Why Do You Need to Move Beyond First-Line Therapy for Major Depression?

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Primary care clinicians need to move beyond first-line therapy for major depression. While initial treatment is ineffective in about two-thirds of patients, patients who have not responded to such initial treatments can be managed effectively. The severity of depression is as high in primary care as in specialty care settings. The risk of depression is currently elevated because economic hardship, job insecurity, and low socioeconomic status increase the likelihood of depression and treatment resistance. Depression worsens outcomes for medical comorbidities, such as cardiac disease, chronic obstructive pulmonary disease, and diabetes mellitus, and it increases the risk of rehospitalization. When depression is treatment-resistant (generally defined as not responding to 2 courses of treatment of adequate dose and duration), morbidity and mortality are increased, quality of life and function are reduced, and long-term brain changes may occur. Opportunities for change in care are available. Screening for depression in primary care settings with staff-assisted support, adopting the concepts of the patient-centered medical home and stepped care, and using new treatment options such as atypical antipsychotics and other treatment modalities can improve outcomes for these patients. Now is the time to make these moves because new tools, systems, and treatments offer ways to help these patients.

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PREVALENCE AND RISK OF DEPRESSION IN PRIMARY CARE

In the United States, the estimated prevalence of major depressive disorder (MDD) in primary care settings ranges from 5% to 13% in adults and from 6% to 9% in older adults.[1] Because general practitioners often see patients with similar frequency and severity of depression as psychiatric specialists, family medicine and primary care practices are currently well positioned to improve the care of patients with MDD. Risk factors for chronic and recurrent depression include psychiatric comorbidity, history and long duration of depressive episodes, and suicidal ideation.[2] Environmental factors that can compound depression risk include economic hardship and job insecurity.

Impact of Economic Downturn

Many people's lives have been adversely affected by the recent economic downturn, and these individuals are at increased risk of depression and associated morbidities because of economic upset and low economic status. In a Belgian survey[3] of 11,909 people, the incidence of major depression increased by about 50% (OR = 1.47; 95% CI, 1.30–1.66; $P < .001$) within 1 year of financial strain.

Further, episodic poverty increases the cumulative risk of subsequent chronic major depression. According to a meta-analysis,[4] low socioeconomic status was more strongly associated with persistence of depression (OR = 2.06, $P < .001$) than with onset of a new episode (OR = 1.24, $P = .004$). Additionally, Lynch and colleagues[5] found that prior economic hardship on physical, cognitive, psychological, and social functioning led to a 3-fold increase in MDD in those who had dropped below 200% of the federal poverty level at least 3 times (OR = 3.24; 95% CI, 1.32–7.89; $P = .01$; Figure 1).

Job insecurity and debt are risk factors for depression. Among 3,581 respondents to a national survey[6] of psychiatric morbidity in Great Britain, the incidence of a depressive episode was higher among those who feared losing their jobs (OR = 1.86; 95% CI, 1.47–2.35; $P < .001$) and those who were in debt (OR = 2.17; 95% CI, 1.58–2.98; $P < .001$) compared with those who had no job insecurity or debt, respectively. Thus, primary care clinicians should expect that, during times of economic hardship, an increasing proportion of patients will present with depression.

Treatment-Resistant Depression

Patients who have treatment-resistant depression are often seen in primary care practices. *Treatment-resistant depression*, according to a growing consensus, is depression

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For Clinical Use

- Recognize risk factors for treatment-resistant depression.
- Set up staff-assisted support for depression care and routinely screen for depression.
- Measure patients' progress through treatment with objective tools and use a registry to track the progress of depressed patients.
- Follow a stepped-care approach using a treatment algorithm.

that has not remitted after at least 2 trials with antidepressants from different pharmacologic classes with adequate dose, duration, and compliance.[7]

Before the onset of the current economic decline, about 3% of the US population was estimated to be experiencing *Stage 1 treatment-resistant depression*, which is depression that failed to respond to 1 adequate trial of an antidepressant.[8] Further, the 12-month prevalence rate for *Stage 2 treatment-resistant depression*, which involved failure to respond to 2 adequate trials of treatment, was estimated to be about 2% of the American population.[8] Thus, clinicians can currently expect at least 2% of the American population to have treatment-resistant depression.

Poor clinical outcomes for depression over the long-term are associated with treatment resistance. The long-term impact of treatment-resistant depression on patients was evaluated in a systematic review[9] of 9 outcome studies with 1,279 participants who had been followed between 1 and 10 years. Treatment-resistant depression was found to be highly recurrent, and 80% of those who required multiple antidepressant medications had relapsed within 1 year of achieving remission.

