, including clinical subtypes of depression and medical or psychiatric comorbidities that could affect the course of treatment. When evaluating a patient who has not responded to a first course of antidepressant treatment, the clinician should verify the primary diagnosis and ensure that the patient has adhered to a treatment regimen that was of adequate dose and duration.

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Depression is recognized as a major public health problem and a leading cause of disease burden worldwide.[1] Because more than half of all patients with depression do not achieve remission after first-line antidepressant treatment,[2] treatment-resistant depression (TRD) accounts for much of the disability and cost associated with the disorder.[3] The greater severity and duration of illness, the higher likelihood of comorbid disorders, and the higher risk of recurrence—all associated with TRD—add to the burden.[4] Better understanding of TRD is needed to more effectively treat this common and—in terms of both human suffering and health care dollars—extremely costly illness.

DEFINITION OF TREATMENT-RESISTANT DEPRESSION

At this time, no agreed-upon definition of TRD exists. A review[5] of randomized controlled trials for therapeutic strategies for TRD chronicled the various criteria that have been used to define treatment nonresponse, and the criteria included failure of treatment to reduce depressive severity by at least 50%, failure to reduce absolute depressive scores below a specific cut-off point or remission threshold, and failure to produce an asymptomatic state. In the studies reviewed, the minimum number and type of failed antidepressant trials required to assess the presence of treatment resistance differed greatly (Table 1). Additionally, various measures were used regarding the necessary dose and duration of the prescribed treatment required to qualify a patient as having treatment resistance. The studies did not consistently assess the patient's degree of adherence to previous antidepressant trials as a factor in treatment resistance, differed on the number of baseline depressive symptoms necessary for enrollment in the trials or did not use baseline at all to determine eligibility, and often employed different assessment scales to determine those symptoms. However, the basic definition of TRD that is emerging from the literature is an inadequate response to at least 2 antidepressant trials of adequate dose, duration, and treatment adherence. Some have suggested that the patient's drug trials should involve 2 different pharmacologic classes before assigning the label of treatment resistance. However, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial[6] data did not support such a distinction; treatment resistance rates did not differ on the basis of switching within or outside the class of the initial agent.

Several methods for staging TRD in a more systematic and consistent way have also been proposed.[7] Most recently, Fekadu et al[8] proposed a staging model that incorporates treatment, severity of illness, and duration of the presenting episode (Table 2). Whether any of these methods have been used consistently is unclear; again, consensus is needed in order to translate a model for staging treatment resistance into widespread clinical practice.

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For Clinical Use

- Treatment-resistant depression is a common clinical presentation and a leading cause of disease burden worldwide.
- Clinicians should identify risk factors for treatment resistance in their patients with depression to guide treatment choices and management.
- Clinicians should evaluate treatment-resistant patients by verifying the initial diagnosis, identifying untreated medical or psychiatric comorbidities, and ensuring patient adherence to a treatment regimen of adequate dose and duration.

RESIDUAL SYMPTOMS AND RELAPSE

Partial response is a serious problem that requires aggressive management, as the presence of residual symptoms puts patients at risk for relapse and recurrence of major depressive disorder (MDD). In one long-term naturalistic study,[9] patients with asymptomatic recovery were approximately 2.5 times more likely to remain well over 10 years of follow-up than patients with residual symptoms, and patients with residual symptoms relapsed to a new major depressive episode 3 times faster than asymptomatic patients.

The STAR*D trial[10] results supported these findings; patients who had more residual symptom domains had a higher risk of relapse. In the trial, approximately one-third (36.8%) of the patients remitted after an initial antidepressant treatment, and another 30.6% remitted after treatment with a second antidepressant.[2] Rates dropped off substantially in the third and fourth steps (13.7% and 13.0%, respectively). However, remission was associated with a better prognosis at follow-up, even if that remission required several treatments.

DIAGNOSTIC STRATEGIES TO IMPROVE TREATMENT RESPONSE

Several risk factors for inadequate response to antidepressant treatment have been identified, including misdiagnosis, specific depressive subtypes, and psychiatric and medical comorbidities. Physician-related factors and individual patient compliance or pharmacokinetics can also play a role. A key initial strategy for clinicians then is to identify those patients who are at risk of nonresponse or partial response and aggressively treat and monitor them.

