This supplement was jointly sponsored by the North Carolina Academy of Family Physicians (NCAFP) and Spire Learning and was supported by an educational grant from Takeda Pharmaceuticals International, Inc, US Region and Lundbeck. It was edited and peer reviewed by The Journal of Family Practice.

SUPPLEMENT TO
THE JOURNAL OF FAMILY PRACTICE®

1.25 CME CREDITS AVAILABLE

VOL 64, NO 9 | SEPTEMBER 2015 | www.jfponline.com

Major Depressive Disorder in the Primary Care Setting

STRATEGIES TO ACHIEVE REMISSION AND RECOVERY

BRADLEY N. GAYNES, MD, MPH
Professor and Associate Chair
of Research Training and Education
Department of Psychiatry
University of North Carolina
School of Medicine
Chapel Hill, North Carolina

W. CLAY JACKSON, MD, DipTh
Clinical Assistant Professor
of Family Medicine and Psychiatry
University of Tennessee
College of Medicine
Memphis, Tennessee

KASHEMI D. RORIE, PhD
Clinical Director, Spire Learning
Clinical Editor, RapidCME
Parsippany, New Jersey

Major Depressive Disorder in the Primary Care Setting: Strategies to Achieve Remission and Recovery

PROVIDER STATEMENT

This educational activity is jointly provided by the North Carolina Academy of Family Physicians (NCAFP) and Spire Learning.

SUPPORT STATEMENT

Supported by an educational grant from Takeda Pharmaceuticals International, Inc, US Region and Lundbeck.

TARGET AUDIENCE

Family physicians and other health care providers who treat patients with major depressive disorder (MDD).

LEARNING OBJECTIVES

- Examine key clinical factors that impede optimal therapeutic management of individuals with MDD in the primary care setting
- Implement into practice symptom management strategies that promote symptomatic remission, full functional recovery, and relapse prevention in persons with MDD

PROGRAM OVERVIEW

Family physicians (FPs) are on the frontline for depression care, often being the first line of defense for diagnosis and management. This 1.25 hour, CME-certified activity will provide clinicians with a comprehensive review on the following:

- Clinical factors in the primary care setting that influence treatment outcomes in MDD
- Identification and management of residual symptoms
- Tools for effective monitoring of treatment outcomes
- Nonpharmacologic and pharmacologic therapies to treat patients to goal: remission and recovery
- Strategies to promote patient-focused, recovery-oriented care

AUTHORS

Bradley N. Gaynes, MD, MPH
Professor and Associate Chair of Research Training and Education
Department of Psychiatry
University of North Carolina School of Medicine
Chapel Hill, North Carolina

W. Clay Jackson, MD, DipTh
Clinical Assistant Professor of Family Medicine and Psychiatry
University of Tennessee College of Medicine
Memphis, Tennessee

Kashemi D. Rorie, PhD
Clinical Director
Spire Learning
Parsippany, New Jersey

Clinical Editor
RapidCME
Parsippany, New Jersey

ACCREDITATION

This enduring activity, Major Depressive Disorder in the Primary Care Setting: Strategies to Achieve Remission and Recovery, from 09/04/2015 to 09/03/2016, has been reviewed and is acceptable for up to 1.25 Prescribed credit(s) by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AMA/AAFP Equivalency: AAFP Prescribed credit is accepted by the American Medical Association as equivalent to *AMA PRA Category 1 credit(s)*™ toward the AMA Physician's Recognition Award. When applying for the AMA PRA, Prescribed credit earned must be reported as Prescribed, not as Category 1.

HOW TO PARTICIPATE IN THIS ACTIVITY AND OBTAIN CME CREDIT

To participate in this CME/CE activity, you must read the objectives and articles. Once you have completed the activity, please visit the online link: **http://www.rapidcme.com/clinibriefs.aspx** and complete the CME posttest and evaluation. A satisfactory score is defined as answering 80% of the posttest questions correctly. Upon confirmation of the completed survey, if a satisfactory score on the posttest is achieved, NCAFP will issue a credit certificate within 4 to 6 weeks via e-mail.

DISCLOSURE STATEMENTS

In accordance with the Accreditation Council for Continuing Medical Education, the NCAFP requires that any person who is in a position to control the content of a CME activity must disclose all relevant financial relationships they have with a commercial interest.

Activity Planning Faculty

The activity content was developed by Bradley N. Gaynes, MD, MPH, and W. Clay Jackson, MD, DipTh.

Activity Faculty

Bradley N. Gaynes, MD, MPH
Grant/Research Support: National Institute of Mental Health; Agency for Healthcare Quality and Research.

W. Clay Jackson, MD, DipTh
Consultant: Forest Pharmaceuticals, Inc; Merck & Co; Pamlab, Inc; Otsuka America Pharmaceutical, Inc; Sunovion Pharmaceuticals Inc; Takeda Pharmaceutical Company Ltd. Speakers Bureau: Sunovion Pharmaceuticals Inc.

In order to resolve conflict of interest, presentations of this activity were peer reviewed by an independent reviewer. The reviewer has no relationship with a commercial interest. The resulting certified activity was found to provide educational content that is current, evidence based, and commercially balanced.

Independent Reviewer
Alisa C. Nance, MD
Nothing to disclose with regard to commercial support

Educational Planning Committee
NCAFP
Marietta Ellis
Nothing to disclose with regard to commercial support

Spire Learning
Kashemi D. Rorie, PhD
Nothing to disclose with regard to commercial support

Karin McAdams
Nothing to disclose with regard to commercial support

Jeanne Prater
Shareholder (Spouse/Partner): Johnson & Johnson
Employee (Spouse/Partner): Novo Nordisk

DISCLAIMER

The content and views presented in this educational activity are those of the presenters and do not necessarily reflect those of the NCAFP, Spire Learning, Takeda Pharmaceuticals International, Inc, US Region and Lundbeck. This material is prepared based upon a review of multiple sources of information, but it is not exhaustive of the subject matter. Therefore, health care professionals and other individuals should review and consider other publications and materials on the subject matter before relying solely upon the information contained within this educational activity.

OFF-LABEL STATEMENT

The faculty presenters do not intend to discuss the use of agents that are not indicated by the FDA. The opinions expressed in the educational activity are those of the faculty. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings. Further, attendees/participants should appraise the information presented critically and are encouraged to consult appropriate resources for any product or device mentioned in this program.

FACULTY BIOGRAPHIES

Bradley N. Gaynes, MD, MPH
Bradley N. Gaynes, MD, MPH, is Professor and Associate Chair of Research Training and Education in the Department of Psychiatry at the University of North Carolina (UNC) at Chapel Hill. Dr Gaynes earned his medical degree from the University of Virginia School of Medicine, and completed his residency in psychiatry at the University of Colorado Health Sciences Center. His postgraduate training has included a Robert Wood Johnson Clinical Scholar Fellowship at UNC, where he also received his Master of Public Health degree in epidemiology and completed a fellowship in preventive medicine. With funding including that from the National Institute of Mental Health (NIHM) and having worked on a US Preventive Services Task Force (USPSTF), Dr Gaynes' work is at the crossroads between clinical trials research and mental health services research (including comparative effectiveness reviews). He focuses his clinical and research efforts on treatment-resistant depression and improving the delivery of depression care in nonpsychiatric settings, including primary care, obstetrical, and HIV practices.

W. Clay Jackson, MD, DipTH
W. Clay Jackson, MD, DipTh, is a Clinical Assistant Professor of Family Medicine and Psychiatry at the University of Tennessee College of Medicine in Memphis, where he maintains a private practice in family and palliative medicine. He is Medical Director of Comprehensive Primary Care, and Medical Director for Methodist Hospice and Palliative Services, also in Memphis. In addition, Dr Jackson is the Fellowship Director for Palliative Medicine at the University of Tennessee College of Medicine. From this professional platform, he has led a team of dedicated clinicians who have helped to transform the experience of seriously ill patients in the Mid-South.

Dr Jackson earned his medical degree at the University of Tennessee Health Science Center in Memphis and completed his residency at the University of Tennessee/Baptist Tipton Family Medicine. He earned his Diploma in Theology at Oxford University in England. He is a Fellow of the American Academy of Family Physicians, holds a Certificate of Added Qualification in Hospice and Palliative Medicine, and is a member of the Alpha Omega Alpha Medical Honor Society.

COPYRIGHT

CME QUESTIONS?

Please contact Marietta Ellis at mellis@ncafp.com.