BIDIRECTIONAL RELATIONSHIP BETWEEN DEPRESSION AND MEDICAL COMORBIDITY

The need for aggressive primary care approaches to depression treatment is highlighted in patients with comorbid medical conditions. Often, primary care patients have not only psychiatric illness but also medical comorbidity. The comorbidity of depression and medical illness is a marker for severe and treatment-resistant depression as well as poor outcome of the medical condition.[10]

A review[10] of depression treatment in the medically ill found that the presence of depression raised morbidity and lowered functional status associated with the medical condition(s). Similarly, the presence of medical illness may lower rates of recovery and remission of depressive symptoms. If patients with medical comorbidities do achieve remission of their depressive symptoms, they have higher rates of relapse during follow-up. Medical illnesses frequently seen in primary care settings, such as cardiac disease, chronic obstructive pulmonary disease (COPD), and diabetes mellitus, are often worsened by depression, which also increases the risk of rehospitalization.

Cardiac Disease

Depression, particularly treatment-resistant depression, is a risk factor for morbidity, mortality, and poor adherence to medication in patients with coronary heart disease. A recent review[11] found that treatment-resistant depression was a substantial risk factor for cardiac morbidity and mortality in patients with coronary heart disease, especially following acute coronary syndrome. Glassman and colleagues[12] completed the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), a landmark study that first demonstrated the potential value and safety of using antidepressants to treat depression in patients with acute coronary syndrome. Over an average 6.7 years, participants treated with an antidepressant for MDD over 6 months following a coronary event had 2 factors that independently resulted in more than twice the risk of mortality: (1) greater baseline severity of major depression (measured within a few weeks of hospitalization for acute coronary syndrome) (hazard ratio = 2.30), and (2) lack of improvement in MDD during antidepressant treatment (hazard ratio = 2.39). Persistent depression not only increased mortality but also decreased adherence to cardiovascular drug therapy in study participants.

Chronic Obstructive Pulmonary Disease

In patients with COPD, depressive symptoms are independently associated with increased mortality. In an 8.5-year follow-up study of 121 patients admitted to the hospital with COPD, de Voogd and colleagues[13] found that depressive symptoms at baseline almost doubled the odds of mortality (OR = 1.93; 95% CI, 1.12–3.33; $P < .05$).

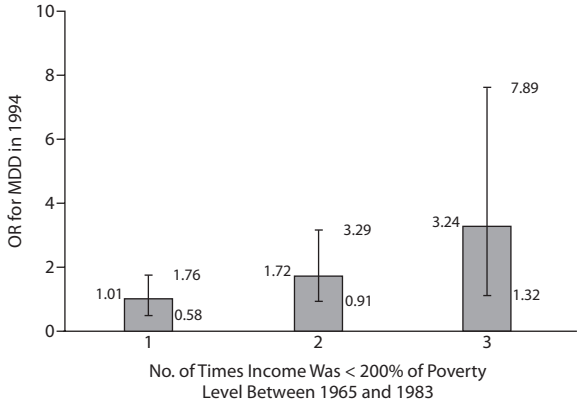
Diabetes Mellitus

Depression is associated with poor adherence to diabetes control regimens. Among 4,117 patients with diabetes, major depression was found to be significantly associated with poor adherence to diabetes, hypertension, and lipid control medications ($P < .05$).[14]

Rehospitalization

Major depression also increases the risk of rehospitalization in patients with medical illness. Kartha and colleagues[15] examined depression as a risk factor for rehospitalization in 144 subjects. After controlling for most other conditions related to rehospitalization, the presence of MDD tripled

Figure 1. Odds Ratios for MDD in 1994 Relative to Occurrences of Economic Hardship Between 1965 and 1983[a]



[a]Data from Lynch et al.[5]
Abbreviations: MDD = major depressive disorder, OR = odds ratio.

the odds of rehospitalization within 3 months of the initial hospital discharge (OR = 3.34; 95% CI, 1.20–9.25; $P = .02$). Screening for depression and depression control was recommended for frequently hospitalized inpatients.

