Functional Recovery in Major Depressive Disorder:
Focus on Early Optimized Treatment

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ABSTRACT

Objective: This article presents the case that a more rapid, individualized approach to treating major depressive disorder (MDD) may increase the likelihood of achieving full symptomatic and functional recovery for individual patients and that studies show it is possible to make earlier decisions about appropriateness of treatment in order to rapidly optimize that treatment.

Data Sources: A PubMed search was conducted using terms including *major depressive disorder*, *early improvement*, *predictor*, *duration of untreated illness*, and *function*. English-language articles published before September 2015 were included. Additional studies were found within identified research articles and reviews.

Study Selection: Thirty antidepressant studies reporting predictor criteria and outcome measures are included in this review.

Data Extraction: Studies were reviewed to extract definitions of predictors, outcome measures, and results of the predictor analysis. Results were summarized separately for studies reporting effects of early improvement, baseline characteristics, and duration of untreated depression.

Results: Shorter duration of the current depressive episode and duration of untreated depression are associated with better symptomatic and functional outcomes in MDD. Early improvement of depressive symptoms predicts positive symptomatic outcomes (response and remission), and early functional improvement predicts an increased likelihood of functional remission.

Conclusions: The approach to treatment of depression that exhibits the greatest potential for achieving full symptomatic and functional recovery is early optimized treatment: early diagnosis followed by rapid individualized treatment. Monitoring symptoms and function early in treatment is crucial to ensuring that patients do not remain on ineffective or poorly tolerated treatment, which may delay recovery and heighten the risk of residual functional deficits.

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Major depressive disorder (MDD) is a common illness with a lifetime prevalence of 3%–17%,[1] characterized by a persistent low mood and the loss of interest or pleasure in many aspects of life. Unfortunately, for many people who experience an episode of depression, MDD can become a chronic and recurrent condition.[2,3] The World Health Organization estimates that MDD affects 350 million people worldwide.[4] Twelve-month prevalence rates for MDD were estimated at 6.6% (95% CI, 5.9%–7.3%) in the US National Comorbidity Survey Replication (NCS-R)[5] and 4.7% (95% CI, 4.3%–5.1%) in the Canadian Community Health Survey—Mental Health (2012; CCHS-MH).[6] Rates of MDD were higher in women in both the CCHS-MH (4.9% [women] vs 2.8% [men] past-year MDD) and the NCS-R (lifetime odds ratio [95% CI] for women vs men = 1.7 [1.5–2.0]).[5,6] The odds ratio for 12-month MDD among lifetime cases was highest for patients 18 to 29 years of age in the NCS-R, and 12-month prevalence in the CCHS-MH sample was highest for patients 15 years of age—the youngest patients included in each survey.[6,7] CCHS-MH data suggest that the estimated past-year prevalence of major depressive episode has remained steady in Canada over the past decade.[6]

MDD is the second leading cause of disability worldwide[8] and the leading cause of disability in adolescents aged 10 to 19 years.[9] Depressive symptoms can impair an individual's ability to perform at work or school, to fulfill family responsibilities, and to enjoy leisure activities.[10,11] Indeed, 87.4% of NCS-R respondents with 12-month MDD reported at least moderate impairment in home, work, relationship, or social role functioning.[5] The cost of MDD for patients who do not respond to treatment includes the increased use of health care resources and lost productivity compared with patients who achieve remission.[12–14] Impairment in role function is a critical driver of the cost of MDD. Both absenteeism and presenteeism (health-related reduction in performance at work[15]) contribute to the cost of lost work productivity and increase significantly with depression severity.[16,17] In an analysis based on the NCS-R,[18] MDD was associated with an estimated 225 million lost workdays per year and US $36.6 billion in lost productivity annually.

Clinical Points

- Evidence suggests that delay in treatment of major depressive disorder (MDD) (longer duration of episode or duration of untreated illness) is associated with poorer outcome; longer time to remission is associated with poorer functional outcomes.
- By utilizing individualized measurement-based care, early improvement, or lack of improvement, can be used to assess the effectiveness of a treatment as early as 2 weeks to make decisions with regard to dose alterations, switching antidepressants, or adjunctive therapy.
- Clinicians should use rating scales at baseline and during follow-up to monitor improvement of both depressive symptoms and functioning to guide early optimized treatment. Tolerability should also be assessed throughout the course of treatment, so that necessary treatment changes can occur with the least possible delay.
- Early optimized treatment of MDD may improve outcomes for individual patients and increase the number of patients who are able to return to full function.

