

Difficult-to-Treat Depressions: A Primary Care Perspective

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Depression is common in primary care and more difficult to treat than many clinicians are aware. The goal of treatment is symptomatic remission, and by current estimates 50% or more of patients treated with antidepressant monotherapy may suffer from residual neurovegetative, cognitive, and somatic symptoms. Bipolar disorder, in particular, is more prevalent in primary care than previously recognized, is easily misdiagnosed, and may be a significant source of treatment failure. This article reviews treatment resistance, its causes, and management approaches. Many strategies are straightforward and within the skill set of primary care clinicians. The use of antidepressants with multiple mechanisms of action may reduce first-order resistance. Antidepressant augmentation strategies (e.g., with lithium or atypical antipsychotics) are often very effective and readily instituted by informed and motivated practitioners.

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EMPHASIS ON DEPRESSION IN PRIMARY CARE

The emphasis on recognition and treatment of depression in primary care dates to the late 1980s with studies documenting a significant prevalence of depressive illness in the primary care setting.¹ This development was followed by information that identified the location of mental health services delivery as being primarily in the primary care sector.² That information was additionally buttressed by outcomes investigation indicating that depressive illnesses were disproportionately disabling,³ with only severe coronary artery disease surpassing depression in causing distress and dysfunction in a variety of areas.

The discovery that primary care was filled with patients suffering from depression coincided with the introduction of the first selective serotonin reuptake inhibitor (SSRI), fluoxetine, an agent offering the promise of a combination of efficacy, safety, and tolerability heretofore unavailable in antidepressant medications. Fluoxetine was followed by a number of other SSRIs and novel antidepressants. The 1990s can truly be called the “decade of the antidepressant” in primary care, with government, industry, and advocacy

groups pushing depression awareness, recognition, and treatment. Yet, years of increasing antidepressant use in primary care have highlighted an unanticipated (from the standpoint of primary care clinicians) reality about depression treatment—antidepressants do not work as well as we had been led to believe, or depression is much harder to treat than expected on the basis of the content of current medical education. Perhaps it is a combination of factors.

Depression, an illness still surrounded by mystery and negative stigmata, fits more into chronic illness models for clinical approach, level of clinical challenge, and strength of therapeutic alliance and resources required for optimal management. Patients may also have health beliefs that negatively influence medication adherence and psychosocial contexts that do not support wellness. Clinicians may not approach diagnosis and treatment in a methodical, stepwise fashion because of the limitations of medical education and practice mechanics.

Without minimizing these broader obstacles to success in management, there is an emerging understanding of the limitations of available antidepressant agents in clinical populations. A recent meta-analysis by Thase et al.⁴ served to underscore the suspicions of others when it suggested that dual reuptake agents like tricyclic antidepressants (TCAs) and venlafaxine have higher remission rates in controlled trials compared with SSRIs. However, even remission rates for venlafaxine have a ceiling of about 45%. Remission rates for SSRIs are in the 30% to 35% range. This limitation, combined with previously mentioned obstacles, leaves primary care clinicians and patients with real success rates in depression treatment that are substantially less than ideal. More correctly, effectiveness lags efficacy to a surprising degree. Additionally,

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cases of antidepressant-related activation, agitation, anxiety, and hypomania/mania are not uncommon.⁵⁻⁷ Such reactions are counterintuitive to primary care clinicians and may lead to further doubts about the validity of illness and treatment paradigms promulgated for their setting.^{8,9} Primary care physicians are often surprised to learn that most patients are treatment resistant. Many clinicians would be interested in proceeding with advanced levels of intervention despite the limitations of antidepressant efficacy if they had access to solid information on the identification, assessment, and approach to the difficult-to-treat patient.

IDENTIFYING DIFFICULT-TO-TREAT DEPRESSIONS IN PRIMARY CARE

Robust (complete) and sustained symptom remission is the goal of depression management. Functional studies of nonresponders and partial responders compared with those achieving symptom remissions demonstrate that only patients with illness remission function at a comparable level to non-ill controls.¹⁰ It is important for clinicians to monitor patients carefully in all phases of treatment and ask specific questions about core symptoms of depression and associated vegetative and cognitive symptoms.

The use of well-researched symptom checklists or rating scales is optimal. Hamilton Rating Scale for Depression scores of less than 7 and Montgomery-Asberg Depression Rating Scale scores of less than 8 are associated with remission. Symptom checklists should be further supplemented by functional assessments such as the DSM-IV Global Assessment of Functioning (GAF).¹¹

Less specific, but useful, indications of difficult-to-treat depressions include persistent high utilization of telephone triage, emergency services, and work-in appointments. Missed work days, frequent use of sick leave or the Family Medical Leave Act, and a persistence of the physical symptoms often associated with depression (e.g., headache, back pain, functional bowel complaints) can also lead one to suspect a less than robust response to treatment.

