

# When Should You Move Beyond First-Line Therapy for Depression?

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The probability of achieving and sustaining symptomatic remission in major depressive disorder (MDD) with first-line pharmacotherapy is approximately 30%. Ample documentation shows that the maximal therapeutic effect obtained with antidepressant pharmacotherapy is approximately 4 to 6 weeks, perhaps longer for individuals receiving manual-based psychotherapies. Emerging evidence also indicates that early (ie, at 2 weeks) symptomatic improvement (ie,  $\geq 20\%$  improvement on the 17-item Hamilton Depression Rating Scale score) positively predicts remission at weeks 6 to 8 (nonimprovement at week 2 may be a more robust negative predictor of nonremission at weeks 6 to 8). Notwithstanding the identification of early positive/negative remission prediction, a subgroup of individuals receiving pharmacotherapy evinces initial improvement beyond week 6 of treatment. Available evidence does not support a claim that any antidepressant or class of antidepressants offers a faster onset of action. Identifying moderators and/or predictors of response is a priority research vista; hitherto, no biomarker has emerged as a reliable predictor of treatment efficacy, tolerability, or safety. Emerging evidence suggests that electrophysiological measures, ie, frontal quantitative electroencephalography (QEEG) may be capable of identifying antidepressant remitters within 1 to 2 weeks of exposure. Taken together, practitioners are often faced with the critical question as to when to move beyond index therapy for treating depressive symptoms as part of MDD.

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## DEPRESSION EPIDEMIOLOGY AND IMPACT AND TREATMENT DEFICIENCIES

Major depressive disorder (MDD) is a prevalent condition associated with high rates of nonrecovery, recurrence, and interepisodic dysfunction. Approximately 1 in 8 individuals in the general population in the United States and Canada are estimated to be affected by a depressive episode at some time in their life.<sup>1,2</sup> Major depressive disorder is one of the leading causes of disability and premature mortality in both developed and developing nations.<sup>3</sup> Cost of illness studies have amply documented the staggering costs associated with MDD. A disproportionate burden of the costs is related to impaired role-functioning, notably in the work force.<sup>4</sup> Major depressive disorder compromises human capital more than any other chronic noncommunicable medical

disorder, providing the basis for clarion calls that MDD is a national health priority.

Although MDD is categorized as a psychiatric disorder, it is more accurately and comprehensively referred to as a multisystem disorder. For example, mood disorders are a risk factor for the development of cardiovascular disease, obesity, type 2 diabetes mellitus, pulmonary disorders, neurodegenerative disorders, and osteoporosis.<sup>5–9</sup> Medical comorbidity is discussed in more detail by Larry Culpepper MD, MPH, in “Why Do You Need to Move Beyond First-Line Therapy for Major Depression?”<sup>10</sup> in this supplement. Timely detection, diagnosis, and evidence-based guideline-informed treatment of MDD increase the probability of a more favorable psychiatric and physical health outcome.

Despite the availability of many antidepressants as well as several psychosocial interventions, treatment outcomes in MDD remain rather disappointing. Acute treatment failures, as well as relapse or recurrence following remission, are still common.<sup>11</sup> Discontinuation of therapy, which is estimated to occur in approximately 30% of patients at 1 month of treatment and approximately 50% at 4 months,<sup>12</sup> is one of the most robust factors predisposing a patient to nonrecovery, relapse, and recurrence. Moreover, the presence of residual symptoms in “responding” patients has been identified as a powerful predictor of early relapse and recurrence in prospectively treated individuals with MDD.

## DEFINING AND ASSESSING RESPONSE TO TREATMENT AND REMISSION

### Response

Assessing a patient's progress toward the goal of remission depends upon the clinician's ability to evaluate

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## FOR CLINICAL USE

- ◆ Make a decision to move beyond first-line pharmacotherapy after 4 to 6 weeks of nonresponse to treatment in patients with MDD.
- ◆ Recognize that the time to maximal therapeutic effect with psychotherapy may be 1 to 2 weeks longer when compared with pharmacotherapy.
- ◆ Be aware that early response to treatment, ie, at 2 weeks, may be a predictor of remission at 6 to 8 weeks.
- ◆ Remember that nonresponse to treatment at week 2 may have a powerful predictive value of nonremission at week 8.
- ◆ Recognize that the probability of achieving remission decreases with each unsuccessful acute treatment intervention for depression.