Many patients with MDD remain untreated, and among those who receive treatment, a large percentage does not regain their premorbid level of functioning. On the basis of data from the 2005 and 2006 National Survey on Drug Use and Health surveys,[19] 37.6% of participants with MDD did not seek treatment. Two separate meta-analyses[20,21] examining recognition and diagnosis of depression concluded that in primary care settings, fewer than half of all true cases of depression are diagnosed. Moreover, less than half of those treated for MDD with antidepressant drugs achieve remission. Analyses of randomized controlled trials of selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) found remission rates that ranged from 38% to 61%.[22,23] Although some individual clinical trials have suggested an advantage of one antidepressant drug or class over another,[22,23] no one antidepressant has consistently been shown to be associated with superior efficacy for individual patients.[24,25] The proportion of patients achieving remission in clinical practice is estimated to be even lower than the rates reported in clinical trials.[26] Furthermore, remission of depressive symptoms does not necessarily result in a return to full function. In an analysis[27] examining symptomatic and functional remission during acute treatment, 38% of patients achieved symptomatic remission (17-item Hamilton Depression Rating Scale[28] [HDRS-17] total score ≤7) and 32% achieved functional remission (Sheehan Disability Scale[29] [SDS] total score ≤6); however, only 23% of patients achieved combined symptomatic and functional remission. For many MDD patients, full functional recovery lags behind the improvement of depressive symptoms, even among those treated to symptomatic remission.[27,30,31]

The potential for functional improvement decreases with the chronicity of symptoms and treatment failure,[15,31] thus underscoring the urgency of early diagnosis and effective treatment. Clinicians have previously used a "start low, go slow" approach to treatment of MDD, choosing a first treatment at the lowest effective dose and giving that treatment a trial of up to 6 to 8 weeks before deciding whether an adjustment is warranted.[32–34] Using this one size fits all approach may, however, contribute to low remission rates and the failure to return patients to full function after a depressive episode. This review presents the case that a more rapid, individualized approach to treating MDD—early optimized treatment, characterized by early diagnosis followed by rapid treatment initiation, close monitoring and assessment, and prompt adjustment of treatment—offers the greatest opportunity for full functional recovery. Examination of early response to treatment suggests that it is possible to make earlier decisions about appropriateness of treatment in order to rapidly optimize treatment for individual patients. Factors involved in treatment selection for an individual patient are beyond the scope of this review.

METHOD

A PubMed search was conducted using terms including *major depressive disorder*, *early improvement*, *predictor*, *duration of untreated illness*, and *function*. English-language articles published before September 2015 were included. Additional studies were found within identified research articles and reviews. Thirty antidepressant studies reporting predictor criteria and outcome measures are included in this review.[35–64]

Studies were reviewed to extract definitions of predictors, outcome measures, and results of the predictor analysis. Results were summarized separately for studies reporting effects of early improvement, baseline characteristics, and duration of untreated depression.

RESULTS

Treating to Full Functional Recovery

Core features of MDD. On the basis of criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*),[11] MDD is characterized by the presence of at least 5 of 9 defined symptoms: depressed mood, loss of interest or pleasure in activities, changes in weight or appetite, sleep disturbance, slowing of thought and reduction of movement, fatigue or energy loss, feelings of worthlessness or guilt, difficulty concentrating and making decisions, and suicidal thoughts or behaviors. These symptoms must also "cause clinically significant distress or impairment in social, occupational, or other important areas of functioning."[11(p161)]

Evolution of treatment goals. Symptomatic remission has long been the goal of MDD treatment.[32,65,66] Remission has been defined as "an improvement of sufficient magnitude . . . that the individual is asymptomatic (ie, no longer meets syndrome criteria for the disorder and has no more than minimal symptoms)."[67(p853)] Definitions of remission are based on validated depression rating scales, including a HDRS-17 total score ≤7,[67] a Montgomery-Asberg Depression Rating Scale (MADRS) score ≤10,[68] a Quick Inventory of Depressive Symptomatology–Self-Report

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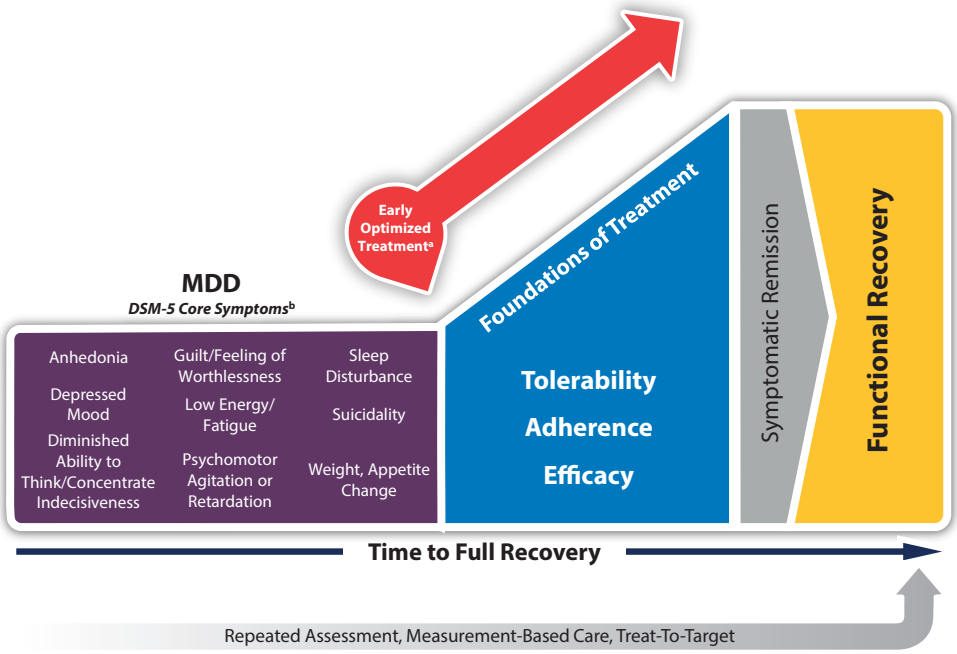
Figure 1. Early Optimized Treatment Is Critical to Bringing Patients to Full Symptomatic and Functional Recovery



