Using Measurement Strategies to Identify and Monitor Residual Symptoms

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Major depressive disorder (MDD) is a persistent, pervasive, and chronic disorder that significantly affects patients' functioning and quality of life. Most patients treated for MDD continue to have residual symptoms after acute treatment with pharmacotherapy. One of the most commonly encountered residual symptoms is cognitive dysfunction, which substantially affects patient outcomes. While antidepressant monotherapy is an effective first-line treatment for some patients with MDD, patients with residual symptoms (eg, cognitive dysfunction) will require an additional treatment intervention such as augmentation or switch to an alternative treatment strategy. Measurement-based care has been demonstrated to improve patient outcomes in MDD. The clinical importance of cognitive dysfunction in MDD invites the need to probe, screen, and measure the extent of cognitive impairment.

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Major depressive disorder (MDD) is a prevalent condition associated with high rates of nonrecovery, recurrence, and illness-associated burden. The therapeutic objectives in MDD are to achieve symptom remission, functional recovery, and return to mental and physical health. Toward this aim, evidence-based treatment strategies that incorporate measurement-based care increase the probability of success. It is also important to incorporate patient reported outcomes (eg, subjective cognitive complaints, quality of life) when determining whether the therapeutic objectives have been achieved.

TREATMENT OBJECTIVES

The treatment goals for MDD have evolved in the past 40 years (Figure 1). Soon after the introduction of antidepressant pharmacotherapy in the 1950s, the overarching goal of managing patients with depression was simply to improve symptoms. Subsequently, emphasis was placed on a categorical response, which typically was defined as a ≥ 50% improvement from baseline in depressive symptom severity. Further refinement of the therapeutic objectives resulted in the emphasis of full symptomatic remission defined as the abatement of active depressive symptoms. The impetus for this change was based on several lines of evidence indicating that subsyndromal depressive symptoms in MDD were associated with increased morbidity and mortality. Moreover, symptomatic remission increased the probability of functional recovery. Cost-of-illness studies[1] have pressed the point that MDD is a highly costly disorder, largely due to impaired role performance in the workplace. A derivative of this observation is the testable hypothesis that improved outcomes in MDD would result in lower costs to individuals, families, and societies.

Several studies[2,3] have documented that cognitive dysfunction in MDD is a principal mediator of functional impairment, notably in workplace settings. Notwithstanding cognitive impairment as a criterion item in a major depressive episode, cognitive dysfunction historically has received relatively little attention in MDD when compared with disturbances in mood or somatic domains. A pivot of sorts toward cognitive impairment is inspired by efforts to reduce cost of illness and to identify clinical pathological correlates that have prognosticative capability in depression.

MEASUREMENT-BASED CARE

Clinicians who provide care for individuals with MDD are encouraged to routinely measure not only symptoms and side effects but also functioning across the major domains.[4] Measurement-based care involves the use of objective tools to quantify the presence and severity of depressive symptoms, to identify and measure functional outcomes, and to determine the presence and severity of adverse events. Evidence[5] indicates that the incorporation of measurement-based care, a component of chronic disease management, increases the probability of remission, treatment persistence, and functional recovery (For a list of tools, see Supplementary eTable 1 at PSYCHIATRIST.COM.).

Screening Tools

Screening tools help clinicians determine whether to conduct a full diagnostic evaluation of an individual who may have depression. These questionnaires are often short and

can be filled out by the patient before a clinical appointment. For example, the 2-item Patient Health Questionnaire (PHQ-2) asks patients 2 questions about decreased interest in activities and feelings of hopelessness or depression.[6] If the PHQ-2 screen is positive, then the clinician can ask the patient to complete the PHQ-9, which queries patients on 9 features of depression.[7] Both of these questionnaires require less than 3 minutes for patients to complete.[8] Another brief and effective screening tool is the 7-item Hamilton Depression Rating Scale (HDRS-7), which takes less than 5 minutes to administer.[9]

While these tools are quick and efficient ways to screen for depressive symptoms in the clinical setting, screening tools should not be confused with diagnostic tools. Screening tools increase or decrease suspicion that an individual may have depression, but they do not diagnose depression.