Table 1. Measures and Criteria for Symptomatic and Functional Remission in MDD<sup>a</sup>

Domain	Measure	Cut-Off Score for Remission	Items, No.	Time to Complete, Min	Patient/ Clinician Rated
Symptoms	9-item Patient Health Questionnaire (PHQ-9)	≤4	9	<3	Patient
	17-Item Hamilton Depression Rating Scale (HDRS <sub>17</sub> )	≤7	17	30	Patient or clinician
	Beck Depression Inventory (BDI)	NA	21	5–10	Patient
	Montgomery-Åsberg Depression Rating Scale (MADRS)	≤10	10	10–15	Patient or clinician
	Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR)	≤5	16	5–10	Patient or clinician
	Toronto 7-Item Hamilton Depression Rating Scale (HDRS <sub>7</sub> )	≤3	7	NA	Clinician
Functioning	Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)	Return to functional normality, no agreed cut-off scores	16–60	<5–60	Patient
	Quality of Life in Depression Scale (QLDS)		34	NA	Patient
	Sheehan Disability Scale (SDS)		3	1–2	Patient or clinician
	Social Adjustment Scale–Self Report (SAS-SR)		48	15–20	Patient

<sup>a</sup>Data from Gelenberg,<sup>14</sup> McIntyre et al,<sup>15</sup> Rush et al,<sup>16</sup> and Galen Research.<sup>17</sup> Abbreviations: MDD = major depressive disorder, NA = not available.

the patient's treatment response. Defining and measuring therapeutic endpoints in MDD has become a standard of care and has been demonstrated to independently contribute to improved outcomes in MDD.<sup>13</sup> *Measurement-based care* refers to the systematic and quantitative assessment of symptoms, functioning, and quality of life, as well as assessment of medication adherence and tolerability. Response could be evaluated by objective and/or subjective measures of improvement in symptoms or functioning or by a change in biomarkers. Unfortunately at this time, no biomarker is available to reliably assess efficacy with antidepressant treatment.

As shown in Table 1,<sup>14–17</sup> objective improvement can be measured with symptom assessment tools, such as 17-item Hamilton Depression Rating Scale (HDRS<sub>17</sub>), Toronto 7-item Hamilton Depression Rating Scale (HDRS<sub>7</sub>), or Montgomery-Åsberg Depression Rating Scale (MADRS). Subjective improvement can be measured with tools such as the Beck Depression Inventory (BDI) or the 9-Item Patient Health Questionnaire (PHQ-9). Functional outcomes can be evaluated with the Sheehan Disability Scale (SDS) or the Social Adjustment Scale–Self Report (SAS-SR). Although most practitioners do not routinely employ measures of quality of life, studies evaluating treatment interventions in MDD often use disparate measures including, but not limited to, the Quality of Life Enjoyment and Satisfaction Questionnaire

(Q-LES-Q) and Quality of Life in Depression Scale (QLDS). An emerging area in psychometrics is the measurement of positive human domains including self-esteem, resiliency, and vitality. The impetus behind this development rests on qualitative research unambiguously indicating that the absence of psychopathology does not equate with health.

Definitions of onset of action or response are arbitrary, but many practitioners define response categorically as a percentage of improvement (eg, a 20%–30% decrease) in a depression rating scale score at a particular point in time (ie, by week 2).

No consistent evidence supports claims that any antidepressant or class of antidepressant exhibits a faster onset of action than any other antidepressant. Each of the available antidepressants, from the various classes of antidepressant, is capable of offering robust symptomatic relief in individuals with MDD compared with placebo. Unfortunately, practitioners do not have reliable predictors of remission (or nonremission) for each of the available antidepressants.

Research results are challenging the conventional wisdom that antidepressants require 4 to 6 weeks “to work” or for maximal efficacy. For example, a small, double-blind, placebo-controlled study<sup>18</sup> indicated that cognitive symptoms associated with depression may begin to improve within hours. Among 33 depressed patients, those who received one dose of reboxetine had improved cognitive

reactivity and cognitive interpretation of emotional stimuli compared with depressed individuals who received placebo. Those who were treated were better able to recognize, respond to, and remember positive information, although subjective ratings of mood did not change. This finding challenges the conventional view that vegetative symptoms improve before cognitive symptoms.