[a]Early diagnosis followed by rapid, optimal treatment.
[b]Alphabetical order.

(QIDS-SR-16) score ≤ 6,[69] a Beck Depression Inventory (BDI) score ≤ 8,[67] and a 9-item Patient Health Questionnaire (PHQ-9) score < 5.[70] However, it is not uncommon for patients meeting criteria for remission to continue to experience disabling residual symptoms of depression.[71]

Ninety percent of remitted patients may have at least mild or moderate residual symptoms.[71] Residual symptoms increase the risk of relapse substantially and reduce the time to depression recurrence, even in those patients whose symptoms are treated to remission as defined by scores on depression rating scales.[71–73] Residual symptoms can have a profound effect on functioning, even in patients meeting the definition for remission. The most prevalent residual symptoms are also the symptoms most likely to have an impact on psychosocial functioning: sleep disturbance, low energy or fatigability, anxiety, problems with concentration/decision making, lack of sexual interest, and pessimism about the future.[71,74] Residual symptoms in remitted MDD patients can affect their ability to function at work, at home, and in social settings.[72] In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,[15] improved depression scores were associated with functional improvement, including work productivity, less time away from work, and general functionality. In STAR*D patients who met the criteria for symptom remission, work productivity improved; however, impairment continued for some in other areas of functioning.[15,75]

Current MDD treatment guidelines suggest that the achievement of symptomatic remission should be considered an important first step toward the more challenging and no less crucial goal of full functional recovery.[24,25] Treatment objectives in depression have evolved from being based purely on symptomatic remission and now include full functional recovery.[76,77] Functional improvement does not always parallel the improvement of scores on depression symptom rating scales and may lag behind.[27,30,31] Functional assessments and depression symptom rating scales measure different aspects of MDD. Functional improvement may begin well after symptoms of depression begin to improve[78] and often takes additional time to become consistent and quantifiable.

Achieving full functional recovery requires resolution of all core features of MDD, including residual symptoms that can have a direct impact on functioning (Figure 1).[79] This definition of full functional recovery is in line with the patients' view that symptom resolution is one factor in determining remission from depression, but returning to their usual level of function and regaining enjoyment of their usual activities and relationships are just as important.[80] Critical end points in depression treatment should be empirically supported and measurable, and there exists a range of assessment tools for measuring functional outcomes. Those tools most commonly used in clinical trials include the SDS, the Quality of Life Enjoyment and Satisfaction Questionnaire[81] (Q-LES-Q), the Medical Outcomes Study 36-Item Short-Form Health Survey[82] (SF-36) or the 12-item version[83] (SF-12), the Lam Employment Absence and Productivity Scale[84] (LEAPS), and the Social Adjustment Scale–Self-Report version[85] (SAS-SR).[86,87] These instruments focus on a variety of functional domains such

Table 1. Duration of Current Episode as a Predictor of Treatment Outcome

Reference	Treatment	N	Predictor	Outcome	Finding
Trivedi et al, 2006[35]	Citalopram	2,876	Duration of current episode	QIDS-C score ≤ 5, last observed score	+
Howland et al, 2008[36]	Duloxetine	249	Duration of current episode	Poorer treatment outcome (HDRS-17 total score, ≥50% decrease in HDRS-17, HDRS-17 ≤ 7), wk 12	+
Fava et al, 2009[37]	Duloxetine or placebo	278	Duration of current episode	Relapse (increase in CGI-S score ≥ 2 points), 26 wk	–
Hennings et al, 2009[38]	Antidepressant drugs (naturalistic study)	842	Duration of current episode	HDRS-17 total score ≤ 7, mean 11.8 wk	+
Seemüller et al, 2010[39]	Antidepressant drugs (naturalistic study)	1,014	Duration of current episode	Decrease in HDRS-17 total score, final visit	+
Soares et al, 2014[40]	Desvenlafaxine or placebo	2,706	Duration of current episode	≥ 50% decrease in SDS and SDS total score ≤ 12, wk 8	–
				≥ 50% decrease in SDS and SDS total score ≤ 12 and ≥50% decrease in HDRS-17, wk 8	–
				SDS total score ≤ 7, wk 8	–
				SDS total score ≤ 7 and HDRS-17 total score ≤ 7, wk 8	–
Joel et al, 2014[41]	Venlafaxine	219	Duration of current episode	MADRS total score ≤ 10, 2 consecutive assessments at end of treatment (wk 12)	+
Smagula et al, 2015[42]	Venlafaxine	466	Duration of current episode	MADRS total score ≤ 10, wk 12	+