Major Depressive Disorder in the Primary Care Setting: Strategies to Achieve Remission and Recovery

Bradley N. Gaynes, MD, MPH; W. Clay Jackson, MD, DipTh; Kashemi D. Rorie, PhD

Major depressive disorder (MDD) has become one of the most prevalent public health concerns worldwide due to its high rate of morbidity, recurrence, and suicide, resulting in a profound burden to both the individual and society. Depression affects approximately 350 million people worldwide—a figure that has nearly tripled in the last 10 years.[1] Moreover, depression is expected to become the most common cause of loss of disability-adjusted life years in the world by 2030 (**TABLE 1**).[2]

Concomitant with the profound disability that depression creates is the significant economic burden that it imposes. The estimated cost of depression in 2000 was $83 billion, with 70% of that cost related to indirect expenses, such as workplace costs (ie, productivity loss and sick days) and suicide-related costs (**FIGURE 1**).[3,4] These data, in conjunction with increased expenditures and frequent treatment failures in MDD, reveal the need to implement health care delivery models that provide high-quality health care that promotes patient-centered outcomes, efficiency, and effective care. As outlined in the National Quality Strategy (NQS), clinical best practices and outcomes should be aligned with health care delivery systems that reduce and/or eliminate waste.[5]

Among the most accessible health professionals for a host of medical conditions, primary care physicians (PCPs) are on the frontline for depression care, particularly considering that they write about 2 of every 3 antidepressant prescriptions in the United States.[6] However, PCPs are often so challenged by their patients' medical needs that residual symptoms of MDD may be overlooked.[7] The increased number of novel and emerging therapies, which potentially render safer and more effective care than traditional therapies, highlight the importance of PCPs honing their skills in the effective long-term management of patients with depression. Among the priorities of the NQS are to reduce the rate of delayed care from 14.1% to less than 10% and the lack of patient-centered decision making from 15.9% to less than 10% by 2017.[5] Providing PCPs with the tools to implement patient-centered, quality, effective strategies that facilitate long-term symptom remission and recovery is central to achieving these initiatives.

Bradley N. Gaynes, MD, MPH, Professor and Associate Chair of Research Training and Education, Department of Psychiatry, University of North Carolina School of Medicine, Chapel Hill, North Carolina

W. Clay Jackson, MD, DipTh, Clinical Assistant Professor of Family Medicine and Psychiatry, University of Tennessee College of Medicine, Memphis, Tennessee

Kashemi D. Rorie, PhD, Clinical Director, Spire Learning, Clinical Editor, RapidCME, Parsippany, New Jersey

DISCLOSURES

Dr. Gaynes discloses that he has received grant/research support from the National Institute of Mental Health and the Agency for Healthcare Quality and Research.

Dr. Jackson discloses that he is a consultant for Forest Pharmaceuticals, Inc; Merck & Co; Pamlab, Inc; Otsuka America Pharmaceutical, Inc; Sunovion Pharmaceuticals Inc; and Takeda Pharmaceutical Company Ltd. He is on the speakers bureau of Sunovion Pharmaceuticals Inc.

Dr. Rorie has nothing to disclose with regard to commercial support.

Diagnosis of depression in the primary care setting

Screening

The plurality of care for depression is provided by general medical practitioners, who see almost twice as many mental health patients as psychiatrists.[8] Although some mental health patients may see more than one health care provider for treatment, prevalence data indicate that general medical providers see nearly twice as many mental health patients as psychiatrists (**FIGURE 2**).[8]

While depression has been reported as the second most common chronic disorder in primary care settings,[8] initially it is often undiagnosed or misdiagnosed.[9,10] Despite this observation, screening for depression in primary care settings has been controversial.[11,12] In 2002 and again in 2009, the US Preventive Services Task Force (USPSTF) recommended routine depression screening in primary care settings that provided staff-assisted depression care programs to help monitor follow-up; these recommendations were based on a systematic review and meta-analysis of the

TABLE 1 **Rankings of major depressive disorder and other diseases/ injuries by their impact on disability-adjusted life years[2]**

Rank	Disease or injury: 2004	Disease or injury: 2030
1	Lower respiratory infections	Major depressive disorder
2	Diarrheal diseases	Ischemic heart disease
3	Major depressive disorder	Road traffic accidents
4	Ischemic heart disease	Cerebrovascular disease
5	HIV/AIDS	Chronic obstructive pulmonary disease
6	Cerebrovascular disease	Lower respiratory infections
7	Prematurity and low birth weight	Hearing loss, adult onset
8	Birth asphyxia and birth trauma	Refractive errors
9	Road traffic accidents	HIV/AIDS
10	Neonatal infections	Diabetes

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

FIGURE 1 **The economic burden of major depressive disorder[3,4]**

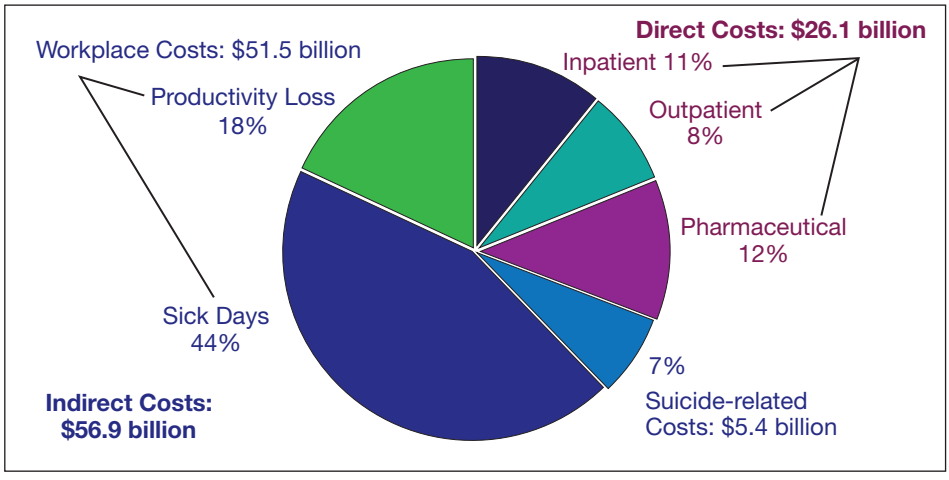
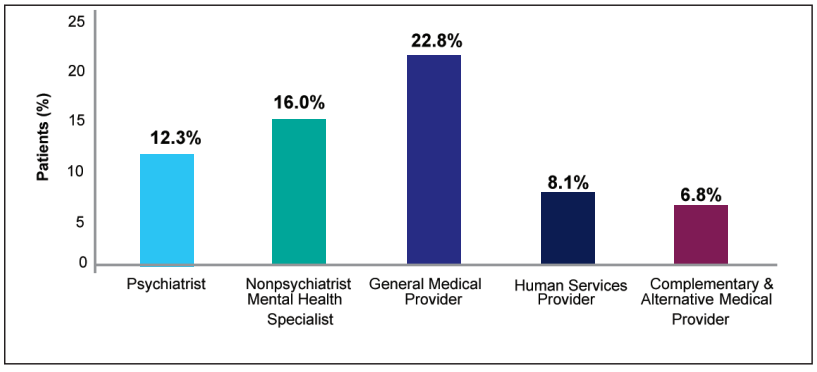


FIGURE 2 **Proportion of mental health patients managed by different health care providers*†[8]**



*Percentages represent prevalence data obtained over a 12-month period from the National Comorbidity Survey Replication.

†Treatment could be received by more than one source.