Differential Diagnosis

When a patient appears to have TRD, the first question a clinician should ask is whether the primary diagnosis is correct. The initial differential diagnosis may not have uncovered factors that are affecting treatment. For example, is there a primary disorder, such as a substance use disorder, that is not being treated? Does the patient have an untreated primary medical condition? Rather than treatment resistance, the patient's problem may actually be related to receiving treatment for an incorrect diagnosis.

Subtypes

The patient's apparent treatment resistance may also be related to the presence of a different primary disorder (eg, a bipolar disorder presenting with a current depressive episode, or a dysthymia) or an undiagnosed depressive subtype that might require different treatment than pure MDD (Table 3).[11,12] Clinically relevant subtypes include psychotic depression, atypical depression, chronic depression, and severe depression.

In patients with bipolar disorder, depressive symptoms are more prevalent than manic symptoms, making it more likely that a patient will present in a depressive episode.[13,14] Bipolar depressive episodes can be difficult to distinguish from MDD, so obtaining key facts from the patient's history as well as corroborating information from friends and family of the patient may be necessary to identify a bipolar history.

Atypical depression is characterized by reversed vegetative signs such as oversleeping, overeating, rejection sensitivity, leaden paralysis, and reactive mood. Patients with atypical depression appear to respond preferentially to treatment with monoamine oxidase inhibitors.[15,16]

Depression with psychotic features is relatively common and is associated with longer time to syndromal recovery and a higher likelihood of severe depression.[17] However, psychotic features can be present in patients with mild or moderate depressive episodes.[18] Determining the presence of psychotic symptomatology can be difficult but is important because antidepressant monotherapy may exacerbate psychotic symptoms,[19] and antipsychotic agents may be needed.

Dysthymic disorder, a chronic low-grade but impairing depressive subtype, puts patients at risk of difficult-to-treat depression. More than 75% of patients with dysthymic disorder will meet the criteria for a major depressive episode at some point,[20] and this double depression (MDD superimposed on dysthymic disorder) is associated with a high rate of relapse and a protracted course of illness.[21,22]

Depressive severity is an important additional specifier that indicates risk of a difficult-to-treat depression.[23] Greater severity is associated with more comorbidities, longer time to achieve response, greater functional impairment, a greater risk of recurrent episodes, and a greater likelihood

Table 1. Categorical Definitions of Treatment-Resistant Depression According to Current Randomized Controlled Trials[a]

Required Number/Type of Previous Antidepressant (AD) Trials	Number of Studies (%)
= 1 trial	5 (10.6)
≥ 1 trial	8 (17)
= 2 trials	6 (12.8)
= 2 trials with DIFF ADs	3 (6.4)
≥ 2 trials	9 (19.1)
≥ 2 trials with DIFF ADs	8 (17)
NA	8 (17)

[a]Reprinted with permission from Berlim and Turecki.[5]
Abbreviations: DIFF = different classes and/or mechanisms of action, NA = information not available.

of suicidal ideation.[4] The STAR*D[24] study found that patients with greater symptom severity were approximately 3 times less likely to remit than those with mild or moderate depression.

Chronic depression, in which patients are symptomatic more days than not over a 2-year period, is associated with a high rate of treatment resistance.[23] A study[25] that contrasted patients with chronic depression with patients with episodic depression (in which patients reach full remission between the 2 most recent depressive episodes) showed that patients with chronic depression had more comorbid anxiety-related and somatic syndromes, had an earlier age at onset of symptoms, and needed treatment more often than patients with episodic depression.

Comorbidities

Comorbid psychiatric disorders. Anxiety disorders commonly coexist with major depression.[26] These comorbidities increase the likelihood of greater severity of depressive symptoms, a history of suicide attempts, decreased responsiveness to treatment, and greater susceptibility to side effects.[23,24,26] The more clinically relevant of these disorders include social anxiety disorder, posttraumatic stress disorder, panic disorder, obsessive-compulsive disorder, and generalized anxiety disorder. Variables associated with treatment resistance in a study of MDD are listed in Table 4, and comorbid anxiety disorder was found to have the highest statistical significance.