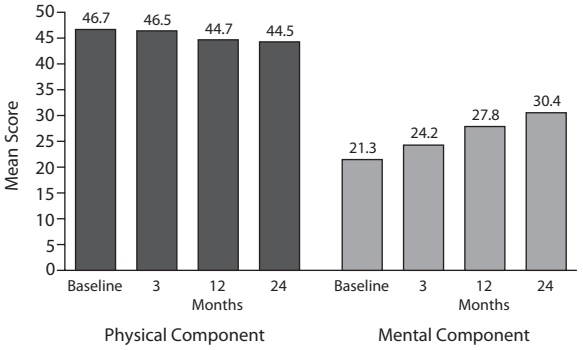
IMPACT OF TREATMENT-RESISTANT DEPRESSION ON QUALITY OF LIFE AND DISABILITY

Not only does depression adversely affect the outcomes of comorbid chronic medical illness, but it also has a negative impact on patients' functional and clinical status as well as on global disease burden. Moreover, substantial symptomatic and functional disabilities are likely to persist when these patients receive treatments usually selected when depression is first diagnosed. Thus, primary care physicians need to be prepared to move beyond first-line therapy and may also need to move beyond "treatment as usual" when managing patients considered to be treatment resistant.

An observational study[16] examined outcomes in 124 patients with treatment-resistant depression who received treatment as usual, which was any regimen agreed to by patients and psychiatrists, including medications, psychotherapy, and electroconvulsive therapy (ECT). Over the 2-year follow-up period, 81% of the participants did not achieve remission; treatment resistance continued and was associated with persistently poor quality of life. Changes in physical and mental component scores for quality-of-life measures were minimal, and the scores mostly remained below average throughout the study (Figure 2). Subscale scores remained low in role functioning (both physical and emotional) and social functioning. Thus, when receiving treatment as usual, most patients with a considerable degree of treatment resistance continue to have substantial symptomatic and functional disability.

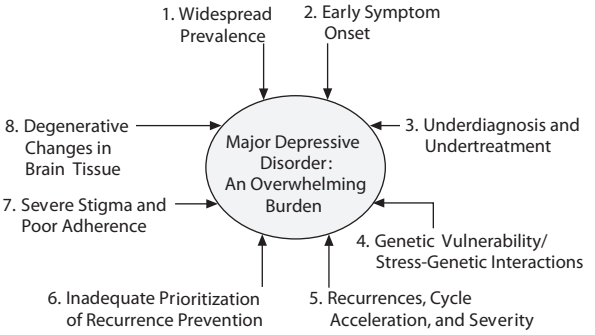
When years lived with disability (YLD) were assessed worldwide for 100 disorders, unipolar depressive disorders

Figure 2. Quality-of-Life Measures (Mean SF-36 Component Score Changes) Over 24 Months in 124 Patients With Treatment-Resistant Depression[a]



[a]Reprinted with permission from Dunner et al.[16] Scores below 50 are considered below average.
Abbreviation: SF-36 = 36-item Short Form Health Survey of the Medical Outcomes Study.

Figure 3. Contributors to the High Morbidity of Major Depressive Disorders and Treatment-Resistant Depression[a]



[a]Reprinted with permission from Greden.[18]

were the leading global cause of YLD, regardless of sex or of the country's income level.[17] The most severely disabled are likely to be those with treatment-resistant depression. Greden[18] suggested that some contributors to the high morbidity of MDD and treatment-resistant depression include widespread prevalence and underdiagnosis and undertreatment (Figure 3). Over time, depression is accompanied not only by a tremendous disease burden but also by possible brain changes leading to further functional decline. Recurrent depressive episodes have been shown to lead to possible suppression of brain neurogenesis, neuronal atrophy, cell death, hippocampal dysfunction, and changes visible on magnetic resonance imaging.

IMPROVING DEPRESSION TREATMENT IN PRIMARY CARE

The evidence that treatment-resistant depression results in significant functional limitations, high economic costs, decreased adherence to medical care regimens, and

Table 1. The IMPACT Model of a Patient-Centered Medical Home: Essential Elements[a]

Element	Description
Collaborative care	A primary care physician works with a care manager/behavioral health consultant to develop and implement a treatment plan
Care manager/ behavioral health consultant	A nurse, social worker, or psychologist (who may be supported by a paraprofessional) educates individuals about depression, supports medication therapy, coaches individuals in behavioral activation and self-management, offers brief course of counseling, monitors symptoms, and completes relapse prevention plans
Designated psychiatrist	A psychiatrist consults with the care manager, behavioral health consultant, and primary care physician on care of individuals who do not respond to treatment as expected
Outcome measurement and registry tracking	Care managers measure depressive and other symptoms at the start of treatment and regularly thereafter using a validated measurement tool
Stepped care	Treatment is adjusted based on clinical outcomes and according to an evidence-based algorithm. The goal is a 50% reduction in depression symptoms within 10 to 12 weeks. If significant improvement is not seen after 10 to 12 weeks, change the treatment plan, eg, increase medication dosage, switch medication, add psychotherapy, or make other treatment changes suggested by the team psychiatrist

[a]Based on the National Council for Community Behavioral Healthcare.[21]
Abbreviation: IMPACT = Improving Mood-Promoting Access to Collaborative Treatment.

increased morbidity and mortality is compelling. Treatment as usual is not effective for many patients with MDD. However, primary care is undergoing change, and ideas such as the patient-centered medical home may offer opportunities for improving outcomes in patients with treatment-resistant MDD.