Abbreviations: CGI-S = Clinical Global Impressions–Severity, HDRS-17 = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-C = Quick Inventory of Depressive Symptomatology–Clinician rating, SDS = Sheehan Disability Scale.
Symbols: + = positive, – = negative.

as work, social life, family activities, and self-care. Among these scales, the easiest to administer (with 3 brief self-report items) is the SDS, which also has a validated threshold score for functional remission. On the basis of a receiver operating characteristic (ROC) analysis of SDS total scores in 3,530 patients in 10 clinical trials, a cutoff defining functional remission has been determined as a total score ≤ 7.[88] A clinically meaningful difference in SDS score was determined to be 2.8 in the same study.[88] Because of its ease of use, the patient-administered SDS is an excellent, validated tool to assess functioning quickly in a primary care setting. The tool can be used at the initial diagnostic assessment and also to track change over time, as treatment is implemented, in order to assess whether treatment adjustment may be warranted.

Early Optimized Treatment of Depression

There is a wide range of pharmacotherapy options available for treating patients with MDD.[24,34] A substantial percentage of patients will fail to remit on any given antidepressant drug,[22,23] however, and the tolerability of a particular drug will differ among patients.[24,34,89] Therefore, effective pharmacotherapy for depression requires that antidepressant treatment is optimized for each patient, determining the drug and dosage best suited to the individual.[24,34] Ideal management of depression is therefore a multistep, ongoing process that includes screening and early diagnosis, evaluating symptoms and functional impairment, initial selection of treatment, monitoring tolerability and adherence, assessing clinical response, adjusting treatment, and continuing to monitor and assess symptomatic and functional improvement until treatment goals are achieved.[34]

A start low, go slow approach to treatment selection may be appropriate for specific, at-risk patient populations.[34,90,91] However, results from studies reviewed in this section suggest that shortening the time between onset of depression and providing optimized treatment may result in better clinical outcomes, increasing the likelihood of achieving full functional recovery from the depressive episode. Further, optimization of treatment can take place earlier in the course of treatment if guided by earlier systematic monitoring of symptoms, functional status, side effects of medication, and adherence.

Time to treatment and efficacy outcomes. Patient clinical characteristics that are generally related to the delay between onset of symptoms and initiation of treatment have been assessed as predictors of treatment outcomes (Tables 1–3).[35–49] Findings for different measures related to depression history are mixed. Studies[35,36,38,39,42,44] have been largely consistent in reporting that a longer duration of current episode is associated with more negative clinical outcomes, including depression symptom scores, and symptomatic response and remission. One study[37] showed that duration of current episode did not predict time to relapse (Table 1). In the single study[40] that examined functional outcomes, duration of current episode did not predict functional response or remission at week 8. Number of previous depressive episodes, as either a continuous or categorical (previous episode vs no previous episode) measure, did not predict HDRS-17 total score or response and remission[35–38,42,44] but was associated with time to recurrence[45,46] (Table 2).

Although measures of duration of current depressive episode and number of previous episodes provide information about the duration of the patient's illness, they do not address time to first treatment of depression, as study patients may have been treated in previous episodes. Several studies were specifically designed to assess duration of untreated depression (Table 3). In these studies, duration of untreated illness—the interval between the onset of the patient's first depressive episode and appropriate treatment—significantly predicted response,[48] remission,[48,49] and time to remission.[47] A systematic review and meta-analysis designed

Table 2. Number of Previous Episodes as a Predictor of Treatment Outcome

Reference	Treatment	N	Predictor	Outcome	Finding
McGrath et al, 2006[43]	Fluoxetine or placebo	627	Chronicity of depression	Relapse (2 consecutive CGI-I scores > 2), 52 wk	+
Trivedi et al, 2006[35]	Citalopram	2,876	No. of previous episodes	QIDS-C score ≤ 5, last observed score	–
Howland et al, 2008[36]	Duloxetine	249	No. of previous episodes	Poorer treatment outcome (HDRS-17 total score, ≥50% decrease in HDRS-17, HDRS-17 ≤ 7), wk 12	–
Fava et al, 2009[37]	Duloxetine or placebo	278	No. of previous episodes	Relapse (increase in CGI-S score ≥ 2 points), 26 wk	–
Hennings et al, 2009[38]	Antidepressant drugs (naturalistic study)	842	No. of previous episodes	HDRS-17 total score ≤ 7, mean 11.8 wk	–
Ciudad et al, 2012[44]	Antidepressant drugs (observational study)	930	Previous episodes vs no previous episode	HDRS-17 total score ≤ 7, months 6 through 12	–
Hardeveld et al, 2013[45]	SSRIs, TCAs, other antidepressants (longitudinal cohort study)	375	Previous major depressive episode	Time to recurrence (≥ mild symptoms for ≥ 1 month with CIDI-confirmed major depressive disorder diagnosis)	+
Hardeveld et al, 2013[46]	Unspecified (naturalistic survey)	7,076	Single or recurrent major depressive episode	Time to recurrence (return of symptoms after remission)	+
Smagula et al, 2015[42]	Venlafaxine	466	Single or recurrent major depressive episode	MADRS total score ≤ 10, wk 12	–