Additional comorbid diagnoses important for the clinician to identify are substance use and personality disorders, both of which are indicators of a harder-to-treat depression that may require multiple treatment modalities. Substance use or dependence disorders frequently co-occur with depression and are associated with increased symptom severity and a lower likelihood of remission.[24,27] Even among patients with depression who do not abuse alcohol, the degree of alcohol use at baseline—including even moderate consumption—correlates with poorer response to antidepressant treatment.[28] Personality disorders have been implicated as a factor in treatment resistance to antidepressants, particularly in relation to tricyclic antidepressants.[23]

Table 2. Maudsley Staging Parameters and Suggested Scoring Conventions[a]

Parameter/Dimension	Parameter Specification	Score
Duration	Acute (≤ 12 months)	1
	Subacute (13–24 months)	2
	Chronic (> 24 months)	3
Symptom severity (at baseline)	Subsyndromal	1
	Syndromal	
	Mild	2
	Moderate	3
	Severe without psychosis	4
	Severe with psychosis	5
Treatment failures		
Antidepressants	Level 1: 1–2 medications	1
	Level 2: 3–4 medications	2
	Level 3: 5–6 medications	3
	Level 4: 7–10 medications	4
	Level 5: > 10 medications	5
Augmentation	Not used	0
	Used	1
Electroconvulsive therapy	Not used	0
	Used	1
Total		(15)

[a]Reprinted with permission from Fekadu et al.[8] Resistance may be presented as a single numerical digit between 3 and 15; as 1 of 3 severity categories (mild, scores = 3–6; moderate, scores = 7–10; severe, scores = 11–15); or descriptively, incorporating the main factors in the description (eg, moderate, subacute level 2 resistance).

The STAR*D study provided information on the clinical relevance of comorbid symptom clusters—as opposed to full comorbid diagnoses—that can increase the likelihood of TRD. Patients with major depression with anxious features were approximately one-third as likely to remit compared to those without these features.[29] Additionally, patients with melancholic features appear less likely to remit.[24,30]

Comorbid medical disorders. Comorbid medical conditions are a risk factor for nonresponse to treatment and for recurrent depressive episodes, underscoring the need for a complete patient history and physical and laboratory evaluation.[31,32] Further, Iosifescu et al[33] showed that the correlation between poor treatment response and medical comorbidity increases with the overall burden of comorbid medical illness, with a patient's likelihood of responding to treatment decreasing by approximately 20% for each additional organ system affected by illness.

Many medical conditions are associated with an increased likelihood of MDD treatment resistance. For example, patients with greater numbers of cardiovascular disease risk factors (including diabetes, hypertension, and hypercholesterolemia) have higher rates of treatment resistance than patients with fewer risk factors.[34] Chronic painful conditions are reported among more than 40% of patients with MDD and are associated with a greater severity and longer duration of depressive symptoms.[35] Other medical conditions highly comorbid with depression include cancer,[36] hypertension,[37] stroke,[38] Parkinson's disease, dementia, and migraine.[39]

Specific medical conditions may be associated with particular types of depression, which could affect treatment choice. A STAR*D report[40] found that patients with MDD

Table 3. Paradigm Errors Identifying Potential Antidepressant Treatment Failure[a]

Paradigm Error	Description	Quantifying Data
Paradigm error 1	Failure to diagnose and manage bipolar disorder	>30% of patients never diagnosed with or treated for bipolar disorder
Paradigm error 2	Failure to diagnose and manage psychotic depression	5 patients (3%) incorrectly diagnosed with psychotic depression by referring physician
Paradigm error 3	Failure to diagnose and manage melancholic depression	>70% of patients misdiagnosed with non-melancholic depression by referring physician (46% satisfied criteria for DSM-IV melancholia; 28% for clinical melancholia). ≤77% of patients treated with an SSRI rather than a TCA, MAOI, or SNRI
Paradigm error 4	Diagnosing and/or managing a nonmelancholic condition as if it were melancholic depression	54 patients misdiagnosed with melancholic depression. 93% experienced ≥1 contributing psychosocial factor. Adequate psychotherapy (91%) and/or social support/interventions (59%) were not administered to address these factors
Paradigm error 5	Misdiagnosing secondary depression	Comorbid psychiatric conditions (ie, anxiety, panic, social phobia, obsessive-compulsive behavior, and other personality functioning disorders) found to be inadequately diagnosed in patients
Paradigm error 6	Failing to identify organic determinants	≤10% of patients assessed to have other medical conditions, such as dementia or stroke, which had not been considered as contributing to patient's depression