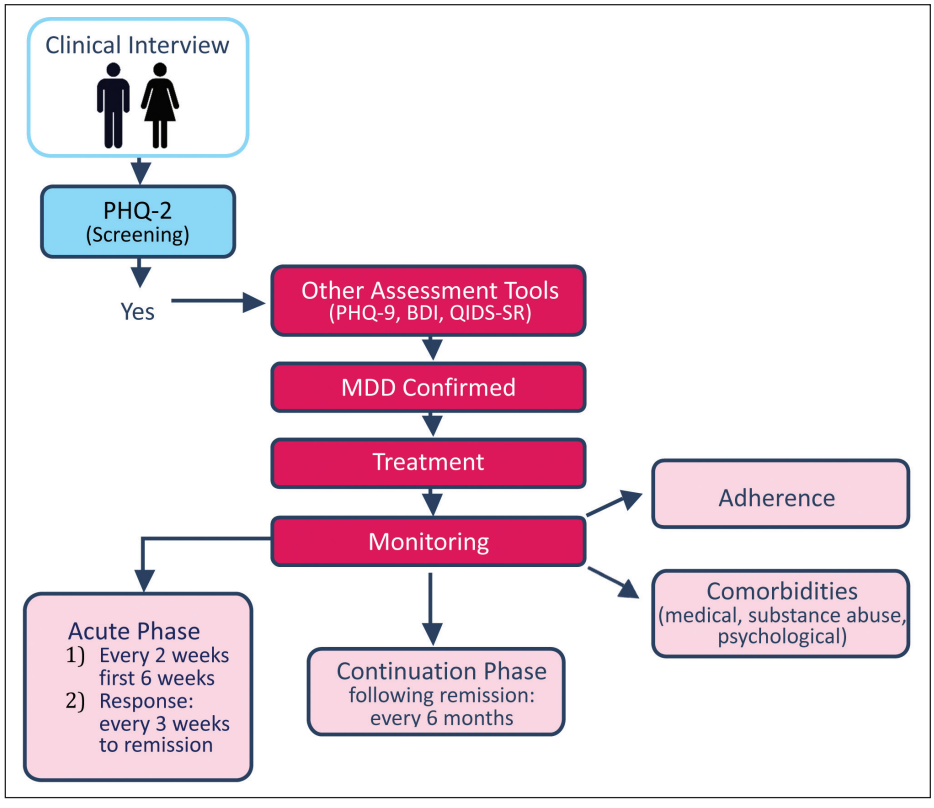
available data.[13,14] The USPSTF recommendations for depression screening in primary care settings are currently under review, with an update anticipated in 2015.[15] Despite these recommendations, other meta-analyses have concluded that there is no clinical evidence to demonstrate a benefit,[16,17] suggesting that depression screening could contribute to overdiagnosis and overtreatment. Of note, the Centers for Medicare and Medicaid Services (CMS) has determined that evidence is adequate to support depression screening in adults for the prevention or early detection of depression and its concomitant disability.[18]

As shown in the flowchart created by the authors (**FIGURE 3**), the diagnosis of depression is a stepwise process and should begin with a clinical interview to screen for the presence of depressive symptomatology (including altered mood states, sleep disturbances, and cognitive dysfunction).[19] The Patient Health Questionnaire-2 (PHQ-2)[20] can be used to screen for frequency of depressed mood and anhedonia; at least one of these must be present over the past 2 weeks for a diagnosis of MDD according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5).[19] The PHQ-2 includes the first 2 items of the Patient Health Questionnaire-9 (PHQ-9) and is intended to screen for, not diagnose, depression as a first-step approach.

SIG-E-CAPS is a useful mnemonic:

- **S**leep – increased or decreased (if decreased, often early morning awakening)
- **I**nterest – decreased
- **G**uilt/worthlessness
- **E**nergy – decreased or fatigued
- **C**oncentration/difficulty making decisions

FIGURE 3 Stepwise management of depression



BDI, Beck Depression Inventory; MDD, major depressive disorder; PHQ, Patient Health Questionnaire; QIDS-SR, Quick Inventory of Depressive Symptomatology–Self-Report.

- **A**ppetite and/or weight increase or decrease
- **P**sychomotor activity – increased or decreased
- **S**uicidal ideation.

Should depressive symptoms be detected via clinical interview and/or PHQ-2 screening, validated assessment tools should be used to confirm the presence and duration of depressive symptoms and establish a baseline for symptom tracking.[21] **TABLE 2** provides a sample of common assessment tools for depression.[22] It is also worth noting that there is a high rate of misdiagnosis between major depression and bipolar depression in primary care settings. Some studies have reported that up to 50% of individuals diagnosed with bipolar depression actually have MDD, while others have reported a sample in which 23% of patients currently diagnosed with MDD screened positive for bipolar disorder.[23-26] Subsequently, when an index of suspicion is positive for depression, clinicians should also assess whether there has been a history of mania or hypomania to rule out bipolar disorder. The Mood Disorder Questionnaire (MDQ) is widely used to screen for bipolar disorder and may be useful in ruling out bipolar depression in patients who have positive screens for depression.[27]

Diagnostic accuracy in the primary care setting

Although depression is often first seen in the primary care setting, up to 50% of individuals with depression are not diagnosed.[9] A likely contributing factor is that PCPs primarily focus on acute and/or chronic medical conditions seen in the primary care setting. In addition, depression is often comorbid with medical illnesses,[28] complicating both the recognition and effective management of the disease.

Conversely, depression can be overestimated in some clinical settings. The National Comorbidity Survey (NCS; 1990–1992) and the National Comorbidity Survey Replication (NCS-R; 2001–2003) reported that nearly half of individuals receiving treatment for mental illnesses did not meet diagnostic criteria for a mental disorder.[8,29] These results include patients in general medicine, subspecialty, and other mental health settings.

Multiple competing demands, limited time and training, and complicated presentations contribute to the challenges PCPs face in identifying depression. In a meta-analyses of more than 50,000 patients pooled across 41 global studies, PCPs accurately identified depression in 47% (95% CI, 41.7% to 53%) of their patients.[30] In a subset of the data examining the ability of PCPs to identify depression in depressed patients as well as rule out depression in nondepressed patients, the positive predictive value was 42% (39.6% to 44.3%) and the negative predictive value was 85.8% (84.8% to 86.7%).[30] **FIGURE 4** provides a theoretical perspective of the diagnostic accuracy of depression in the general medical setting. In essence, it conveys the importance of not only accurately diagnosing depression, but also possessing the skills to rule out depression in patients who may present with related disorders or symptoms.[30]

Treatment of depression

Goals of therapy

Traditionally, the goal of antidepressant therapy has been symptomatic remission. However, full symptomatic remis-

TABLE 2 Assessment tools for depression[22]

Instrument	Number of items	Scoring range	Typical cut-point
Symptom rating scales			
Research rating scales			
Center for Epidemiological Studies Depression Screen (CESD)	20	0–16	16
Geriatric Depression Scale (GDS)	30 15	0–30 0–15	14 5
Hamilton Depression Rating Scale (HAM-D or HDRS)*	17 21		8 mild 14 moderate 19 severe 23 very severe
Montgomery-Asberg Depression Rating Scale (MADRS)*	10	0–60	None found
Clinical practice scales			
Beck Depression Inventory (BDI)	21	0–63	11 mild 17 borderline clinical 21 moderate 31 severe
Primary Care Evaluation of Mental Disorders, Mood Module (PRIME-MD) Patient Health Questionnaire (PHQ-9)	9	0–27	5 mild 10 moderate 15 moderately severe 20 severe
Quick Inventory of Depressive Symptomatology (QIDS) • QIDS-C (clinician administered) • QIDS-SR (patient self-report)	16	0–27	6 mild 11 moderate 16 severe 21 very severe
PRIME-MD screening items	2	0–2	2
Composite International Diagnostic Interview (CIDI), 2 "stem" items for depression section*	2	0–2	2
Diagnostic interview tools			
CIDI*	Varies, depending on responses	Diagnostic code	NA
PRIME-MD	Varies, depending on responses	Diagnostic code	NA

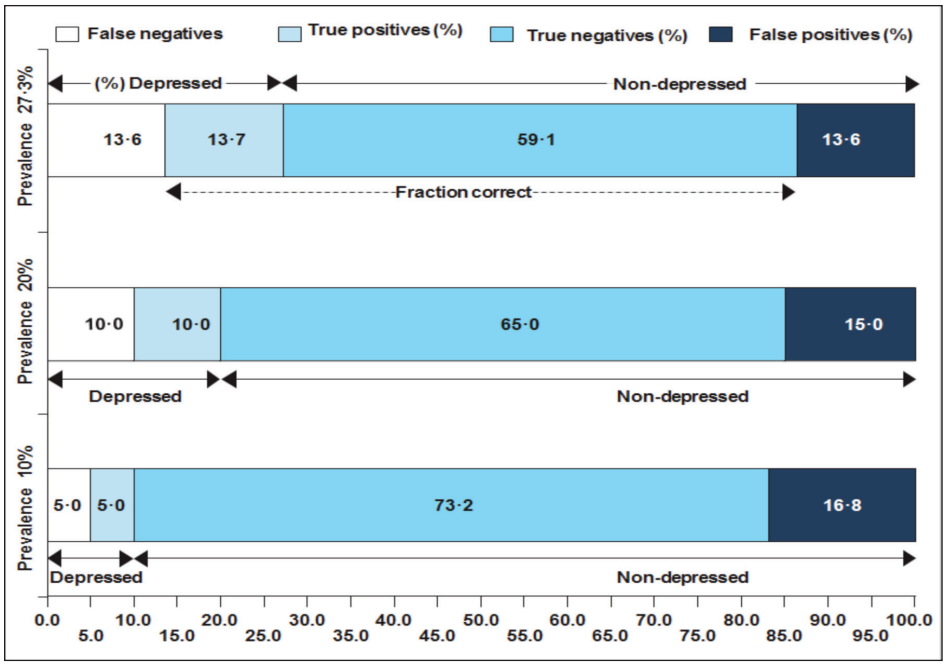
*Clinician administered, training required.