Abbreviations: CGI-I = Clinical Global Impressions–Improvement, CGI-S = Clinical Global Impressions–Severity, CIDI = Composite International Diagnostic Interview, HDRS-17 = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, QIDS-C = Quick Inventory of Depressive Symptomatology–Clinician Rating, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.
Symbols: + = positive, – = negative.

Table 3. Duration of Untreated Depression as a Predictor of Treatment Outcome

Reference	Treatment	N	Predictor	Outcome	Finding
Gormley et al, 1999[47]	TCA, MAOI, SSRI (naturalistic survey)	100	Duration of no-treatment interval	HDRS-17 total score ≤ 8, 2 consecutive wk, over 52 wk	+
Okuda et al, 2010[48]	Fluvoxamine	679	Duration of no-treatment interval	≥ 50% decrease in HDRS-17 total score, wk 8 HDRS-17 total score ≤ 7, wk 8	+ +
Bukh et al, 2013[49]	SSRIs, mirtazapine, SNRIs, or TCAs (naturalistic survey)	399	Duration of no-treatment interval ≥ 6 vs < 6 months	Remission (TRAQ score = 4 or 5 and HDRS-17 total score ≤ 7), over 2 y	+

Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, MAOI = monoamine oxidase inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TRAQ = Treatment Response to Antidepressants Questionnaire.
Symbols: + = positive, – = negative.

to assess the relationship between clinical outcomes and duration of untreated illness reported a positive effect of shorter duration of untreated illness on both response to treatment (*RR* = 1.70; only 2 studies reported data on this) and remission (*RR* = 1.65; 3 studies).[92] Duration of untreated episode (for patients who had multiple episodes) was also examined, but methodological issues limited conclusions for that measure. Taken together, studies assessing baseline measures related to time to treatment generally suggest that recognizing depression early and ideally treating during the first episode may substantially improve outcomes in patients treated for MDD. When optimal treatment is delayed—by failing to diagnose and begin treatment early in the course of the depressive episode—the likelihood of optimal outcome may decline.

Time to remission. Patient outcomes over the course of the 4 treatment steps in STAR*D provide evidence that early remission benefits the patient, not only by reducing the duration of depressive symptoms, but also by giving the patient the best chance for functional recovery. In the STAR*D trial,[93,94] patients who had minimal response to treatment, defined as < 15% reduction in QIDS–Clinician Rating (QIDS-C-16) score by week 6 or < 25% reduction by week 9, or could not tolerate the assigned treatment at each treatment step could move to a successive treatment step (augmentation with or switch to a new antidepressant drug or cognitive therapy). Patients could enter up to 5 treatment steps, with remission rates reported for the first 4.[94] Progressively lower remission rates were observed for each successive treatment step (step 1, 37%; step 2, 31%; step 3, 14%; step 4, 13%).[94] Further, STAR*D patients who remitted during the first treatment step had greater improvements in function and hours of work missed on the basis of Work Productivity and Activity Impairment[95] (WPAI) scores compared with patients who had partial or nonresponse to first-step treatment.[15] However, among patients who did not achieve remission with step 1 treatment and who entered a second treatment step, remission in step 2 was not associated with greater functional improvement: improvements in function for patients who remitted at step 2, after a treatment switch, were similar to those for step 2 nonresponders.[15] This finding underscores the idea that effective treatment in the first, early steps in MDD management has the greatest potential for bringing the patient to full functional recovery.[96]

Although the STAR*D findings suggest that patients who receive an effective treatment (one that will eventually bring them to remission) earlier in their course of illness are likely

to have better functional outcomes, that supposition is not addressed directly. STAR*D patients who entered successive treatment steps differed from those who remitted in step 1 in that they had both a longer overall duration of treatment and at least 1 failed treatment trial prior to achieving remission.[94,97] Would reducing the amount of time on the ineffective treatment by making a treatment change earlier improve outcomes for those patients who needed a second treatment step? Romera and colleagues[98] addressed this question by comparing outcomes at week 16 in nonresponders who were switched from escitalopram to duloxetine at week 4 versus week 8. Although week 16 HDRS-17 remission rates and pain scale scores were similar between those switched early versus late (duloxetine effectively treated symptoms in both groups), a significantly greater percentage of patients who were switched at week 4 returned to normal function (on the basis of SDS scores) and did so earlier in treatment compared with those who were switched later.[98]