[a]Reprinted with permission from Souery et al.[7] Based on data from Parker et al.[11]
Abbreviations: MAOI = monoamine oxidase inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Table 4. Factors Associated With Treatment Resistance (2-step logistic regression model using nonresistance/resistance as the dependent variable), N = 702[a,b]

	Initial Univariate Logistic Regression		
Variable	*P* Value	Odds Ratio	95% CI of Odds Ratio
Comorbid anxiety disorder	<.001	2.6	1.8 to 3.6
Comorbid panic disorder	<.001	3.2	2.1 to 5.0
Current suicidal risk	<.001	2.2	1.6 to 3.0
Severe intensity vs moderate intensity	.001	1.7	1.2 to 2.3
No. of hospitalizations >1	.003	1.6	1.2 to 2.1
Social phobia	.008	2.1	1.2 to 3.6
Recurrent episodes vs single episode	.009	1.5	1.1 to 2.0
Age at onset before 18 y	.009	2.0	1.2 to 3.3
Melancholic features	.018	1.5	1.1 to 2.3
Nonresponse to first antidepressant treatment lifetime	.019	1.6	1.1 to 2.5
Personality disorder (*DSM-IV* criteria)	.049	1.7	1.0 to 2.9

[a]Reprinted with permission from Souery et al.[12]
[b]Table includes only variables where $P < .05$. Variables are ranked from highest to lowest level of statistical significance on the basis of the univariate analysis.

and diabetes were more likely to experience certain physical symptoms of depression (eg, increased appetite, psychomotor slowing, and leaden paralysis) than patients with MDD without diabetes. Hypothyroidism is recognized as a cause of depression, but subclinical hypothyroidism has also been associated with an increased prevalence of depressive and anxiety symptoms and with refractory depression.[41–43]

Some medications used for somatic conditions, including opiate analgesics and calcium channel blockers, are associated with either causing or exacerbating depression, at least in certain subsets of the population.[44] Especially strong evidence is available for the corticosteroids[44] and the interleukins and interferons.[45,46]

Clinician and Patient Risk Factors

Several factors should be considered when evaluating a patient who has not responded to an initial course of treatment. Once the clinician has established that another primary psychiatric disorder or depressive subtype has not gone undiagnosed, he or she should then verify that the dose and duration of the antidepressant treatment trial was adequate. Prescribing inadequate doses of medication for an inadequate period of time can contribute to patients being incorrectly labeled as treatment resistant.[47,48] The STAR*D trial[31] results have provided support for the need for longer periods of treatment and for adequate dosing strategies tailored to individual patients for optimal outcomes.

Patient factors such as noncompliance with treatment[47] or unusual pharmacokinetics[49] can contribute to difficult-to-treat depression. A patient who is a poor metabolizer may be especially sensitive to adverse side effects despite receiving the standard dose of an antidepressant, whereas a patient with an ultrarapid metabolism may need higher doses of the same medication to achieve response.[49] Lack of response and intolerable side effects contribute to poor treatment adherence, which may account for as many as 20% of patients labeled as treatment resistant.[50] Other factors that may affect treatment adherence are the ease of use and cost of a particular agent, the treatment history of the patient, and the patient's family members.

CONCLUSION

Treatment-resistant depression is a common clinical presentation that requires aggressive identification and management. However, consensus is needed on the criteria used to define treatment response and resistance. When evaluating patients with apparent treatment resistance, clinicians should clarify that the primary diagnosis is correct, identify particular clinical subtypes that increase

the risk of TRD, ascertain whether psychiatric or medical comorbidities or medications that might affect the course of treatment are present, and ensure that the patient is adhering to a treatment regimen of adequate dose and duration. Properly evaluating treatment resistance risk factors can guide the clinician in choosing treatment strategies for optimum outcomes for individual patients.