NA, not applicable.

sion and recovery of function has emerged as the optimal therapeutic goal. Nevertheless, most depressed people seeking treatment fail to receive optimal care. According to data from the NCS-R, only 42% (95% CI, 35.9% to 47.9%) of individuals diagnosed with depression and requiring treatment actually received "adequate" care.*[31] Of these 42%, 64% (95% CI, 55.4%

*Adequate treatment was defined as receiving either (1) at least 4 outpatient visits with any type of physician for pharmacotherapy that included use of either an antidepressant or mood stabilizer for a minimum of 30 days or (2) at least 8 outpatient visits with any professional in the specialty mental health sector for psychotherapy lasting a mean of at least 30 minutes.[31]

FIGURE 4 Real-world proportions of correct and incorrect diagnoses of depression in primary care settings*[30]



*Republished with permission of Elsevier Science and Technology Journals from Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. *Lancet*. 2009:374(9690):609-619; permission conveyed through Copyright Clearance Center, Inc.

to 73.1%) were seen in specialty care and 41% were seen in general medical settings.[31] Rates of remission were nearly 33% after 12 weeks of treatment with a first antidepressant, and approximately 67% after up to 3 depression treatment strategies.[32]

Suboptimal treatment response, the inability to effectively treat all symptoms of depression, and potential adverse effects of available antidepressant agents are key barriers to achieving clinical remission and recovery. Subsequently, the focus of intervention has expanded beyond a mere response to therapy to address the unmet treatment needs of residual symptoms of depression (eg, cognitive dysfunction, sleep disturbances) and their impact on symptom remission and recovery.

Response, remission, recovery

Response, remission, and recovery are terms associated with depression management, but clinically and phenomenologically they represent vastly different constructs. According to the American College of Neuropsychopharmacology task force, ***response,*** typically defined as a clinically meaningful degree of symptom reduction, is an insufficient outcome in depression management.[33] On the other hand, ***remission*** implies that the signs and symptoms of the disease are completely absent (full remission) or nearly absent (partial remission) and functioning has returned to normal, whereas ***recovery*** implies the anticipation of an extended period of remission.

The movement in mental health care to promote recovery has received support from the President's New Freedom Commission on Mental Health.[34] Recovery is increasingly thought of as not merely the remission of symptoms or the achievement of various psychosocial milestones but rather as a process and not an outcome. The multiple elements of recovery include significant improvements in depressive symptoms and relapses, life satisfaction and daily activities, and adequate or suitable function in everyday life. Despite the progression toward recovery-oriented care, this operational definition remains a work in progress.[33,35]

Clinical significance of residual symptoms

Response may be the initial goal of treatment, but it is insufficient as the end goal. Remission does not imply the same symptomatic improvements as recovery but serves as a standardized way to measure symptoms that have remained at a low level for a period of time. The clinical impact of response versus remission on recovery is profound. Patients who respond to antidepressant therapy but do not remit experience persistent symptoms and impaired psychosocial functioning.[36-39] Data suggest significant functional impairment can also occur in partial remitters and even in remitters with residual symptoms.[40,41] In conjunction, functional impairment has been significantly associated with decreased likelihood of recovery from a major depressive episode.[42]

Residual depressive symptoms also increase the likelihood of relapse and recurrence of MDD.[38,39] Relapse and recurrence refer to the return of a major depressive episode; however, they differ in that **relapse** occurs *before* recovery but after remission, while **recurrence** occurs only *after* recovery.[33] Recurrence is common in MDD, occurring in 20% of patients within 6 months following remission.[43] Moreover, between 50% and 85% of patients who have an episode of MDD will experience at least one lifetime recurrence.[43] The persistence of residual symptoms and the attendant propensity for recurrence and relapse negatively impact the clinical course and outcomes of MDD.

TABLE 3 Impact of not attaining remission from depression[51-53]

Impact on individual	Impact on society
Higher risk of relapse	Increased workplace costs (eg, productivity loss and sick days)
Increased suicidality	More benefits received via welfare and disability insurance
Decreased life span	More psychiatric hospitalizations
Less symptom-free weeks	Increased medical, psychiatric, and emergency care

In addition to the functional consequences of residual symptoms, both physiologic and neuropathologic consequences have been reported. A meta-analysis of 143 studies revealed that patients with MDD had smaller hippocampal and frontal brain volume than did healthy controls.[44] In a sample of older individuals without dementia, it was likewise observed that people with MDD, relative to nondepressed controls, had more global brain atrophy (B = –1.25%; 95% CI, –2.05% to –0.44%), including gray and white matter atrophy in most lobes in addition to the hippocampus and thalamus.[45] A comparison of patients with current vs past MDD revealed significantly more global brain atrophy in those with current MDD (B = –1.44%; 95% CI, –2.26% to –0.63%; *P*=.001).[45] Remission also has a significant clinical impact on metabolism. Insulin sensitivity has been shown to increase in individuals who remit from depression with antidepressants.[46] One study revealed that insulin sensitivity was significantly lower in untreated depressed individuals compared with patients on antidepressants and those without depression, $F(2,55) = 4.38$, $P<.05$.[47]

The medical morbidity and mortality of untreated depression are often underestimated with respect to those of other serious medical disorders.[48] Depressed patients are much more likely to have cardiovascular illness and 6 times more likely to die within 6 months of an acute myocardial infarction.[49] Depression carries an increased risk for many other medical conditions as well, including diabetes, stroke, cancer, epilepsy, and Parkinson's disease.[48] Depressed patients are also much more likely to become nonadherent with medications prescribed for other chronic conditions, inflicting an additional disease burden that is often overlooked.[50]

The consequences of failing to attain remission from depression are profound, impacting both the individual and

TABLE 4 Commonly used antidepressants with traditional mechanisms of action[58-60]

Agents	Safety and efficacy of drug class
Selective serotonin reuptake inhibitors (SSRIs)	
Examples: citalopram, fluoxetine, paroxetine	Modest improvements in MDD, leaving many patients with residual symptoms Adverse effects: GI adverse effects, drowsiness, nervousness, insomnia, sexual dysfunction
Tricyclic antidepressants (TCAs) (or first-generation serotonin-norepinephrine reuptake inhibitors [SNRIs])	
Examples: amitriptyline, doxepin, desipramine	Efficacy similar to SSRIs; however, significantly more adverse events Adverse effects: Drowsiness, anticholinergic effects, weight gain, sexual dysfunction, orthostatic hypotension
Monoamine oxidase inhibitors (MAOIs)	
Examples: phenelzine, isocarboxazid, selegiline	Considered especially efficacious in atypical symptoms of depression and in refractory patients, with slight efficacy advantage over TCAs Adverse effects: Orthostatic hypotension, sexual dysfunction, weight gain, daytime sleepiness; hypertensive crisis with certain foods, drugs, and OTC medications
SNRIs (second generation)	
Examples: venlafaxine, duloxetine, levomilnacipran	Theorized that enhanced norepinephrine transmission could address depressive symptoms not adequately addressed by SSRIs Adverse effects: Similar to those of SSRIs, but higher risk of causing hypertension and/or tachycardia; risk of sweating, nausea, and other GI adverse effects

GI, gastrointestinal; MDD, major depressive disorder; OTC, over the counter.