Diagnostic Tools

After an initial screening, clinicians should employ diagnostic tools to identify a more precise diagnosis of MDD. The diagnosis is made clinically using the *Diagnostic and Statistical Manual (DSM)*,[10] but tools can supplement the manual. For example, the Structured Clinical Interview for *DSM-IV* Axis I Disorders has a clinician-rated version that is designed for clinical practice.[11] The Mini-International Neuropsychiatric Interview, which is based on both *DSM-IV-TR* and *International Classification of Diseases, Tenth Revision* criteria, is also appropriate for clinical practice.[12]

Unfortunately, many diagnostic tools are better suited for the research setting and are not practical for the busy office practice because they are often lengthy and cumbersome. However, some screening tools may also function as diagnostic tools, such as the PHQ-9.

Symptom Severity and Adverse Effect Tools

As in other areas of chronic disease management (eg, hypertension, diabetes), clinicians are encouraged to systematically probe and measure depressive symptomatology over time in patients with MDD. The PHQ-9 and the HDRS-7 are suitable to use in clinical practice.[9] The 16-item Quick Inventory of Depressive Symptomatology (QIDS)[13] can be completed by the clinician or by the patient and is also effective in clinical settings. Additionally, adverse effects of treatment should be tracked at each follow-up visit, and the

■ Monitoring patients' symptoms from baseline with measurement tools increases the chances of success in MDD treatment.

■ Using evidence-based treatments and intervening early in treatment with switching, combination, or adjunctive therapies can improve therapeutic outcomes for patients with MDD.

Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) is a useful tool for this purpose.

RESIDUAL SYMPTOMS IN DEPRESSION

The last 20 years have brought about substantial progress in the development of pharmacotherapy, psychosocial interventions, neurostimulation, and nutraceutical approaches to depression. Notwithstanding these developments, outcomes in depression remain disappointing. After acute pharmacotherapy, the majority of patients do not achieve the therapeutic objective of remission.[14] Common ongoing symptoms reported by patients include fatigue, sleep difficulties, and cognitive problems.[15]

Remission and Residual Symptoms

Patients who experience full remission of depressive symptoms are more likely than those who do not to achieve premorbid levels of psychosocial functioning.[16] Incomplete remission increases the risk of relapse and recurrence and predicts a chronic course of depression.[17] Remission with residual symptoms also increases the use of health care services and disability benefits[18] and the risk of suicide.[19] Incomplete remission stands in the way of recovery, affects the patient's children and other loved ones, and deprives employers and society of productive individuals.[20]

Many barriers can prevent full remission in depression, including lack of timely access to coordinated primary and/or preventative health care, lack of use of measurement-based care and evidence-based care, lack of resolution of comorbidities, nonadherence to and insufficient duration of treatment, and failure to address psychosocial matters.[4,20] Clinicians must do their best to address as many barriers as possible to help patients achieve asymptomatic remission.[4]