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. Ustün TB, Ayuso-Mateos JL, Chatterji S, et al. Global burden of depressive disorders in the year 2000. *Br J Psychiatry.* 2004;184(5):386–392.
2. Rush AJ, Trivedi JH, 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.
3. Crown WH, Finkelstein S, Berndt ER, et al. The impact of treatment-resistant depression on health care utilization and costs. *J Clin Psychiatry.* 2002;63(11):963–971.
4. Thase ME. Treatment of severe depression. *J Clin Psychiatry.* 2000; 61(suppl 1):17–25.
5. Berlim MT, Turecki G. What is the meaning of treatment resistant/ refractory major depression (TRD)? a systematic review of current randomized trials. *Eur Neuropsychopharmacol.* 2007;17(11):696–707.
6. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion SR, sertraline, or venlafaxine XR after failure of SSRIs for depression. *N Engl J Med.* 2006;354(12):1231–1242.
7. Souery D, Papakostas GI, Trivedi MH. Treatment-resistant depression. *J Clin Psychiatry.* 2006;67(suppl 6):16–22.
8. Fekadu A, Wooderson S, Donaldson D, et al. A multidimensional tool to quantify treatment resistance in depression: the Maudsley staging method. *J Clin Psychiatry.* 2009;70(2):177–184.
9. 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.
10. 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. [Published online ahead of print May 22, 2009.] *Psychol Med*.
11. Parker GB, Malhi GS, Crawford JG, et al. Identifying "paradigm failures" contributing to treatment-resistant depression. *J Affect Disord.* 2005;87:185–191.
12. Souery D, Oswald P, Massat I, et al. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. *J Clin Psychiatry.* 2007;68(7):1062–1070.
13. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry.* 2002;59(6):530–537.
14. Kupfer DJ, Frank E, Grochocinski VJ, et al. Demographic and clinical characteristics of individuals in a bipolar disorder case registry. *J Clin Psychiatry.* 2002;63(2):120–125.
15. Quitkin FM, Stewart JW, McGrath PJ, et al. Phenelzine versus imipramine in the treatment of probable atypical depression: defining syndrome boundaries of selective MAOI responders. *Am J Psychiatry.* 1988;145(3):306–311.
16. Liebowitz MR, Quitkin FM, Stewart JW, et al. Antidepressant specificity in atypical depression. *Arch Gen Psychiatry.* 1988;45(2):129–137.
17. Maj M, Pirozzi R, Magliano L, et al. Phenomenology and prognostic significance of delusions in major depressive disorder: a 10-year prospective follow-up study. *J Clin Psychiatry.* 2007;68(9):1411–1417.
18. Ohayon MM, Schatzberg A. Prevalence of depressive episodes with psychotic features in the general population. *Am J Psychiatry.* 2002;159(11):1855–1861.
19. Kantrowitz JT, Tampi RR. Risk of psychosis exacerbation by tricyclic antidepressants in unipolar major depressive disorder with psychotic features. *J Affect Disord.* 2008;106(3):279–284.
20. Keller MB, Klein DN, Hirschfeld RMA, et al. Results of the DSM-IV Mood Disorders Field Trial. *Am J Psychiatry.* 1995;152(6):843–849.
21. Klein DN, Shankman SA, Rose S. Ten-year prospective follow-up study of the naturalistic course of dysthymic disorder and double depression. *Am J Psychiatry.* 2006;163(5):872–880.
22. Rhebergen D, Beekman AT, Graaf RD, et al. The three-year naturalistic course of major depressive disorder, dysthymic disorder and double depression. *J Affect Disord.* 2009;115(3):450–459.
23. Kornstein SG, Schneider RK. Clinical features of treatment-resistant depression. *J Clin Psychiatry.* 2001;62(suppl 16):18–25.
24. Rush AJ, Wisniewski SR, Warden D, et al. Selecting among second-step antidepressant medication monotherapies: predictive value of clinical, demographic, or first-step treatment features. *Arch Gen Psychiatry.* 2008;65(8):870–880.
25. Angst J, Gamma A, Rössler W, et al. Long-term depression versus episodic major depression: results from the prospective Zurich study of a community sample. *J Affect Disord.* 2009;115(1–2):112–121.
26. Gaynes BN, Magruder KM, Burns BJ, et al. Does a coexisting anxiety disorder predict persistence of depressive illness in primary care patients with major depression? *Gen Hosp Psychiatry.* 1999;21(3):158–167.