TABLE 5 Antidepressants with nontraditional mechanisms of action[58-60]

Agents	Safety and efficacy of drug class
Examples: bupropion, vilazodone, vortioxetine	Bupropion inhibits both norepinephrine and dopamine; associated adverse effects include anxiety, insomnia, and tremor Vilazodone is a novel 5-HT1A partial agonist and serotonin reuptake inhibitor; adverse effects include nausea, diarrhea, headache, and weight gain Vortioxetine is a multiple serotonin modulator and uptake inhibitor; adverse effects are similar to those of SSRIs, with lower risk of sexual dysfunction

SSRIs, selective serotonin reuptake inhibitors.

society (**TABLE 3**).[51-53] Depression carries an elevated risk of suicide and premature death.[54] For young adults between 15 and 20 years of age, suicide is the second leading cause of death worldwide, and in the United States, nearly 8% of high school students reported suicide attempts.[55] At the other end of the life spectrum, elderly men have a rate of completed suicide that is 5 to 10 times higher than the rest of the adult population.[54] Overall, individuals with severe mood or thought disorders have life spans that are 14 to 32 years shorter than the rest of the population despite recent efforts to improve the quality of their medical care.[56]

Management strategies: Pharmacologic

Despite the availability of a wide variety of antidepressant medications, data from the National Institute of Mental Health (NIMH)–sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial found that only 50% of patients with MDD responded to first-line monotherapy and only about 30% achieved remission.[6] Even in patients with MDD who do achieve remission, roughly half are estimated to continue to experience residual symptoms.[57]

TABLE 4 lists antidepressants commonly used in clinical practice that have traditional mechanisms of action, and **TABLE 5** lists therapies with nontraditional mechanisms of action.[58-60] It is argued that the clinical heterogeneity of depression renders traditional antidepressants—with their selective targeting of the serotonin transporter (SERT)—suboptimal in many patients in achieving sustained remission and recovery.[61-64] Subsequently, there has been a plethora of data on novel depression pharmacotherapies that combine multiple simultaneous pharmacologic mechanisms in addition to SERT inhibition, including 5-HT1A agonism with SERT inhibition,[65] triple reuptake inhibitors with norepinephrine and dopamine reuptake inhibition with SERT inhibition,[66] and multimodal antidepressant activity at the G receptor mode (5-HT1A and 5-HT1B partial agonism and 5-HT7 antagonism), at the ion channel mode (5-HT3 antagonism) as well as the neurotransmitter transporter mode (SERT inhibition).[67,68] These novel therapeutic approaches may facilitate symptomatic remission and recovery across a broad constellation of depressive symptoms. Moreover, the more diverse pharmacodynamics of these novel strategies may mitigate some of the treatment-emergent adverse effects typically observed with traditional antidepressants.[64] As adverse effects can impact not only an individual's functioning and sense of well-being but also his or her perceived value of a pharmacotherapy, therapeutic strategies with greater tolerability may help optimize adherence.[69] It should be noted, however, that meta-analyses have not indicated a clear clinical benefit of one antidepressant over others.[70]

Management strategies: Nonpharmacologic

Although pharmacologic therapy typically constitutes the mainstay of management for MDD, nonpharmacologic strategies are an important and viable component of comprehensive MDD care. The American Psychiatric Association (APA) guidelines suggest that the acute phase of depression management may include pharmacotherapy, psychotherapy, or other somatic therapies such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), or phototherapy.[71] An efficacy comparison of 64 studies on ECT, rTMS, vagus nerve stimulation (VNS), and/or cognitive-behavioral therapy (CBT) or interpersonal therapy (IPT) showed no differences between therapies for depression severity, response rates, and remission rates, although no trial compared psychotherapy with another nonpharmacologic therapy.[72] Only one study in this review compared nonpharmacologic therapy (ECT) to pharmacotherapy (paroxetine); the nonpharmacologic therapy significantly improved depression severity (9 points on the Hamilton Rating Scale for Depression [HAM-D], P=.001) and treatment response (71.4% ECT vs 27.8% paroxetine, P=.006).[72]

TABLE 6 describes various nonpharmacologic therapies and their associated adverse effects and contraindications.[72]

Prior psychotherapy has been shown to have an enduring effect that is at least as efficacious as maintenance with an

TABLE 6 Nonpharmacologic therapies for depression[72]

Intervention	Description	Adverse effects/contraindications
ECT	Passing an electric current through the brain after administering anesthetic and muscle relaxants to produce a convulsion	Potential risks include seizure and adverse cognitive effects, in addition to the risk of adverse effects from anesthesia There is an increased risk of complications in patients with unstable cardiac disease, ischemia, arrhythmias, hemorrhage, or increased intracranial pressure
rTMS	Focal magnetic stimulation through the scalp without the use of anesthesia	Potential adverse effects include mild headaches, scalp pain, syncope, and transient hearing changes Should not be used in patients with a high risk of seizure or patients who have metal objects anywhere in the body (such as cardiac pacemakers, medication pumps, and cochlear implants) except the mouth
VNS	Surgically implanted electrodes around the left vagus nerve to modulate mood and control seizures	Potential adverse effects include voice alteration, cough, neck pain, paresthesia, and dyspnea Should not be used in patients with bilateral or left cervical vagotomy Patients with VNS implants should not receive shortwave diathermy, microwave diathermy, or ultrasound diathermy
Psychotherapies (CBT or IPT)	Psychotherapy to identify negative depressogenic cognitions or interpersonal behaviors	CBT and IPT do not have any serious risks or adverse effects associated with them Should not be used in patients with cognitive disorders, cognitive impairment, or limited cognitive functioning
Exercise	Can be aerobic or anaerobic physical activity	Considerations should be made for exercise intensity and any comorbid medical conditions

CBT, cognitive-behavioral therapy; ECT, electroconvulsive therapy; IPT, interpersonal therapy; rTMS, repetitive transcranial magnetic stimulation; VNS, vagus nerve stimulation.

antidepressant.[73] The enduring effects of psychotherapy were also observed in a study in which psychotherapy reduced the risk of relapse relative to placebo (X^2=6.01, *df*=1, *P*=.01), as did maintenance antidepressant monotherapy (X^2=4.55, *df*=1, *P*=.03) in unstable remitters.[74]

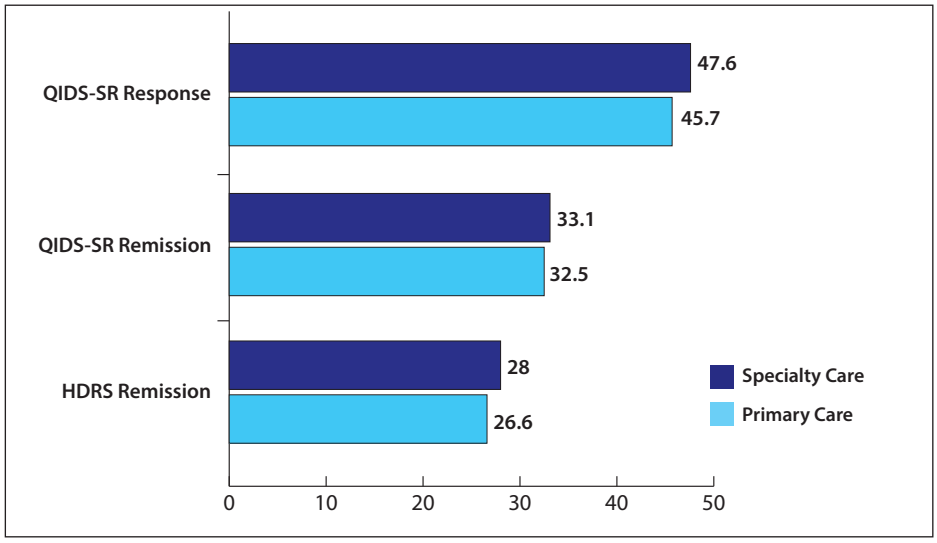
Exercise is another nonpharmacologic intervention that has demonstrated some benefit in reducing depressive symptoms. A meta-analysis of 35 randomized clinical trials revealed a moderate clinical effect of exercise on depression (standardized mean difference [SMD] = –0.62, 95% CI, –0.81 to –0.42).[75] In a prospective, randomized controlled trial of individuals with depression exercising at home or in a supervised group, remission rates for exercise were comparable to those of individuals receiving antidepressant medication (supervised exercise, 45%; home-based exercise, 40%; medication, 47%; placebo, 31%; *P*=.057).[76] Exercise as an adjunctive therapy with antidepressants has also demonstrated therapeutic efficacy in depression. In a comparison of higher- versus lower-dose exercise groups, 12-week remission rates were higher in the high-level group (28.3% vs 15.5%; *P*<.06).[77]

Additional nonpharmacologic therapies that have shown some benefit in symptom reduction in depression include "natural" or herbal approaches, such as St. John's wort, S-adenosyl methionine (SAMe), and omega-3 fatty acids, bibliotherapy (a form of guided self-help), and behavioral activation. See Velehorschi (2014) for a complete review.[78]

Considerations for treatment selection and modification

Treatment selection for MDD should include consideration of the patient's preference, prior positive response to therapy, response in other family members, short- and long-term adverse events, interaction with nonpsychiatric medication, as well as concurrent medical and/or psychiatric disorders.[60,70] Treatment modification may be necessary in patients whose symptoms fail to remit with initial therapy. Modification may involve escalating the dose (to the maximum safe therapeutic dose), augmenting therapy, or switching agents. Augmenting current therapy can maintain the partial therapeutic benefit from initial therapy and avoid negative effects associated with discontinuation. Augmenting with atypical antipsychotics, the most studied augmentation strategy, has the potential to cause adverse effects, including metabolic changes and extrapyramidal symptoms.[79,80] The addition of lithium