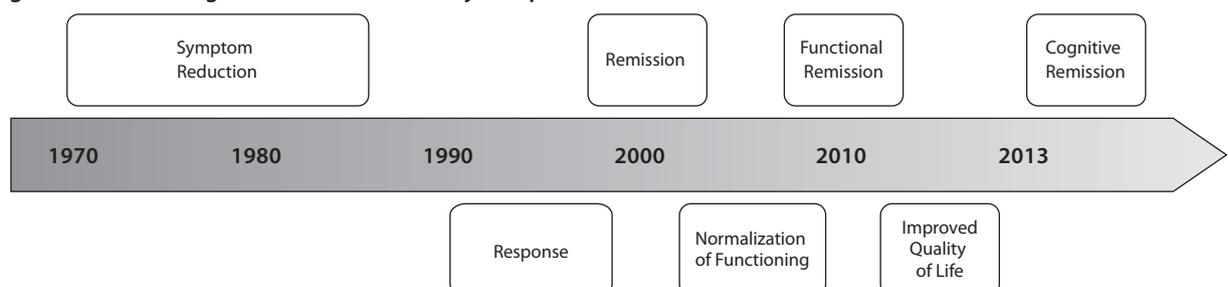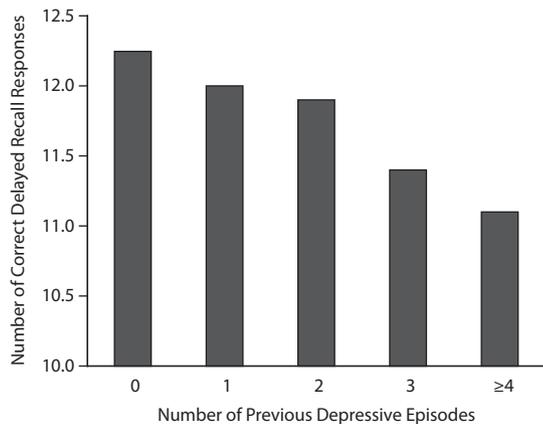**Figure 1. The Evolving Treatment Goals for Major Depressive Disorder**

Figure 2. Number of Correct Delayed Recall Responses at the Second Visit According to the Number of Previous Depressive Episodes in Patients With Major Depressive Disorder[a]

[a]Data from Gorwood et al.[27]

Residual Cognitive Symptoms

Cognitive dysfunction in depression has been defined and operationalized in several ways. A convenient categorization includes the subcategories *cold cognitive dysfunction*, defined as nonemotionally valenced, and *hot cognitive dysfunction*, which is best recognized by information processing biases in MDD.

Cognitive domains such as memory, executive function, attention, and information processing speed are negatively affected by depression.[21] Cognitive dysfunction is a principal mediator of functional impairment,[22] can be a factor in nonadherence to therapy,[23] and is associated with suicidal ideation.[24]

Cognitive impairment is common in patients with MDD. Conradi et al[15] found that 94% of patients in a 3-year prospective study reported cognitive problems during a depressive episode. Of the patients whose depression remitted, 44% continued to complain of residual cognitive impairment. It has also been reported that residual cognitive impairment may predispose and portend recurrence as well as be a principal explanation for suboptimal functional recovery.[25] Although cognitive complaints are frequent in people with depression, self-rated cognitive dysfunction might not be verified by objective measures.[26] Nevertheless, the use of objective and/or subjective measures of cognition increases the likelihood of detecting cognitive dysfunction in patients with MDD.[27]

In subsets of individuals with MDD, cognitive dysfunction may be progressive as a function of the number of depressive episodes. For example, Gorwood and colleagues[27] found a negative correlation between the number of correct responses on the Weschler paragraph recall index and the number of past depressive episodes ($P < .001$) and the length of depressive episodes ($P < .012$). Cognitive performance was reported to be decreased by 2% to 3% per depressive episode for the first 4 episodes (Figure 2).[27]

Information processing bias (hot cognitive dysfunction) in depression refers to the automatic bias that patients have toward negative stimuli; patients with depression have an attentional bias toward negative stimuli and a bias against positive stimuli. Erickson et al[28] empirically measured this paradigm by comparing people with depression who are not medicated with healthy controls on the Affective Go/No-Go Task, in which subjects are asked to respond to sets of happy and sad words. Depressed individuals needed a longer time before reacting to the happy words than the sad words, whereas healthy subjects showed the opposite pattern. Because cognitive problems significantly affect patients' functioning and quality of life, clinicians should work toward cognitive symptom remission. The forgoing series of observations has provided the basis for exploring the efficacy of some of the psychosocial treatments like mindfulness-based cognitive therapy.[29] In some cases, pharmacotherapy can help treat not only the more traditional depressive symptoms but also the cognitive domains affected by depression.

EVIDENCE-BASED TREATMENTS

In a large meta-analysis of 182 clinical trials, Papakostas and Fava[30] found that the rate of response with antidepressant treatment (53.8%) was higher than with placebo (37.3%) in patients with MDD. However, this response rate leaves much room for improvement, and no unequivocal gold standard exists in antidepressant treatment. Clinicians must use measurement tools and evidence to guide treatment selection.