Causes of Treatment Resistance

A number of factors are associated with treatment resistance to antidepressants.¹²

Problems with medication adherence. Studies suggest that adherence is problematic in many patients, particularly after 10 to 12 weeks of therapy.¹³⁻¹⁵

Lack of adequate dose/duration of treatment. Each antidepressant has an individualized starting and target dose. For most antidepressants, some upward titration is necessary to maximize response and remission. Rapid titration within tolerance limits to the usual maintenance dose may minimize dropouts due to lack of efficacy.

Patients should be made aware of the target dose and expectations about dose adjustment.

Comorbid medical illness. Thyroid illness,¹⁶ hypercortisolism, stroke (particularly in the left middle cerebral artery region), and HIV are examples of comorbid medical illnesses that may be associated with poor antidepressant response. High-risk groups should be screened at baseline, and the treatment of the general medical condition maximized. Treatments of comorbid somatic illness (e.g., centrally acting antihypertensives, corticosteroids, progestins) may also be a hindrance to antidepressant response.

Comorbid substance abuse or dependency. Alcohol use may be associated with decreased antidepressant efficacy.¹⁷ Caffeine use can be associated with increased side effects and failure of some symptoms (e.g., anxiety, insomnia) to improve. Mood disorders themselves are associated with higher rates of substance abuse or chemical dependence, and patients with dual diagnoses will often require consultation or referral.^{18,19}

Difficult psychosocial contexts and Axis II disorders. Family, work, and financial difficulties sometimes produce increased stresses on individuals and may limit their responsiveness to treatment interventions.²⁰

Biological heterogeneity of depressive illness. Genetic factors are likely to play a role in the heterogeneity of clinical response in depression and the interindividual differences in drug-related adverse effects. Research into pharmacogenetic approaches to treatment holds promise.

Undiagnosed bipolar depression. Indirect and direct data suggest that undiagnosed bipolar depression is not an uncommon problem in primary care. Some investigations suggest that 20% to 30% of all anxious and depressed patients may be diagnosed in the bipolar spectrum on the basis of careful interviews and prospective follow-up.^{21,22} Antidepressant "misadventures" (e.g., treatment-emergent hypomania/mania, agitation, and rapid cycling) are not uncommon in primary care settings.

General Approach to the Difficult-to-Treat Depressed Patient

The approach to the difficult-to-treat depressed patient in primary care includes consideration of several areas.

- Is the diagnosis complete and accurate? Bipolar depression may be easily overlooked. Obsessive-compulsive disorder and substance abuse also may go unrecognized.
- Is the patient too sick to manage in the outpatient setting? Are there risk factors for suicide or harm to others?
- Is there a clinician-patient mismatch? Is the required level of empathy and therapeutic alliance present? Does the clinician have the training, experience, and/or proven ability required to treat the patient? Are ancillary resources available?

- Is the clinician familiar and comfortable with strategies that offer a high degree of ease of use, safety, tolerability, and, most importantly, efficacy?

Consultation and referral are often helpful for patients who present diagnostic dilemmas or have not responded to one or more interventions or in situations where there is a clinician-patient mismatch in acuity, knowledge base, or practice resources. That being said, the logistics of consultation/referral may pose obstacles in themselves, and resources may be of varying quality. Indeed, it is a combination of patient reluctance and these obstacles to referral that lead many in primary care to venture into more advanced levels of psychopharmacologic intervention.

Depression, like other chronic illnesses, will benefit from an informed, organized, methodical approach. For difficult cases, I recommend creating a summary page in the medical record outlining the working diagnosis, comorbidities, previous treatments, and interventions. A Mood Disorders Worksheet (Figure 1) captures the essential information and may be helpful to a psychiatrist when a referral is made.

Somatic Strategies for the Difficult-to-Treat Patient

Somatic interventions for difficult-to-treat depressions can be divided into several categories.

Optimization or amplification of antidepressant dosage. This intervention includes both increasing the dose above the usual target range for the antidepressant used and extending the length of treatment past the typical 4- to 8-week duration of the acute phase to 12 to 16 weeks.²³ Both strategies may recruit additional levels of response as long as tolerability is acceptable and the therapeutic alliance supports the strategies. These strategies also assume patient adherence. Monitoring plasma levels may assist in verifying adherence or in achieving nominal plasma levels, although evidence linking specific levels to response is lacking for most agents. Plasma level monitoring may help target a therapeutic window for some antidepressants (e.g., nortriptyline).