How rapidly can treatment be optimized? Practice guidelines from the American Psychiatric Association[34] suggest that an adequate trial of an antidepressant treatment is up to 8 weeks of treatment, but the Canadian Network for Mood and Anxiety Treatments clinical guidelines[24] state that decisions about the effectiveness of an antidepressant drug and the necessity for adjustments to treatment could be made earlier, within as few as 1 to 4 weeks of starting treatment in some patients. Numerous studies[50–63] have examined the relationship between early improvement in symptoms and eventual outcomes in patients treated for MDD. Early improvement, most commonly defined as a 20% decrease from baseline in depression rating scale score, has been assessed at various time points between 1 and 4 weeks of treatment. The 2-week time point is the one most commonly used for defining early improvement[55]; however, several of the studies[41,44,50–62] reviewed here assessed early improvement at week 2 and/or other time points. Achievement of a threshold level of improvement at the early time point was then evaluated as a predictor of treatment outcome at study end (4–12 weeks). Depression rating scales (HDRS-17, MADRS, or BDI) have been used to measure both early improvement and treatment outcomes. Response (≥ 50% decrease from baseline) and remission (HDRS-17 total score ≤ 7, MADRS total score ≤ 10, BDI total score ≤ 11) at study end point are the treatment outcomes that have been examined most frequently.

Early improvement, in almost all studies,[41,44,50–62] predicted treatment response and remission of MDD symptoms at study end point (Table 4). The results were similar across treatments (SSRIs, SNRIs, TCAs, and other antidepressant drugs).[41,44,50–61,63] Lack of early improvement (with improvement defined as ≥ 25% decrease in MADRS) within 2 weeks was highly predictive of eventual failure to achieve MADRS response or remission (negative predictive value) in a pooled analysis of 5 studies[58] utilizing combined olanzapine/fluoxetine treatment in patients with treatment-resistant depression. In fact, lack of early improvement was a better predictor of week 8 outcome than was achievement of early improvement.[58] Lack of early improvement was also the better predictor of outcome in a pooled analysis of data from 6 studies utilizing desvenlafaxine versus placebo.[58,63] In studies[41,59,63] using ROC analysis to determine threshold cutoff values for early improvement, optimal week 2 improvement thresholds for predicting eventual positive treatment outcomes ranged from approximately 20%–40% improvement from baseline.

Early improvement analyses similar to those using depression symptom outcomes have examined whether early improvements in depression symptom or function scores predict positive functional outcomes (Table 5). In an observational study[44] of patients treated for MDD, response or remission at week 6 was significantly associated with improvement in Social and Occupational Functioning Assessment Scale scores at month 12 compared with nonresponse or lack of remission, respectively. Early response was also significantly associated with better quality of life scores.[44] In a placebo-controlled trial[64] utilizing desvenlafaxine, week 2 improvement in depression scale (HDRS-17) total score was a significant predictor of improvement on a range of measures of function at week 12, including HDRS-17 psychomotor retardation factor, MADRS lassitude item, SDS total score, and several measures from the WPAI (presenteeism, work productivity loss, and activity impairment). The association between early improvement in function and functional and depression outcomes at study end was explored in a pooled analysis[40] of 7 double-blind, placebo-controlled trials of desvenlafaxine. Functional response, functional/depression response, functional remission, and functional/depression remission at week 8 were all significantly predicted by early functional improvement, as measured by percentage decrease in SDS total score at week 2. The percentage change in SDS total score at week 2 that best predicted functional remission was 26%.[40]

While a growing literature has demonstrated that, on average, early symptomatic or functional improvement is an indication that continued improvement on this treatment is likely—and conversely that the lack of early improvement may signal that the treatment will not be effective for this patient—it is important to remember that response trajectories can vary considerably among individual patients. Studies such as a secondary analysis of data from the Genome-Based Therapeutic Drugs for Depression (GENDEP) study revealed that "both early and delayed improvement are common during treatment with SSRIs and TCAs. Among those who eventually show good response to a 12-week course of antidepressant treatment, 51% show delayed response, which cannot be predicted from measurements in the first 2 weeks."[60(p1482)] The GENDEP results underscore the fact that, although evaluating early progress is critical to rapid treatment optimization, decisions about changes to a treatment plan must be made on a case-by-case basis, as ending an antidepressant trial based on strict criteria (eg, 20% improvement at 2 weeks) would be premature for many patients.[60]

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Table 4. Early Improvement in Depressive Symptoms as a Predictor of Treatment Outcome