Antidepressant treatments have differing success rates in treating various aspects of depression. In the process of treating patients, a particular aspect of their symptomatology (such as cognition) may need to be targeted. For example, a study by Raskin and colleagues[31] found that duloxetine is effective in improving cognitive outcome measures in patients with recurrent MDD who are ≥ 65 years old. Four cognitive tests were selected as outcome measures to target the following aspects of cognitive functioning: verbal learning and memory, attention, executive function, and working memory. The composite scores of these 4 tests—the Verbal Learning and Recall Test, the Symbol Digit Substitution Test, the Two-Digit Cancellation Test, and the Letter-Number Sequencing Test—significantly improved in patients who were treated with duloxetine (60 mg/d) compared with placebo ($P < .02$). Scores on the 4 tests individually showed that significant improvements occurred in learning and memory via the Verbal Learning ($P = .003$) and Recall ($P = .02$) Tests, but the other tests did not show significant improvements in attention, information processing speed, and executive function. Duloxetine also significantly improved depression more than placebo according to HDRS total scores at 8 weeks ($P < .001$). The Verbal Learning and Recall Test, the Symbol Digit Substitution Test, the Two-Digit Cancellation Test, and the Letter-Number Sequencing Test can be completed in a short amount of time and may be practical tools for clinical practice.

The multimodal antidepressant vortioxetine has also been studied in older adults with recurrent MDD. Katona

et al[32] compared the efficacy of vortioxetine, duloxetine, and placebo in depression and cognitive impairment in elderly patients. Patients treated with vortioxetine (5 mg/d) showed significantly more improvement on total HDRS scores than placebo at 8 weeks ($P=.0011$); duloxetine was also superior to placebo. Secondary outcomes from this study also indicated that vortioxetine significantly improved measures of learning and memory as well as information processing speed when compared with placebo. The benefit in cognitive performance was determined to be largely a direct effect of the treatment rather than an indirect effect as a consequence of depressive symptoms mitigation. As a consequence of these findings with vortioxetine, buttressed by preclinical observations supporting a procognitive effect, this particular agent has been primarily studied to determine if it offers a direct procognitive effect in younger adults with MDD.

Modifying Treatment

Measurement-based care is important in determining whether the current course of treatment is effective or not. Some patients require longer exposure to antidepressants or psychosocial treatments before achieving remission, and clinicians have to decide how long to wait before modifying therapy. Recent data[33] suggest that a lack of antidepressant efficacy can be predicted early in the course of treatment.

The results of a meta-analysis[33] indicated that if patients experience little to no benefit (ie, < 20% improvement from baseline) with an adequate antidepressant dose within 2 weeks, they have a 4% to 18% chance of response and only a 0% to 5% chance of remission with that treatment. Full treatment benefit may take 6 to 8 weeks or longer, but an early lack of improvement can help the clinician decide to modify therapy. Evidence-based and consensus-based recommendations encourage clinicians to intervene by switching to another antidepressant, combining antidepressants, or adding another agent to the existing antidepressant within the first 4 to 6 weeks of treatment (Table 1).[4,34–36] It is generally recommended that if insufficient benefit is seen in the first 2 weeks of treatment, then dose optimization can be considered.

Adding atypical antipsychotics to antidepressant treatment is the most thoroughly studied augmentation approach in MDD.[37] A meta-analysis by Nelson et al[37] found that atypical antipsychotics used in conjunction with antidepressants were significantly more effective in reducing depressive symptoms than placebo ($P<.00001$). However, some of the possible disadvantages of atypical antipsychotics are weight gain, metabolic decompensation, sedation, and extrapyramidal side effects, making tolerability of these treatments a concern. Monitoring side effects closely can improve outcomes with these treatments.