Antidepressant switches. Changing antidepressants is usually, but not always,²⁴ accomplished by cross-taper (gradual reduction in dose of primary agent combined with gradual introduction of its replacement). Switches can be within an antidepressant class or to a different class. Switches to a different class attempt to take advantage of different mechanisms of action, dual reuptake inhibition, etc.²⁵ However, switches within a class may also be helpful.^{26,27}

Antidepressant combinations. Combinations of antidepressants have been used to treat side effects of the primary agent (e.g., trazodone to manage insomnia, bupropion for SSRI-related sexual dysfunction). Most antidepressant combinations for difficult-to-treat depressions focus on the combination of synaptic effects afforded by

this strategy. For example, a combination of an SSRI plus a low dose of desipramine or nortriptyline is an attempt to achieve dual monoamine reuptake (serotonin [5-HT] + norepinephrine [NE]) inhibition. Other combinations seek to add α_2 antagonism (mirtazapine) and 5-HT_{1A} antagonism (buspirone, an atypical anxiolytic). Controlled studies of various combinations are lacking.²⁸ The National Institute of Mental Health (NIMH)-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D; Web site <http://www.edc.gsph.pitt.edu/stard/>) trial is underway to compare the efficacy of various approaches.

Antidepressant augmentation. Non-antidepressant medications can be added to antidepressants to overcome both nonresponse and partial response. Some augmentation choices are psychotropic medications themselves. Others are not. The mechanisms by which various augmentation strategies are effective remains unclear.

1. **Lithium.** This is the best-studied augmentation and is most supported by controlled trials.²⁹ Lithium augmentation has the additional advantages of efficacy in acute mania and bipolar disorder and prophylaxis of mania (see below). Lithium augmentation may provide rapid improvement in some patients at low doses, but 6 weeks at a plasma level of at least 0.7 mEq/L should be maintained before assessing its benefits. Lithium's disadvantages include negative stigmata for some patients; the need for plasma level, renal, and thyroid monitoring; annoying side effects (although plasma levels in the lower part of the therapeutic range are often well tolerated); the potential for drug-drug interactions to increase lithium levels (e.g., non-steroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors); the potential for lithium-induced hypothyroidism; and the potential for toxicity. The management of lithium-related hypothyroidism is straightforward with levothyroxine replacement therapy.

2. **Thyroid preparations.** Liothyronine (T₃) is often preferred,³⁰ but some clinicians use levothyroxine for augmentation. Typical T₃ doses are 25–50 mg daily. An adequate trial is 6–8 weeks.³¹ Thyroid augmentation may have an additional use in rapid-cycling bipolar states.³²

3. **Stimulants.** Methylphenidate and dextroamphetamine are the agents most often used in augmentation. Some favor this strategy in depression with comorbid attention-deficit/hyperactivity disorder.

4. **Atypical neuroleptics.** This strategy recalls previous fixed-dose combinations of amitriptyline and perphenazine that fell out of favor because of concerns about tardive dyskinesia. That concern is greatly reduced with the atypical agents. Olanzapine is the member most studied³³; lesser evidence exists for risperidone.^{34,35} The efficacy of olanzapine in combination with fluoxetine has recently been reported in the treatment of bipolar depression.³⁶ Olanzapine (6 or 12 mg/day) plus fluoxetine (25 or 50 mg/day) significantly improved depressive symptoms compared with both

Figure 1. Mood Disorders Worksheet^a

Patient Name: _____ DOB: _____ ID: _____

Working Diagnosis (circle)

Bipolar I (296.7)	Bipolar II (296.89)	Bipolar NOS (296.80)
Dysthymia (300.4)	Major depression, single episode (296.20)	Major depression, recurrent (296.30)
Depression NOS (311)	Adjustment disorder with depressed mood (309.0)	Other _____

Anxiety Comorbidity (circle)

Generalized (300.02) Panic (300.01) OCD (300.3) PTSD (308.81) Social phobia (300.23) Other _____

Substance-Related Comorbidity (circle)

Alcohol abuse (305.00)	Alcohol dependence (303.90)	Cocaine abuse (305.60)
Cocaine dependence (304.20)	Amphetamine abuse (305.70)	Amphetamine dependence (304.40)
Cannabis abuse (305.20)	Cannabis dependence (304.30)	Caffeine-related disorder NOS (292.9)
Other _____		

Axis II Disorder(s) (circle)