Moreover, evidence indicates that early response (ie, at week 2) predicts remission at week 6. A review<sup>19</sup> of 41 clinical trials examined the predictive value of early improvement (ie,  $\geq 20\%$  improvement in HDRS<sub>17</sub> scores within 2 weeks) in 6,907 outpatients with MDD treated with an antidepressant or placebo. Overall, early improvement was a highly sensitive, but not highly specific, predictor of stable response and stable remission. Early improvers constituted approximately 90% of the stable response and stable remission groups, indicating that those who improve within 2 weeks of treatment are likely to respond or remit after 4 or more weeks of treatment. Conversely, about 90% of those who did not improve within 2 weeks did not achieve stable response with treatment.

### Remission

During the past decade, a concatenation of study results, expert opinion, and regulatory bodies have emphasized that achieving symptomatic remission is a critical therapeutic endpoint when treating depressed patients. *Remission* is defined as the presence of minimal or no symptoms (ie, the patient no longer meets diagnostic criteria), and *sustained remission* is defined as having no significant symptoms of depression for at least 8 weeks.<sup>20</sup> Although most definitions of remission do not mention functional recovery, available evidence indicates that achieving remission increases the probability of functional recovery.<sup>21</sup> Remission can be measured with any of the metrics enumerated in Table 1; different cut-off scores for remission exist for each depression scale.

Patients who do not achieve remission are at risk for ongoing chronicity and further relapse of illness,<sup>22</sup> particularly when psychiatric or medical comorbidity is present.<sup>23</sup> The risk for psychosocial nonrecovery as well as absenteeism and reduced productivity at work is increased when depressive symptoms remain.<sup>24</sup> Use of medical services<sup>5</sup> and the need for disability benefits rise.<sup>25</sup> Further, when patients are not in full remission, they may continue to exhibit suicidal ideation and/or behavior.<sup>26</sup>

A minority of patients remit with initial treatment, and a smaller percentage remit after subsequent treatment trials. Using a real-world setting, the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) trial<sup>22</sup> provided relapse and remission rates for 4 sequenced treatment steps. Approximately one-third of patients (36.8%) remitted with initial antidepressant treatment; however, remission rates dropped in subsequent treatment steps (30.6% at level 2, 13.7% at level 3, and 13.0% at level 4).

## FACTORS THAT MAY AFFECT RESPONSE AND REMISSION

Variability in individual response to antidepressant treatment is influenced by socioeconomic, clinical, and comorbidity factors. The STAR\*D trial<sup>23</sup> indicated that being female, white, well educated, and well paid increased the likelihood of achieving remission, as did having private insurance and a shorter current episode. Clinical factors associated with lack of remission and an increased risk of relapse included greater baseline severity of depression and the presence of Axis I, II, or III disorders.

### WHEN SHOULD A CHANGE IN THERAPY BE MADE?

The STAR\*D trial provided empirical evidence regarding time to onset of therapeutic action with antidepressants. In both primary and specialty care settings, the mean time to response with initial treatment was 5.7 weeks and the mean time to remission was 6.7 weeks.<sup>23</sup> The chance of response at week 8 or later was lower than that during weeks 2 to 6. This evidence suggests that 6 weeks is the optimal duration for a treatment trial, although some groups of patients may require less time to achieve response or remission and others may require more time.

The STAR\*D evidence<sup>23</sup> raises questions about how results of augmentation trials should be interpreted. For example, symptomatic improvement with an adjunctive treatment may represent relatively later response to the index agent versus an "augmentation response." In practice, however, many patients who have not responded within 4 to 6 weeks are unlikely to wish to remain on the same therapy for 8 to 12 weeks.

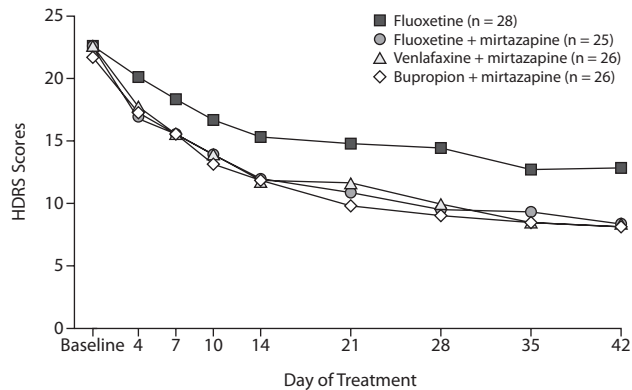
### HOW LONG DOES ONSET OF ACTION OF SUBSEQUENT TREATMENTS TAKE?