27. Ostacher MJ. Comorbid alcohol and substance abuse dependence in depression: impact on the outcome of antidepressant treatment. *Psychiatr Clin North Am.* 2007;30(1):69–76.
28. Worthington J, Fava M, Agustin C, et al. Consumption of alcohol, nicotine, and caffeine among depressed outpatients: relationship with response to treatment. *Psychosomatics.* 1996;37(6):518–522.
29. Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in patients with anxious versus nonanxious depression: a STAR*D report. *Am J Psychiatry.* 2008;165(3):342–351.
30. McGrath PJ, Khan AY, Trivedi MH, et al. Response to a selective serotonin reuptake inhibitor (citalopram) in major depressive disorder with melancholic features: a STAR*D report. *J Clin Psychiatry.* 2008; 69(12):1847–1855.
31. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry.* 2006;163(1):28–40.
32. Swindle RW Jr, Cronkite RC, Moos RH. Risk factors for sustained nonremission of depressive symptoms: a 4-year follow-up. *J Nerv Ment Dis.* 1998;186(8):462–469.
33. Iosifescu DV, Nierenberg AA, Alpert JE, et al. The impact of medical comorbidity on acute treatment in major depressive disorder. *Am J Psychiatry.* 2003;160(12):2122–2127.
34. Iosifescu DV, Clementi-Craven N, Fraguas R, et al. Cardiovascular risk factors may moderate pharmacological treatment effects in major depressive disorder. *Psychosom Med.* 2005;67(5):703–706.
35. Ohayon MM. Specific characteristics of the pain/depression association in the general population. *J Clin Psychiatry.* 2004;65(suppl 12):5–9.
36. Evans DL, Staab JP, Petitto JM, et al. Depression in the medical setting: biopsychological interactions and treatment considerations. *J Clin Psychiatry.* 1999;60(suppl 4):40–55.
37. Bosworth HB, Bartash RM, Olsen MK, et al. The association of psychosocial factors and depression with hypertension among older adults. *Int J Geriatr Psychiatry.* 2003;18(12):1142–1148.
38. Hackett ML, Yapa C, Parag V, et al. Frequency of depression after stroke: a systematic review of observational studies. *Stroke.* 2005; 36(6):1330–1340.
39. Nuyen J, Schellevis FG, Satariano WA, et al. Comorbidity was associated with neurologic and psychiatric diseases: a general practice-based controlled study. *J Clin Epidemiol.* 2006;59(12):1274–1284.
40. Bryan CJ, Songer TJ, Brooks MM, et al. A comparison of baseline sociodemographic and clinical characteristics between major depressive disorder patients with and without diabetes: a STAR*D report. *J Affect Disord.* 2008;108(1–2):113–120.
41. Guimarães JM, de Souza Lopes C, Baima J, et al. Depression symptoms and hypothyroidism in a population-based study of middle-aged Brazilian women. [Published online ahead of print January 23, 2009.] *J Affect Disord*.
42. Almeida C, Brasil MA, Costa AJ, et al. Subclinical hypothyroidism: psychiatric disorders and symptoms. *Rev Bras Psiquiatr.* 2007;29(2):157–159.
43. Howland RH. Thyroid dysfunction in refractory depression: implications for pathophysiology and treatment. *J Clin Psychiatry.* 1993;54(2):47–54.
44. Patten SB, Lavorato DH. Medication use and major depressive syndrome in a community population. *Compr Psychiatry.* 2001;42(2):124–131.

45. Wilson DR, Warise L. Cytokines and their role in depression. *Perspect Psychiatr Care.* 2008;44(4):285–289.
46. Van De Putte DE, Fischer K, Posthouwer D, et al. Occurrence, course and risk factors of depression during antiviral treatment for chronic hepatitis C in patients with inherited bleeding disorders: a prospective study. *Haemophilia.* 2009;15(2):544–551.
47. Hirschfeld RM, Keller MB, Panico S, et al. The National Depressive and Manic-Depressive Association Consensus Statement on the Undertreatment of Depression. *JAMA.* 1997;277(4):333–340.
48. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA.* 2003;289(23):3095–3105.
49. Bertilsson L, Dahl ML, Tybring G. Pharmacogenetics of antidepressants: clinical aspects. *Acta Psychiatr Scand Suppl.* 1997;391:14–21.
50. Souery D, Mendlewicz J. Compliance and therapeutic issues in resistant depression. *Int Clin Psychopharmacol.* 1998;13(suppl 2):S13–S18.