Cluster A [Odd] Cluster B [Erratic] Cluster C [Avoidant]

Affective Temperament(s) (circle)

Hyperthymic Dysthymic Cyclothymic Irritable

Longitudinal Course

Age at onset of 1st significant episode _____ Number of episodes _____ Duration of most recent episode _____
 Preceded by NOS prodrome? Yes / No Significant trigger? Yes / No

Pedigree description (attach genogram if available): _____

Bipolar Spectrum Illness

Manic episode? Yes / No	Age at 1st episode _____	Mixed state? Yes / No
Hypomanic episode? Yes / No	Duration ____ mean ____ longest ____	External corroboration? Yes / No
Bipolar or lithium-responding first-degree relative? Yes / No	Loaded pedigree? Yes / No	
First depression prior to age 26 years? Yes / No	Antidepressant-associated mania/hypomania? Yes / No	

NIMH BP II Predictors^b:

Mood lability? Yes / No Energy/activity? Yes / No Intense fantasy? Yes / No Social anxiety? Yes / No

Longitudinal Course Predictors:

Onset < age 25 years? Yes / No > 2 Divorces? Yes / No Seasonality? Yes / No

Other:

Atypical depressions? Yes / No Psychotic features? Yes / No

continued

Figure 1. Mood Disorders Worksheet^a (cont.)

Previous Treatment:

Antidepressant	Month/Year	Maximum Dose	Duration @ Maximum Dose	Response	Remission (Duration)

Mood Stabilizer	Month/Year	Maximum Dose/Blood Level	Duration @ Maximum Dose	Response	Remission (Duration)
Lithium					
Olanzapine					
Divalproex					
Lamotrigine					

Antidepressant Combinations	Month/Year	Maximum Doses	Duration @ Maximum Doses	Response	Remission (Duration)

Adjuvants/Other Augmentations or Strategies	Month/Year	Doses/Type	Duration	Response	Remission (Duration)
Estrogen					
Thyroid					
Benzodiazepine					
Psychotherapy					
ECT					

Comments: _____

^aMethod of J. Sloan Manning, M.D., University of Tennessee, Department of Family Medicine, Memphis. Rev. 7/02.
^bAkiskal HS, Maser JD, Zeller PJ, et al. Switching from unipolar to bipolar II: an 11-year prospective study of clinical and temperamental predictors in 559 patients. Arch Gen Psychiatry 1995;52:114-123.
 Abbreviations: BP II = bipolar II, ECT = electroconvulsive therapy, NIMH = National Institute of Mental Health, NOS = not otherwise specified, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder.

placebo and olanzapine monotherapy. In addition, a pilot study by Shelton and colleagues³⁷ has demonstrated the superior efficacy of olanzapine plus fluoxetine compared with either agent alone in treating patients diagnosed with recurrent, nonbipolar, treatment-resistant depression. Like lithium augmentation, olanzapine augmentation offers the advantage of recognized efficacy in bipolar spectrum illness and treatment-resistant depression, but olanzapine has no significant drug-drug interactions and does not require plasma level monitoring. Sedation and increased appetite are the principal side effects encountered.

5. Others. Estrogen (for perimenopausal and postmenopausal women), pindolol, buspirone, pramipexole (dopamine agonist), and various antiepileptics drugs have been reported useful in augmentation roles. Evidence for these agents in controlled trials is negative, mixed, or lacking thus far.

Electroconvulsive therapy (ECT). ECT is still an effective option for highly resistant depression. Of significant concern is the rate of relapse after ECT and the need to employ strategies to maintain remission.³⁸

Nonsomatic Interventions in Difficult-to-Treat Depressions

Psychosocial interventions and psychotherapies (especially cognitive-behavioral therapy) may be beneficial in select cases.^{39,40} This is reasonable given the complex nature of treatment resistance and the influence of psychosocial context, chronicity, and other factors that may be operative in any given clinical situation.

THE PROBLEM OF UNRECOGNIZED BIPOLAR SPECTRUM ILLNESS

Depression in the primary care setting was once assumed to be overwhelmingly unipolar. This conclusion was based on cross-sectional analysis using structured interviews that were insensitive to mania and hypomania. This phenomenon is similar to that in outpatient psychiatric settings over the last decade, whereby many heretofore “unipolar” depressions have been reclassified based on sensitive interviews and expanded pedigree inquiries, longitudinal observation, and treatment response. Current evidence suggests that bipolar spectrum conditions have a 5% prevalence in the general population.⁴¹ This prevalence has been documented to be in the 40% range in some outpatient psychiatric settings⁴² and in the 25% to 30% range in recent investigations in primary care populations.²¹

Misdiagnosis of bipolar depression is common in psychiatric practice and even more problematic in primary care because information of this expanded definition of bipolar disorder has yet to permeate primary care training programs and practice. Consequently, resistant or difficult-to-treat depressions in both psychiatry and primary care may in reality be unrecognized bipolar illness. Most pa-

tients with bipolar illness present in the depressed phase of the illness. Bipolar II depression is thought to be the most common presentation of the illness overall.