Need for Improvement

Ani and colleagues[19] reported that, among 315 patients at inner-city outpatient primary care clinics who screened positive for depression but had no previous diagnosis of depression, physician diagnosis of depression and guideline-concordant initial depression treatment each occurred in only about one-third of patients. While the presence of chronic medical illness did not significantly affect these aspects of care, the severity of depression did affect these rates. Participants with severe depression were twice as likely to receive a diagnosis of depression than those with moderate depression (adjusted OR = 2.10; 95% CI, 1.11–3.98; $P = .02$), but there was a trend that those with moderately severe and severe depression were less likely to receive guideline-concordant initial care compared with participants with less severe depression. Guideline-concordant follow-up care was less likely to occur in those with comorbid medical illness, and much less likely among those with moderately severe (adjusted OR = 0.11; 95% CI, 0.02–0.55; $P = .01$) and severe depression (adjusted OR = 0.04; 95% CI, 0.01–0.41; $P = .01$).

New Screening Guidelines for Depression

In 2009, the US Preventive Services Task Force[20] released an update recommending screening adults for depression in primary care practice, but only when staff-assisted depression care supports are in place that can assure accurate diagnosis, effective treatment, and follow-up of the patient. A staff-assisted depression care support system requires the time, money, and ability to train nurses and others in the office to assist with activities such as screening, patient education, and coordination with specialists. The task force recommended against routine screening for depression when staff-assisted supports are not available but did note that there may be considerations that support screening for depression in an individual patient. This recommendation is resulting in an increased redesign of primary care settings to implement such supports.

Patient-Centered Medical Home

The concept of the patient-centered medical home is an example of an opportunity for change in primary care depression treatment. Elements of this concept are built into many federal, state, foundation, and insurance-sponsored initiatives that provide the tools required to improve outcomes of patients with major depression in keeping with the US Preventive Services Task Force guideline.[20] According to the National Council for Community Behavioral Health care (NCCBH),[21] a principle of the patient-centered medical home is to establish an ongoing relationship between the patient and his or her physician, in which the physician leads a team of care providers to address all of the patient's health care needs in an integrated fashion. Care should be easily accessible with quality and safety as hallmarks. The idea is to have less episodic acute care, more preventive care, and chronic disease management supported by the physician's team, with the patient's self-management also encouraged and supported.

As an example, the NCCBH[21] highlighted the Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) model (Table 1),[22,23] created by the University of Washington, which identified practices and established a collection of resources that can lead to greatly improved outcomes in MDD care. During the collaborative care process, the primary care physician works closely with a care manager or behavioral health consultant, who provides direct support to patients as they progress through treatment. Standardized tools, such as the 9-item Patient Health Questionnaire (PHQ-9),[24] are used to screen for depression and to monitor response to treatment. Patients with positive screenings or a depressive diagnosis are tracked in a registry. The use of standardized tools and a registry provides a framework in which treatment can be adjusted according to a stepped-care, evidence-based algorithm.

Stepped-Care Approach

In a stepped-care approach, whether within a primary care or other practice setting, the key is to recognize patients

with treatment-resistant depression. Compared with treatment responders, these patients have been shown to have more severe depression, more past suicide attempts, more hospitalizations, and longer episodes; have received more treatments, including benzodiazepines, antipsychotics, and ECT; and have experienced more job loss, financial stress, and negative life events.[25]

Souery and colleagues[26] identified 11 clinical variables associated with treatment-resistant MDD that may serve as warning signs. Among these variables were several anxiety comorbidities, including panic disorder and social phobia; personality disorder; suicidality; depression severity; melancholia; and the number of prior hospitalizations. Past history for recurrent episodes, initial onset at an early age, and nonresponse to the first antidepressant ever received were additional warning signs.

Once the primary care physician has identified a patient as not responding to a second adequate trial of antidepressant therapy, a 2-step approach may be appropriate[7]: (1) evaluate factors that might contribute to treatment nonresponse, such as medical and psychiatric comorbidities; and (2) progress care through a classic 4-strategy series for enhancing antidepressant efficacy (ie, optimize, augment, combine, or switch treatments).