Reference	Treatment	N	Predictor	Outcome	Finding
Koran et al, 1995[50]	Fluoxetine or placebo	671	≥ 20% decrease in HDRS-21 total score, wk 1, 2, or 3	≥ 50% decrease in HDRS-21 total score, wk 6	+
				HDRS-21 total score ≤ 8, wk 6	+
Szegedi et al, 2003[51]	Mirtazapine or paroxetine	275	≥ 20% decrease in HDRS-17 total score, wk 1, 2, 3, or 4	≥ 50% decrease in HDRS-17 total score, wk 4 and 6	+
				HDRS-17 total score ≤ 7, wk 4 and 6	+
Henkel et al, 2009[52]	Antidepressant drugs (naturalistic study)	1,073	≥ 20%[a] decrease in HDRS-21 total score, wk 2 or 4	≥ 50% decrease in HDRS-21 total score at discharge (mean duration, 60 d)	+
				HDRS-21 total score ≤ 7 at discharge	+
Katz et al, 2009[53]	Duloxetine, escitalopram, or placebo	684	20% or 30% decrease in HDRS-17 total and subscale scores, wk 2	HDRS-17 total score ≤ 7, over 8 mo	+ (except sleep scale for duloxetine)
Kok et al, 2009[54]	Venlafaxine or nortriptyline	81	≥ 20%[a] decrease in HDRS-17 total score, wk 1, 3, or 5	HDRS-17 total score ≤ 7, wk 12	+
				MADRS total score ≤ 10, wk 12	+
Szegedi et al, 2009[55]	Mirtazapine, SSRIs, TCAs, venlafaxine, or placebo	6,562	≥ 20% decrease in HDRS-17 total score, wk 2	≥ 50% decrease in HDRS-17 total score, wk 4	+
				HDRS-17 total score ≤ 7, wk 4	+
Farabaugh et al, 2010[56]	Fluoxetine	169	≥ 30% decrease in Depression, Anxiety, and Anger/Hostility SQ subscale score, wk 2	≥ 50% decrease in HDRS-17 total score, wk 8	+
				HDRS-17 total score ≤ 8, wk 8	+
Farabaugh et al, 2010[57]	Fluoxetine	510	Decrease in HDRS-17 anxiety/somatization factor item scores, wk 1	HDRS-17 total score ≤ 8, wk 12	+ somatic symptoms (gastrointestinal) only
Tohen et al, 2010[58]	Olanzapine + fluoxetine	1,146	Lack of ≥ 25% decrease in MADRS total score, wk 2	Lack of ≥ 50% decrease in MADRS total score, wk 8	+
				MADRS total score ≤ 10, wk 8	+
Lin et al, 2011[59]	Fluoxetine	131	≥ 25%[b] decrease in HDRS-17 total score, wk 1; ≥39%, wk 2; ≥43%, wk 3; ≥50%, wk 4	≥ 50% decrease in HDRS-17 total score, at wk 4 and 6	+
Uher et al, 2011[60]	Escitalopram or nortriptyline	811	≥ 20% decrease in MADRS total score, wk 2	≥ 50% decrease in MADRS total score, wk 12	+
				MADRS total score ≤ 10, wk 12	+
Casey et al, 2012[61]	Antidepressant (SSRI or venlafaxine) + adjunctive aripiprazole or adjunctive placebo	1,064	≥ 50% decrease in MADRS total score, wk 2	≥ 50% decrease in MADRS total score and MADRS total score ≤ 10, wk 6	+
Ciudad et al, 2012[44]	Antidepressant drugs (observational study)	930	≥ 50% decrease in HDRS-17 total score, wk 6 HDRS-17 total score ≤ 7, wk 6	HDRS-17 total score ≤ 7, mo 6 through 12	+
Joel et al, 2014[41]	Venlafaxine	277	%[b] decrease in MADRS, wk 2 (low % decrease, predictor of low remission rate)	MADRS total score ≤ 10, 2 consecutive assessments at end of treatment (wk 12)	+
Mikoteit et al, 2014[62]	Duloxetine	31	≥ 20% decrease in HDRS-17 total score, wk 1 or 2	≥ 50% decrease in HDRS-17 total score, wk 6	–
				HDRS-17 total score ≤ 8, wk 6	–
Soares et al, 2014[63]	Desvenlafaxine or placebo	2,274	%[b] decrease in HDRS-17 total score, wk 2 or 3	≥ 45% decrease in HDRS-17 total score, wk 8	+
				≥ 50% decrease in HDRS-17 total score, wk 8	+
				≥ 65% decrease in HDRS-17 total score, wk 8 and HDRS-17 total score ≤ 7, wk 8	+

[a]Other percentage change was also assessed.
[b]Examined using receiver operating characteristic analysis.
Abbreviations: HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, SNRI = serotonin-norepinephrine reuptake inhibitor, SQ = Symptom Questionnaire, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.
Symbols: + = positive, – = negative.

Table 5. Early Improvement in Function as a Predictor of Treatment Outcome

Reference	Treatment	N	Predictor	Outcome	Finding
Ciudad et al, 2012[44]	Antidepressant drugs (observational study)	930	≥ 50% decrease in HDRS-17, wk 6 HDRS-17 ≤ 7, wk 6	SOFAS score, mo 12 EQ-5D score, mo 12	+ +
Lam et al, 2014[64]	Desvenlafaxine or placebo	427	% change in HDRS-17 total score (continuous variable), wk 2	HDRS-17 psychomotor retardation factor, wk 12 MADRS lassitude item, wk 12 SDS total score, wk 12 WPAI domain scores, wk 12	+ + + + (except absenteeism)
Soares et al, 2014[40]	Desvenlafaxine or placebo	2,706	%[a] decrease in SDS total score, wk 2	≥ 50% decrease in SDS total score and SDS total score ≤ 12, wk 8 ≥ 50% decrease in SDS total score and SDS total score ≤ 12 and ≥50% decrease in HDRS-17 total score, wk 8 SDS total score ≤ 7, wk 8 SDS total score ≤ 7 and HDRS-17 total score ≤ 7, wk 8	+ + + +

[a]Examined using receiver operating characteristic analysis.
Abbreviations: EQ-5D = EuroQol Health State-5 Dimensions, HDRS-17 = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale, SOFAS = Social and Occupational Functioning Assessment, WPAI = Work Productivity and Activity Impairment.
Symbols: + = positive, – = negative.