FIGURE 5 **Impact of measurement-based care on depression outcomes in primary care vs specialty care settings[84]**



HDRS, Hamilton Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology–Self-Report.

demonstrated efficacy with tricyclic antidepressants (TCAs) but not more novel therapies.[79,80] It is important to consider the risk of drug-drug interactions and nonadherence when implementing augmentation strategies for depression.[80-82]

If a patient shows partial or no response to current therapy, clinicians may decide to switch to another agent within the same drug class (eg, a serotonin-norepinephrine reuptake inhibitor [SNRI] to an SNRI) or to a drug class with a different mechanism of action (eg, a TCA to a selective serotonin reuptake inhibitor [SSRI]). Some benefits are associated with switching as opposed to augmenting depression therapy, including potentially lower costs and risks of adverse effects.[80] However, clinicians must be vigilant in noting symptoms of discontinuation as the result of abrupt cessation of medication.[80,83]

Measurement-based care for MDD

Measurement-based care (MBC) is the systematic, quantitative assessment of symptoms in patients with MDD. To enhance clinical judgment, APA treatment guidelines recommend the regular and systematic evaluation of illness course and treatment impact (every 4 to 8 weeks) using standardized tools to assess depressive symptoms.[71] Use of MBC can facilitate detection of unresolved symptoms, adequacy of treatment response, and adherence to prescribed therapy. Moreover, the use of MBC has been shown to enable PCPs to render comparable quality of care and clinical outcomes as those achieved in specialty care settings (**FIGURE 5**).[84]

However, clinicians are not using MBC with the indicated frequency. Electronic records from a large integrated health system of 84,418 patients (with 207,265 completed PHQ-9s) revealed that only 30% of patients completing a baseline PHQ-9 completed more than one subsequent PHQ-9, despite clinicians being advised to administer the PHQ-9 at every visit for depression treatment.[85] Notably, 45% of the PHQ-9s were administered by specialty mental health care providers while 54% were administered by PCPs.

The routine use of MBC to assess symptoms and adverse effects using standardized tools—with guidance at critical decision points relative to how and when to modify treatment—provides a flexible therapeutic strategy to ensure the delivery of safe, effective antidepressant care.[84] This approach also facilitates the use of a more comprehensive, yet less complicated, decision support system.[86] An essential component of MBC is the use of staff to closely monitor response and manage care.[87-91] In conjunction, MBC further involves the use of critical decision points wherein—at specified scheduled times—the clinician can evaluate the need for treatment modification based on time on medication, total depressive severity score, and adverse effect tolerability.[84] Collectively, these key features have been demonstrated feasible in a busy, real-world primary care setting.[92]

Monitoring depressive symptoms

Despite the availability of numerous diverse antidepressant pharmacotherapies for MDD, response and remission rates, particularly following adequate drug trials, remain disappointing.[7,91,93] It is therefore critical for clinicians to monitor for residual depressive symptoms as well as treatment effectiveness so they can determine when to adjust, switch, or augment therapy. Evidence demonstrates that regular patient symptom monitoring improves clinical outcomes in depression management in the primary care setting, including greater adherence to treatment.[94,95] APA guidelines recommend assessing treatment response every 4 to 8 weeks.[21] Using an MBC model, however, others have suggested more aggressive monitoring, particularly in the acute phase of treatment. That is, depressive symptoms should be assessed every 2 weeks for the first 6 weeks of treatment, followed

by every 3 weeks until remission or an adequate treatment response is achieved.[96] Following remission (continuation phase), assessment should occur every 3 months for prevention of relapse and recurrence.[97]

Managing comorbidities

Depression is common in patients with chronic medical conditions and may have an adverse impact on disease course, resulting in decreased quality of life, increased functional impairments, and increased mortality.[98] Depression comorbid with chronic illness significantly reduces health-related quality of life relative to depression with no chronic illness.[99] Depression comorbid with chronic medical conditions is also associated with increased health care utilization, disability, and work absenteeism relative to chronic medical illness without depression, even when controlling for the burden of a chronic medical condition.[100]

A meta-analysis examining the correlation between depression care and clinical outcomes of chronic medical conditions confirmed the effectiveness of collaborative care interventions for managing depression in the primary care setting.[101] Individuals with depression and one or more chronic medical conditions who received collaborative care achieved greater improvement in depression symptoms, response, remission, and depression-free days, as well as greater quality of life and satisfaction with care, than did controls.[101]

Monitoring treatment adverse effects

Adverse events often impair patient adherence to treatment. Common adverse events of antidepressant therapy include nausea, insomnia, dizziness, headache, sexual dysfunction, and weight gain.[102] Researchers conducting a meta-analysis of effectiveness of interventions to improve adherence to antidepressant therapy observed that collaborative care interventions demonstrated significant improvements in adherence during both the acute and continuation phase and improved clinical outcomes.[103] Education strategies alone did not demonstrate significant improvement, an outcome supported by another meta-analysis.[104] Clinicians should implement systematic strategies to monitor for treatment-related adverse effects and adjust therapy accordingly as soon as possible.

Monitoring treatment adherence

People with mental illness are often dissatisfied with the quality of care they receive. A survey by the National Alliance on Mental Illness (NAMI) reported that only about one-third (35%) of adults living with depression are very/extremely satisfied with their current treatment, while caregivers reported that only 20% of depressed individuals for whom they care are satisfied with their current treatment.[105] Adherence to antidepressant therapy is a critical component of depression management. However, if patients are not satisfied with their prescribed therapy, they are not likely to remain adherent. Rates of nonadherence to antidepressant therapy have been reported as high as 28% in the first 4 weeks of therapy and 44% to 52% after 3 months.[106] Patients have indicated a desire to be more involved in their mental health treatment decisions and have indicated preferences for therapeutic strategies, with an emphasis on recovery as opposed to an amelioration of symptoms.[107,108] Developing treatment strategies that address patient needs and preferences is a critical component of MDD care and may facilitate treatment adherence.

Conclusion

Major depression is a complex disorder that is often underdiagnosed and undertreated. The President's New Freedom Commission on Mental Health report highlighted the extensive barriers for patients in the mental health system and emphasized the role of collaborative relationships in achieving wellness and recovery.[109] As recovery and remission, not mere response, are the optimal therapeutic goals, clinicians should incorporate metrics to assist in the recognition and management of patients with MDD and use pharmacologic and nonpharmacologic therapies within a collaborative treatment plan to help patients achieve maximally beneficial outcomes. ●

REFERENCES

1. Abi-Dargham A. Do we still believe in the dopamine hypothesis? New data bring new evidence. *Int J Neuropsychopharmacol*. 2004;7(suppl 1):S1-5.
2. World Health Organization. *The Global Burden of Disease: 2004 Update*. Geneva, Switzerland: World Health Organization; 2008; http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. Accessed June 27, 2013.
3. Greenberg PE, Kessler RC, Birnbaum HG, et al. The economic burden of depression in the United States: how did it change between 1990 and 2000? *J Clin Psychiatry*. 2003;64(12):1465-1475.
4. Greenberg PE, Leong SA, Birnbaum HG, et al. The economic burden of depression with painful symptoms. *J Clin Psychiatry*. 2003;64(suppl 7):17-23.
5. US Department of Health and Human Services. 2013 Annual Progress Report to Congress: National Strategy for Quality Improvement in Health Care. 2013. http://www.ahrq.gov/workingforquality/nqs/nqs2013annlrpt.htm. Accessed June 26, 2015.
6. Mark TL, Levit KR, Buck JA. Datapoints: psychotropic drug prescriptions by medical specialty. *Psychiatr Serv*. 2009;60(9):1167.
7. 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.
8. Wang PS, Lane M, Olfson M, et al. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):629-640.
9. Egede LE. Failure to recognize depression in primary care: issues and challenges. *J Gen Intern Med*. 2007;22(5):701-703.
10. 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.
11. Palmer SC, Coyne JC. Screening for depression in medical care: pitfalls, alternatives, and revised priorities. *J Psychosom Res*. 2003;54(4):279-287.
12. Thombs BD, Coyne JC, Cuijpers P, et al. Rethinking recommendations for screening for depression in primary care. *CMAJ*. 2012;184(4):413-418.
13. US Preventive Services Task Force. Screening for depression: recommendations and rationale. *Ann Intern Med*. 2002;136(10):760-764.
14. O'Connor EA, Whitlock EP, Beil TL, et al. Screening for depression in adult patients in primary care settings: a systematic evidence review. *Ann Intern Med*. 2009;151(11):793-803.