Antidepressant monotherapies are ineffective in bipolar depression and may induce hypomanic or manic episodes, depressions mixed with excitement and/or agitation, and rapid-cycling states. In fact, patients who have failed 3 or more antidepressant trials should be strongly suspected to have bipolar illness and be evaluated closely. Even in the absence of treatment-related complications, the delay in diagnosis exposes patients and significant others to prolonged debilitating depressions, psychosocial disruptions that often accompany bipolar illness, and the risk of suicide.

RECOMMENDATIONS FOR PRIMARY CARE

Emerging evidence from controlled trials suggests that antidepressants with multiple monoamine receptor effects may have advantages over single receptor agents in the likelihood of inducing illness remission when used as a monotherapy for major depression. Venlafaxine at doses at or above 225 mg daily, TCAs like clomipramine, mirtazapine, nefazodone, and monoamine oxidase inhibitors all possess such properties, although side effects and ease of use may limit the clinical appeal of some. Duloxetine also possesses dual reuptake inhibition of 5-HT and NE at therapeutic doses⁴³ and will offer an additional choice in the near future. Given the potential advantages of multiple reuptake inhibitors, primary care clinicians should seriously consider these agents as antidepressants of first choice in the treatment of major depression, advancing doses well into the therapeutic range, and monitoring adherence to avoid pseudo-resistance. This may obviate the need for combination strategies (e.g., SSRI-TCA, SSRI-bupropion) based on the recruitment of additional monoamine targets.

Unfortunately, the increased utilization of multiple reuptake inhibitors like venlafaxine and duloxetine will not eliminate treatment resistance. Bipolar disorder is also common and subtle in its manifestations, and unrecognized bipolar illness may be the source of much treatment resistance. Clinicians must be ready to intervene effectively when the need arises. Primary care clinicians interested in advanced psychopharmacologic interventions in difficult cases will naturally want to focus their acquisition of new skills in areas that maximize opportunities for success, while maintaining acceptable margins of safety and tolerability.

Augmentation strategies offer advantages over switch strategies in that partial responses to the first agent can be maintained and augmentation may convert nonresponders or partial responders to full responders relatively quickly. Two of the above-listed augmentations may be of particular interest. Lithium and olanzapine have established evidence of efficacy in both treatment-resistant

major depression and bipolar illness. Pragmatically, efficacy on both ends of the affective spectrum may help overcome inherent difficulties in recognizing the subtleties of “soft” (non-manic) bipolar illness and afford clinicians and patients an extra margin of safety and success. Clearly, when antidepressant therapy is introducing symptoms of activation that suggest bipolar illness, the antidepressant should be reduced in dose or discontinued. However, clinicians and patients may be unaware of antidepressant activation or mood switching triggered by antidepressants as important phenomena. Sudden switches into hypomania may even be misinterpreted as desirable clinical responses.⁹ Consequently, an important line of evidence for correct diagnosis and treatment may be lost.

The addition of lithium or olanzapine to an antidepressant in the setting of nonresponse or partial response may overcome resistance regardless of the exact diagnosis. Both lithium augmentation and olanzapine augmentation have limitations, but when evidence-based efficacy is the primary criterion for strategy selection (as it arguably should be), they have much to offer. Primary care clinicians interested in improving their ability to treat depression will find augmentation strategies of significant value^{22,44} and these 2 agents useful in clinical practice.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), divalproex sodium (Depakote), fluoxetine (Prozac and others), lamotrigine (Lamictal), levothyroxine (Synthroid, Levoxyl, and others), liothyronine (Cytomel), methylphenidate (Ritalin, Concerta, and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Aventyl and others), olanzapine (Zyprexa), perphenazine/amitriptyline (Etrafon and others), pindolol (Visken and others), pramipexole (Mirapex), risperidone (Risperdal), trazodone (Desyrel and others), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, bupropion is not approved by the U.S. Food and Drug Administration as a combination antidepressant treatment and buspirone, dextroamphetamine, levothyroxine, liothyronine, methylphenidate, olanzapine, pindolol, pramipexole, and risperidone are not approved for antidepressant augmentation.

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