Table 6. Considerations for Antidepressant Selection[a]

Category	Factors
Demographic	Age Gender
Disease-related	Severity Diagnostic subtype (target symptoms) Comorbid disorders
Medical history	Past response Potential sensitivity to side effects Family history
Drug-specific	Real-world effectiveness Potential for drug-drug interactions Simplicity of use Issues associated with abrupt discontinuation Cost Branded vs generic formulation

[a]In the absence of reliable biomarkers, the clinician should consider a range of factors when selecting an antidepressant.

CLINICAL IMPLICATIONS AND CONCLUSIONS: PROVIDING EARLY OPTIMIZED TREATMENT FOR THE INDIVIDUAL PATIENT

Evidence reviewed here indicates that the greatest potential for achieving full functional recovery from depression lies in early diagnosis and rapid implementation of optimal treatment (early optimized treatment). Analysis of clinical trial data shows that a delay between onset of symptoms and starting antidepressant treatment (longer duration of untreated episode or longer duration of untreated illness) is associated with poorer efficacy outcomes, and that reducing the time to treatment improvement is associated with better functional outcomes. More rapid optimization is possible in treatment of depression: early improvement, or lack of improvement, can be used to assess the effectiveness of a treatment as early as 2 weeks in order to ensure that the dose is optimized as early as possible.

Screening and early diagnosis, development of specific and targeted treatment goals, treatment selection, and assessment of improvement early in the course of treatment with subsequent adjustment in treatment if required are all critical factors in providing the best treatment for the individual patient. Primary care practitioners have the first opportunity to screen for, diagnose, and treat MDD.[99] By intercepting and optimally treating depression earlier, there is potential to reduce, sometimes by many years, the substantial morbidity, mortality, and functional impairment associated with this illness. Patient self-report instruments such as the PHQ-9,[100] for evaluating symptoms of depression, and the SDS, for assessing function, can be used efficiently in clinical practice for patients presenting with symptoms of depression, individuals at high risk, or those with common comorbid conditions.[1,101,102] Diagnosing a young patient early in the course of his or her first depressive episode and treating to full symptomatic remission and full functioning (symptomatic and functional recovery), ideally with no residual symptoms, offers the greatest chance of success for best possible quality of life.

Ideal management of MDD should include assessment of both depressive symptoms and function at baseline utilizing rating scales (measurement-based care). The patient's symptoms, associated functional impairment, and comorbidities, among other potential factors (summarized in Table 6), should be considered in the selection of an effective, well-tolerated treatment with minimal side effects. On average, the efficacy of antidepressants is similar, among and within classes[25,103,104]; however, for individual patients, there may be important efficacy and tolerability differences between drugs.[23,104–108] Effective long-term treatment of MDD often involves maintenance therapy for at least 6 to 24 months after remission.[1,24] Therefore, consideration of possible barriers to both short-term and long-term adherence (poor tolerability, which in itself can contribute to functional impairment; delayed onset of efficacy; suboptimal, incompletely effective dosage; and complicated dosing regimen[109–113]) is critical to treatment selection. A review of patients' personal barriers to adherence may also be helpful.

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Finally, monitoring for early improvement during treatment is critical to ensuring that patients do not remain on ineffective treatment, increasing the likelihood of residual symptoms, which can result in a delay in full functional recovery and an increased risk for relapse or recurrence. Clinicians should monitor patients' response to treatment using tools to assess both symptoms and functioning.[114] Although the trajectory of response to treatment varies widely with most studies showing approximately 10% of patients without early improvement may eventually remit without a change in treatment (based on ROC analyses), patients whose symptoms do improve early have the greatest likelihood of achieving the best clinical outcomes.[51,63] Patients slow to improve should be followed closely so that necessary treatment adjustments can be made early to minimize the negative impact on functioning in all aspects of life. The need for psychotherapy (including behavioral activation), which can be critical for achieving full functional recovery, should also be assessed. Early optimized treatment can substantially improve patients' chances of a timely and long-lasting return to best possible functioning.

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Drug names: aripiprazole (Abilify), citalopram (Celexa and others), desvenlafaxine (Pristiq, Khedezla, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine/fluoxetine (Symbyax and others), paroxetine (Paxil, Pexeva, and others), venlafaxine (Effexor and others).

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