More recently, the psychostimulant lisdexamfetamine has been shown to be an effective adjunctive therapy. In a multicenter trial of 173 adults with residual depressive symptoms after 8 weeks of escitalopram treatment, Trivedi et al[38] found that nonremitted patients treated with adjunctive lisdexamfetamine for 6 weeks were significantly improved according to Montgomery-Asberg Depression Rating Scale ($P=.0902$)

Table 1. Recommended Time Points for Modifying Treatment in Patients With Major Depressive Disorder

Guidelines	Modification Recommendations
Canadian Network for Mood and Anxiety Treatments (CANMAT)[34]	If little improvement[a] after 2 weeks, modify treatment (eg, dose increase)
	If more than minimal improvement[b] after 4–6 weeks, continue antidepressant for another 2–4 weeks before considering additional strategies
American Psychiatric Association[4]	If at least moderate improvement[b] is not seen at 4–8 weeks, modify treatment
	Patients with no improvement in the initial weeks of treatment generally need an earlier adjustment
American College of Physicians[35]	If an inadequate response to initial treatment at 6–8 weeks, modify treatment
Texas Medication Algorithm Project[36]	Increase dose every 2–3 weeks as tolerated
	If no response after 4–6 weeks, modify treatment

[a]Little improvement = < 20% improvement in depression scores.
[b]More then minimal improvement = ≥ 20% improvement in depression scores.

and QIDS-SR ($P=.0774$) scores when compared with subjects who received placebo.

Other medications have also proven to be effective adjunctive therapy in treatment-resistant depression. Patients with MDD who had not responded to selective serotonin reuptake inhibitor (SSRI) treatment had significantly greater HDRS response and remission rates when treated with add-on S-adenosyl methionine compared with placebo ($P<.05$).[39] Adjunctive L-methylfolate also improved response rates and depression symptom scores in patients with partial response or no response to SSRI treatment.[40] Likewise, the N-methyl-D-aspartate (NMDA) antagonist ketamine has been shown to improve depressive symptoms and suicidal ideation in treatment-resistant depression.[41] At this time, however, ketamine is considered to be experimental as questions regarding its safe use without inducing psychosis and its long-term therapeutic benefits have not been determined.

Finally, the Treatment with Exercise Augmentation for Depression (TREAD) study[42] found that adding high-dose exercise (16 kcal/kg/wk expenditure) to SSRI treatment in nonremitted patients improved remission rates. However, low-dose exercise (4 kcal/kg/wk expenditure) did not exhibit the same degree of improvement. Along with medications, aerobic exercise may benefit some people with treatment-resistant depression.

CONCLUSION

Major depressive disorder is a common, often severe, and persistent mental disorder and is a leading cause of disability globally. Unfortunately, most individuals with MDD do not achieve full symptom remission, which is the first step toward functional recovery and improved quality of life. Cognitive dysfunction, one of the most common residual symptoms in MDD, plays an important role in functional outcome, compliance, and illness complexity, making resolution of cognitive symptoms an important therapeutic objective.

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Using measurement tools and assigning patients to treatments that have been shown to be effective in large, randomized, controlled trials help to improve therapeutic outcomes. Monitoring symptomatology with measurement tools, such as depression symptom inventories and cognitive testing, increases the chance of success in MDD treatment. With careful monitoring, clinicians can determine within 4 to 6 weeks of treatment (or earlier) whether treatment modification is necessary. Treatment selection and sequencing will need to consider both the beneficial and detrimental effects a chosen strategy has on cognitive dysfunction. Most people with MDD will require treatment beyond the initial first-line choice to reach the therapeutic objectives of remission, premorbid functioning, and asymptomatic recovery.

Drug names: duloxetine (Cymbalta), escitalopram (Lexapro and others), ketamine (Ketalar and others), lisdexamfetamine (Vyvanse).

Disclosure of off-label usage: Dr McIntyre has determined that, to the best of his knowledge, ketamine and vortioxetine are not approved by the US Food and Drug Administration for the treatment of depression.

Supplementary material: Available at PSYCHIATRIST.COM.