15. US Preventive Services Task Force. *Update Summary: Depression in Adults: Screening.* March 2014. http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryDraft/depression-in-adults-screening1. Accessed June 16, 2015.
16. Gilbody S, Sheldon T, House A. Screening and case-finding instruments for depression: a meta-analysis. *CMAJ*. 2008;178(8):997-1003.
17. Thombs BD, Ziegelstein RC, Roseman M, et al. There are no randomized controlled trials that support the United States Preventive Services Task Force Guideline on screening for depression in primary care: a systematic review. *BMC Med*. 2014;12:13.
18. Centers for Medicare and Medicaid Services. Decision memo for screening for depression in adults (CAG-00425N). 2011. http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=251. Accessed May 1, 2015.
19. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
20. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care*. 2003;41(11):1284-1292.
21. Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association. *Am J Psychiatry*. 2000;157(4 suppl):1-45.
22. O'Connor EA, Whitlock EP, Gaynes BN, et al. *Screening for Depression in Adults and Older Adults in Primary Care: An Updated Systematic Review*. Evidence Synthesis No. 75. AHRQ Publication No. 10-05143-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2009:167.
23. Angst J, Gamma A, Lewinsohn P. The evolving epidemiology of bipolar disorder. *World Psychiatry*. 2002;1(3):146-148.
24. Ghaemi SN, Sachs GS, Chiou AM, et al. Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? *J Affective Dis*. 1999;52(1-3):135-144.
25. Kamat SA, Rajagopalan K, Pethick N, et al. Prevalence and humanistic impact of potential misdiagnosis of bipolar disorder among patients with major depressive disorder in a commercially insured population. *J Manag Care Pharm*. 2008;14(7):631-642.
26. Olfson M, Das AK, Gameroff MJ, et al. Bipolar depression in a low-income primary care clinic. *Am J Psychiatry*. 2005;162(11):2146-2151.
27. Hirschfeld RM, Williams JB, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am J Psychiatry*. 2000;157(11):1873-1875.
28. Magellan Health. Treating depression in the primary care setting. 2013. https://www.magellanprovider.com/MHS/MGL/education/member_ed/F-PCE10%20PCP%20Dep.pdf. Accessed September 15, 2014.
29. Kessler RC, Demler O, Frank RG, et al. Prevalence and treatment of mental disorders, 1990 to 2003. *N Engl J Med*. 2005;352(24):2515-2523.
30. Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. *Lancet*. 2009;374(9690):609-619.
31. 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.
32. Gaynes BN, Warden D, Trivedi MH, et al. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr Serv*. 2009;60(11):1439-1445.
33. Rush AJ, Kraemer HC, Sackeim HA, et al. Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology*. 2006;31(9):1841-1853.
34. Substance Abuse and Mental Health Services Administration. *Achieving the Promise: Transforming Mental Health Care in America, Executive Summary*. 2003. http://store.samhsa.gov/product/Achieving-the-Promise-Transforming-Mental-Health-Care-in-America-Executive-Summary/SMA03-3831. Accessed May 1, 2015.
35. Furukawa TA, Fujita A, Harai H, et al. Definitions of recovery and outcomes of major depression: results from a 10-year follow-up. *Acta Psychiatr Scand*. 2008;117(1):35-40.
36. Gaynes BN, Rush AJ, Trivedi MH, et al. The STAR*D study: treating depression in the real world. *Cleve Clin J Med*. 2008;75(1):57-66.
37. McClintock SM, Husain MM, Wisniewski SR, et al. Residual symptoms in depressed outpatients who respond by 50% but do not remit to antidepressant medication. *J Clin Psychopharmacol*. 2011;31(2):180-186.
38. Paykel ES, Ramana R, Cooper Z, et al. Residual symptoms after partial remission: an important outcome in depression. *Psychol Med*. 1995;25(6):1171-1180.
39. 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.
40. Romera I, Perez V, Menchon JM, et al. Social and occupational functioning impairment in patients in partial versus complete remission of a major depressive disorder episode. A six-month prospective epidemiological study. *Eur Psychiatry*. 2010;25(1):58-65.
41. Zimmerman M, Posternak MA, Chelminski I. Heterogeneity among depressed outpatients considered to be in remission. *Compr Psychiatry*. 2007;48(2):113-117.
42. Solomon DA, Leon AC, Coryell W, et al. Predicting recovery from episodes of major depression. *J Affect Dis*. 2008;107(1-3):285-291.
43. Gelenberg AJ, Freeman MP, Markowitz JC, et al. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*. 3rd ed. Arlington, VA: American Psychiatric Association; 2010. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Accessed July 15, 2015.
44. Kempton MJ, Salvador Z, Munafo MR, et al. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. *Arch Genl Psychiatry*. 2011;68(7):675-690.
45. Geerlings MI, Sigurdsson S, Eiriksdottir G, et al. Associations of current and remitted major depressive disorder with brain atrophy: the AGES-Reykjavik Study. *Psychol Med*. 2013;43(2):317-328.
46. Weber-Hamann B, Gilles M, Lederbogen F, et al. Improved insulin sensitivity in 80 nondiabetic patients with MDD after clinical remission in a double-blind, randomized trial of amitriptyline and paroxetine. *J Clin Psychiatry*. 2006;67(12):1856-1861.
47. Wagner J, Allen NA, Swalley LM, et al. Depression, depression treatment, and insulin sensitivity in adults at risk for type 2 diabetes. *Diabetes Res Clin Pract*. 2009;86(2):96-103.
48. Schulz R, Drayer RA, Rollman BL. Depression as a risk factor for non-suicide mortality in the elderly. *Biol Psychiatry*. 2002;52(3):205-225.
49. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction: impact on 6-month survival. *JAMA*. 1993;270(15):1819-1825.
50. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*. 2000;160(14):2101-2107.
51. Fawcett J. Antidepressants: partial response in chronic depression. *Br J Psychiatry Suppl*. 1994(26):37-41.
52. 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.
53. Kennedy N, Foy K. The impact of residual symptoms on outcome of major depression. *Curr Psychiatry Rep*. 2005;7(6):441-446.
54. US Department of Health and Human Services. Report of the US Surgeon General and of the National Alliance for Suicide Prevention. *National Strategy for Suicide Prevention: Goals and Objectives for Action*. 2012. www.surgeongeneral.gov/library/reports/national-strategy-suicide-prevention/index.html.
55. Eaton DK, Kann L, Kinchen S, et al. Youth risk behavior surveillance—United States, 2011. *MMWR Surveill Summ*. 2012;61(4):1-162.
56. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis*. 2006;3(2):A42.
57. Trivedi MH, Hollander E, Nutt D, et al. Clinical evidence and potential neurobiological underpinnings of unresolved symptoms of depression. *J Clin Psychiatry*. 2008;69(2):246-258.
58. Anderson IM, Ferrier IN, Baldwin RC, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *J Psychopharmacol*. 2008;22(4):343-396.
59. Deardorff WJ, Grossberg GT. A review of the clinical efficacy, safety and tolerability of the antidepressants vilazodone, levomilnacipran and vortioxetine. *Expert Opin Pharmacother*. 2014;15(17):2525-2542.
60. Teter CJ, Kando JC, Wells BG. *Major Depressive Disorder*. 9th ed. New York. NY: McGraw Hill; 2014.
61. Krishnan V, Nestler EJ. Linking molecules to mood: new insight into the biology of depression. *Am J Psychiatry*. 2010;167(11):1305-1320.
62. Mnie-Filali O, Faure C, Lambas-Senas L, et al. Pharmacological blockade of 5-HT7 receptors as a putative fast acting antidepressant strategy. *Neuropsychopharmacology*. 2011;36(6):1275-1288.
63. O'Leary OF, Dinan TG, Cryan JF. Faster, better, stronger: towards new antidepressant therapeutic strategies. *Euro J Pharmacol*. 2015;753:32-50.
64. Stahl SM, Lee-Zimmerman C, Cartwright S, et al. Serotonergic drugs for depression and beyond. *Curr Drug Targets*. 2013;14(5):578-585.
65. Celada P, Bortolozzi A, Artigas F. Serotonin 5-HT receptors as targets for agents to treat psychiatric disorders: rationale and current status of research. *CNS Drugs*. 2013;27(9):703-716..
66. Learned S, Graff O, Roychowdhury S, et al. Efficacy, safety, and tolerability of a triple reuptake inhibitor GSK372475 in the treatment of patients with major depressive disorder: two randomized, placebo- and active-controlled clinical trials. *J Psychopharmacol*. 2012;26(5):653-662.
67. Pehrson AL, Cremers T, Betry C, et al. Lu AA21004, a novel multimodal antidepressant, produces regionally selective increases of multiple neurotransmitters—a rat microdialysis and electrophysiology study. *Eur Neuropsychopharmacol*. 2013;23(2):133-145.
68. Guilloux JP, Mendez-David I, Pehrson A, et al. Antidepressant and anxiolytic potential of the multimodal antidepressant vortioxetine (Lu AA21004) assessed by behavioural and neurogenesis outcomes in mice. *Neuropharmacology*. 2013;73C:147-159.
69. Citrome L. Vortioxetine for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant—what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract*. 2014;68(1):60-82.
70. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. *Ann Intern Med*. 2011;155(11):772-785.
71. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*. 3rd