An example of using such a stepped-care approach is the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[27,28] In this study, treatment resistance was associated with concurrent Axis I or III comorbid conditions, socioeconomic disadvantage, chronicity, and melancholic or anxious features. The STAR*D trial demonstrated that, with persistence (ie, if patients remain in treatment for up to 4 steps), about 67% of patients can eventually attain remission. Clinical decision-making based on objective measurement of symptoms and adverse effects at each treatment visit was shown to be feasible in the real-world settings of either private primary care practice or private psychiatric small-group practice and resulted in adequate dosages and duration of treatment. For more information about STAR*D, see the article in this supplement by J. Sloan Manning, MD, "What Alternatives to First-Line Therapy for Depression Are Effective?"[29]

Treatment Options for Resistant Depression

Since the STAR*D study was completed, new pharmacologic and nonpharmacologic treatment options have become available. In the pharmacologic area, possibly the most important advance has been the use of atypical antipsychotics in patients with treatment resistance. Nonpharmacologic options for treatment-resistant depression include a number of new options that usually require referral to a psychiatrist.

Atypical antipsychotics. In a meta-analysis of placebo-controlled trials of adjunctive atypical antipsychotics for treatment-resistant major depression, Nelson and Papakostas[30] identified 16 trials involving 3,480 patients. Compared with placebo augmentation, adjunctive atypical antipsychotics significantly improved the likelihood of response (OR 1.69; 95% CI, 1.46–1.95; $P < .00001$) and doubled the likelihood of remission (OR 2.00; 95% CI, 1.69–2.37; $P < .00001$) in the combined study population. The trial duration, type of atypical antipsychotic, and method of establishing treatment resistance did not affect results. The authors noted that the evidence base for this type of augmentation treatment in treatment-resistant depression is considerably larger than for any other type of agent. Elsewhere in this supplement, pharmacotherapy options are discussed in more detail by J. Sloan Manning, MD, in "What Alternatives to First-Line Therapy for Depression are Effective?"[29] and selecting appropriate medication for particular patients is discussed by Richard H. Weisler, MD, in "How Do You Choose a Second-Line Treatment Option for Depression?"[31]

Nonpharmacologic modalities. Kennedy and Giacobbe[32] reviewed evidence for ECT, magnetic seizure therapy, repetitive transcranial magnetic stimulation (rTMS), vagal nerve stimulation (VNS), and deep brain stimulation (DBS), and reported that, although the level of clinical development for these treatments varies, they are promising efforts in research into ameliorating treatment-resistant depression.

Lam and colleagues[33] conducted a meta-analysis of 24 randomized controlled studies (N = 1,092 patients) of rTMS in patients who had failed at least 1 trial of an antidepressant. The pooled response rate was 25%, compared with 9% for those who received a sham control condition. Remission rates were 17% for the rTMS group and 6% for the control group.

In a small study,[34] 15 patients with chronic, severe, refractory depression were treated with DBS and followed for 6 months to more than 4 years. The response rates were 40% at 6 months and 54% at the last follow-up. The remission rates were 20% at 6 months and 40% at last follow-up.

Psychiatric consultation. As noted in the IMPACT model of a patient-centered medical home, the availability of a consulting psychiatrist is useful. Seeking psychiatric consultation can be helpful at any point at which the primary care physician desires assistance and may be particularly valuable when treating patients with severe depression; depression associated with significant other psychiatric comorbidities, such as substance abuse, personality disorders, or eating disorders; history of treatment-resistant depression; or significant suicidality. Consultation also may be necessary for initial or replacement treatment modalities that are not available in primary care, eg, inpatient and day hospitalization, ECT, VNS, or rTMS.

CONCLUSION

Now is the time for primary care clinicians to move beyond first-line therapy for MDD. Primary care clinicians are in an excellent position to help patients with depression, even those whose depression is resistant to initial treatment

efforts. A first step is recognizing warning signs of treatment resistance. Thereafter, using practice tools recommended by the US Preventive Services Task Force can help improve the management of patients with treatment-resistant depression. Adjunctive atypical antipsychotics can be used effectively in primary care, and other advanced therapies are available in addition to the treatments described in STAR*D. Advice from a psychiatrist can be helpful and may provide access to treatments not available in primary care. The need for aggressive treatment is compelling because of the increased risk for depression created by the economic downturn and the substantial burden created by treatment-resistant depression. Tools and treatments are available to help these patients, and the primary care system can be improved so that the potential for a positive outcome is increased.

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 activity.

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