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See supplementary material for this article at PSYCHIATRIST.COM.
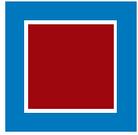
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Supplementary Material

List of Supplementary Material for the article

Supplementary eTable 1. Measurement-Based Tools for Screening, Diagnosing, and Monitoring Patients With Major Depressive Disorder[a]

Scale	URL	Items, No.	Time to Complete, Min	Patient/ Clinician Rated
Screening Scales for Depression				
Center for Epidemiologic Studies Depression Scale (CES-D)[2]	http://www.psychiatrist.com/private/2010/v71e01/v71e0101/v71e0101L1.pdf	20	5	Patient
Hospital Anxiety and Depression Scale (HADS)[3]	http://www.gl-assessment.co.uk/products/hospital-anxiety-and-depression-scale-0	14	< 5	Patient
2-Item Patient Health Questionnaire (PHQ-2)[4]	http://www.cqaimh.org/tool_depscreen.html	2	< 3	Patient
9-Item Patient Health Questionnaire (PHQ-9)[5]	http://www.cqaimh.org/tool_depscreen.html	9	< 3	Patient
Zung Self-Rating Depression Scale (Zung SDS)[6]	http://www.outcometracker.org/library/SDS.pdf	20	5–30	Patient
Diagnostic Scales for Depression				
Mini International Neuropsychiatric Interview (MINI)[7]	http://www.psychiatrist.com/private/2010/v71e01/v71e0101/v71e0101L2.pdf	Varies	15	Clinician
9-Item Patient Health Questionnaire (PHQ-9)[5]	http://www.cqaimh.org/tool_depscreen.html	9	< 3	Patient
Primary Care Evaluation of Mental Disorders (PRIME-MD)[8]	http://www.psychiatrist.com/private/2010/v71e01/v71e0101/v71e0101L3.pdf	26	5–10	Patient
Psychiatric Diagnostic Screening Questionnaire (PDSQ)[9]	http://portal.wpspublish.com/portal/page?_pageid=53,70444&_dad=portal&_schema=PORTAL	126	15–20	Patient
Structured Clinical Interview for *DSM-IV* Axis I Disorders, Clinician Version (SCID-CV)[10]	http://www.scid4.org/	Varies	> 60–180	Clinician
Monitoring Scales for Depression				
Symptom severity				
Beck Depression Inventory (BDI)[11,12]	http://www.pearsonassessments.com/HAIWEB/Cultures/en-us/Productdetail.htm?Pid=015-8018-370&Mode=summary	21	5–10	Patient
Clinically Useful Depression Outcome Scale (CUDOS)[13]	http://www.psychiatrist.com/private/2010/v71e01/v71e0101/v71e0101L4.pdf	18	3	Patient
Hamilton Depression Rating Scale (HDRS)[14]	http://www.psychiatrist.com/private/2010/v71e01/v71e0101/v71e0101L5.pdf	17 and 21	30	Patient or clinician
Hospital Anxiety and Depression Scale (HADS)[3]	http://www.gl-assessment.co.uk/health_and_psychology/resources/hospital_anxiety_scale/hospital_anxiety_scale.asp	14, 7-item depression subscale	< 5	Patient
Inventory of Depressive Symptomatology (IDS)[15]	http://www.ids-qids.org	30	15–20	Patient or clinician
Montgomery-Asberg Depression Rating Scale (MADRS)[16]	http://www.psychiatrist.com/private/2010/v71e01/v71e0101/v71e0101L6.pdf	10	10–15	Patient or clinician
9-Item Patient Health Questionnaire (PHQ-9)[5]	http://www.cqaimh.org/tool_depscreen.html	9	< 5	Patient
Quick Inventory of Depressive Symptomatology (QIDS)[17]	http://www.ids-qids.org	16	5–10	Patient or clinician
Adverse effects				
Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)[18]	http://www.psychiatrist.com/private/2010/v71e01/v71e0101/v71e0101L8.pdf	3	< 5	Patient

[a]Reprinted with permission from Gelenberg et al.[1]

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