ed. Arlington, VA: American Psychiatric Association; 2010. http://psychiatryonline.org/guidelines. Accessed May 7, 2015.
72. Gaynes BN, Lux, L, Lloyd S, et al. *Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults*. Agency for Healthcare Research and Quality comparative effectiveness review no. 33. 2011; http://www.effectivehealthcare.ahrq.gov/trd.cfm. Accessed May 7, 2015.
73. Dobson KS, Hollon SD, Dimidjian S, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the prevention of relapse and recurrence in major depression. *J Consult Clin Psychol*. 2008;76(3):468-477.
74. Segal ZV, Bieling P, Young T, et al. Antidepressant monotherapy vs sequential pharmacotherapy and mindfulness-based cognitive therapy, or placebo, for relapse prophylaxis in recurrent depression. A*rch Gen Psychiatry*. 2010;67(12):1256-1264.
75. Cooney GM, Dwan K, Greig CA, et al. Exercise for depression. *Cochrane Database Syst Rev*. 2013;9:CD004366.
76. Blumenthal JA, Babyak MA, Doraiswamy PM, et al. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med*. 2007;69(7):587-596.
77. Trivedi MH, Greer TL, Church TS, et al. Exercise as an augmentation treatment for nonremitted major depressive disorder: a randomized, parallel dose comparison. *J Clin Psychiatry*. 2011;72(5):677-684.
78. Velehorschi C, Bleau P, Vermani M, et al. Understanding the role of adjunctive nonpharmacological therapies in management of the multiple pathways to depression. *Psychiatry Res*. 2014;220(suppl 1):S34-44.
79. Papakostas GI. Managing partial response or nonresponse: switching, augmentation, and combination strategies for major depressive disorder. *J Clin Psychiatry*. 2009;70(suppl 6):16-25.
80. Manning JS, Jackson WC. Treating depression in primary care: initial and follow-up treatment strategies. *J Clin Psychiatry*. 2015;76(2):e5.
81. Preston TC, Shelton RC. Treatment resistant depression: strategies for primary care. *Curr Psychiatry Rep*. 2013;15(7):370.
82. Shelton RC, Osuntokun O, Heinloth AN, et al. Therapeutic options for treatment-resistant depression. *CNS Drugs*. 2010;24(2):131-161.
83. Gaynes BN, Dusetzina SB, Ellis AR, et al. Treating depression after initial treatment failure: directly comparing switch and augmenting strategies in STAR*D. *J Clin Psychopharmacology*. 2012;32(1):114-119.
84. Gaynes BN, Rush AJ, Trivedi MH, et al. Primary versus specialty care outcomes for depressed outpatients managed with measurement-based care: results from STAR*D. *J Gen Intern Med*. 2008;23(5):551-560.
85. Simon GE, Rutter CM, Peterson D, et al. Does response on the PHQ-9 Depression Questionnaire predict subsequent suicide attempt or suicide death? *Psychiatr Serv*. 2013;64(12):1195-1202.
86. Kawamoto K, Houlihan CA, Balas EA, et al. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. *BMJ*. 2005;330(7494):765.
87. Dietrich AJ, Oxman TE, Williams JW Jr, et al. Re-engineering systems for the treatment of depression in primary care: cluster randomised controlled trial. *BMJ*. 2004;329(7466):602.
88. Hunkeler EM, Meresman JF, Hargreaves WA, et al. Efficacy of nurse telehealth care and peer support in augmenting treatment of depression in primary care. *Arch Fam Med*. 2000;9(8):700-708.
89. Katon W, Robinson P, Von Korff M, et al. A multifaceted intervention to improve treatment of depression in primary care. *Arch Gen Psychiatry*. 1996;53(10):924-932.
90. Rost K, Nutting P, Smith J, et al. Improving depression outcomes in community primary care practice: a randomized trial of the quEST intervention. Quality Enhancement by Strategic Teaming. *J Gen Intern Med*. 2001;16(3):143-149.
91. Unutzer J, Katon W, Callahan CM, et al. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA*. 2002;288(22):2836-2845.
92. Landis SE, Gaynes BN, Morrissey JP, et al. Generalist care managers for the treatment of depressed Medicaid patients in North Carolina: a pilot study. *BMC Fam Pract*. 2007;8:7.
93. Rush AJ, Trivedi M, Carmody TJ, et al. One-year clinical outcomes of depressed public sector outpatients: a benchmark for subsequent studies. *Biol Psychiatry*. 2004;56(1):46-53.
94. Yeung AS, Jing Y, Brenneman SK, et al. Clinical Outcomes in Measurement-based Treatment (Comet): a trial of depression monitoring and feedback to primary care physicians. *Depress Anxiety*. 2012;29(10):865-873.
95. Chang TE, Jing Y, Yeung AS, et al. Depression monitoring and patient behavior in the Clinical Outcomes in MEasurement-Based Treatment (COMET) trial. *Psychiatr Serv*. 2014;65(8):1058-1061.
96. Trivedi MH. Evaluating and monitoring treatment response in depression using measurement-based assessment and rating scales. *J Clin Psychiatry*. 2013;74(7):e14.
97. Suehs BT, Argo TR, Bendele SD, et al. Texas Medication Algorithm Project Procedural Manual: Major Depressive Disorder Algorithms. 2008; http://www.pbhcare.org/pubdocs/upload/documents/TMAP%20Depression%202010.pdf. Accessed May 8, 2015.
98. Kang HJ, Kim SY, Bae KY, et al. Comorbidity of depression with physical disorders: research and clinical implications. *Chonnam Med J*. 2015;51(1):8-18.
99. Moussavi S, Chatterji S, Verdes E, et al. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet*. 2007;370(9590):851-858.
100. Stein MB, Cox BJ, Afifi TO, et al. Does co-morbid depressive illness magnify the impact of chronic physical illness? A population-based perspective. *Psychol Med*. 2006;36(5):587-596.
101. Watson LC, Amick HR, Gaynes BN, et al. Practice-based interventions addressing concomitant depression and chronic medical conditions in the primary care setting: a systematic review and meta-analysis. *J Prim Care Community Health*. 2013;4(4):294-306.
102. Lin EH, Von Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. *Medical Care*. 1995;33(1):67-74.
103. Vergouwen AC, Bakker A, Katon WJ, et al. Improving adherence to antidepressants: a systematic review of interventions. *J Clin Psych*. 2003;64(12):1415-1420.
104. Chong WW, Aslani P, Chen TF. Effectiveness of interventions to improve antidepressant medication adherence: a systematic review. *Int J Clin Pract*. 2011;65(9):954-975.
105. Harris Interactive. Depression Survey Initiative. Created for the National Alliance on Mental Illness (NAMI). 2009. http://www.nami.org/Content/NavigationMenu/Mental_Illnesses/Depression/NAMIDepressionReportFINAL.pdf. Accessed June 26, 2013.
106. 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.
107. Klein E, Rosenberg J, Rosenberg S. Whose treatment is it anyway? The role of consumer preferences in mental health care. *Am J Psychiatr Rehabil*. 2007;10:65-80.
108. Deegan PE. The lived experience of using psychiatric medication in the recovery process and a shared decision-making program to support it. *Psychiatr Rehabil J*. Summer 2007;31(1):62-69.
109. The President's New Freedom Commission on Mental Health. *Achieving the Promise: Transforming Mental Health Care in America. Final Report*. 2003. http://govinfo.library.unt.edu/mentalhealthcommission/reports/FinalReport/downloads/FinalReport.pdf. Accessed September 18, 2014.

Please visit http://www.rapidcme.com/clinibriefs.aspx and complete the posttest and evaluation form for CME credit.

SUPPLEMENT TO
THE JOURNAL OF
FAMILY PRACTICE®