Four to 6 weeks are usually needed to achieve an optimal outcome with an index treatment for MDD, and evidence from the STAR\*D trial suggests that the time to onset of action is similar among available agents. The comparable time to remission was observed whether the second agent had similar or dissimilar mechanisms of action compared with the first agent.<sup>27</sup> Similarly, when the index antidepressant treatment was combined with another antidepressant or augmented with an agent from a different class, no differential onset of action was seen.<sup>28</sup>

### ALTERNATIVE STRATEGIES TO ANTIDEPRESSANT THERAPY

The cumulative acute remission rate for STAR\*D participants was 67%.<sup>22</sup> This leaves about 33% of patients for whom current antidepressant treatments may not be adequate. This unmet need has led to the use of many alternative treatment

**Figure 1. Mean HDRS Scores in Patients With MDD Treated With Antidepressant Monotherapy or Combination Therapy for 6 Weeks<sup>a,b</sup>**



<sup>a</sup>Reprinted with permission from Blier et al.<sup>39</sup> Mean scores were by visit for all patients treated (last observation carried forward).

<sup>b</sup>A statistically significant difference was shown between fluoxetine monotherapy and all combination treatment groups ( $F=3.87$ ;  $df=3, 101, P=.011$ ).

Abbreviations: HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder.

strategies such as prescribing atypical antipsychotics, combining antidepressants, and implementing psychosocial treatments. Other strategies not discussed here include prescribing lithium and using adjunctive thyroid hormone or complementary and alternative medicines.

### Atypical Antipsychotics

To address the unmet needs of patients whose depression does not remit with antidepressant therapy, atypical antipsychotics are being used more frequently as a second-line monotherapy and as an add-on strategy in the treatment of MDD. Atypical antipsychotics have been shown to reduce depressive symptoms in people with bipolar disorder or MDD as monotherapy or augmentation.<sup>29-34</sup> The mechanisms of action of atypical antipsychotics, eg, antagonism of serotonin-2A (5-HT<sub>2A</sub>) receptors; partial agonism of 5-HT<sub>1A</sub>, 5-HT<sub>2C</sub>, and dopamine (D<sub>2</sub>) receptors; and, possibly, action at adrenergic receptors, may account for their efficacy in treating depressive symptoms.<sup>35-37</sup> Atypical antipsychotics are discussed in more detail by J. Sloan Manning, MD, in "What Alternatives to First-Line Therapy for Depression Are Effective?"<sup>38</sup> in this supplement.

### Initiating Combination Therapy From the Start of Treatment

Given that patients with MDD often end up receiving combination treatment to achieve remission, combining more than one agent from the outset may have a role in treating some patients. A double-blind study<sup>39</sup> randomly assigned 105 patients with MDD to take fluoxetine or the combination of mirtazapine and fluoxetine, venlafaxine, or

bupropion. Patients receiving combination therapy exhibited about double the rate of remission (mirtazapine plus fluoxetine [52%], venlafaxine [58%], or bupropion [46%] vs fluoxetine monotherapy [25%]) and showed a trend toward faster onset of action, although data did not reach significance (Figure 1). The agents that were combined with mirtazapine had differing mechanisms of action, suggesting that combining multiple mechanisms of action from the start may be helpful in triggering remission, especially in patients with complex illness.

### Psychotherapy

Manual-based psychotherapy is as effective as pharmacotherapy in treating individuals with nonpsychotic, nonsevere depressive episodes. Results from the STAR\*D trial<sup>22</sup> suggested that cognitive therapy was effective in many patients both as a switch (remission rate = 41.9%) and as augmentation therapy (remission rate = 29.4%). However, onset of response with cognitive therapy was relatively slower (almost 8 weeks) than with pharmacotherapy. In depressed patients receiving psychotherapy, extra time may be needed before making a decision to add medication or change frequency of psychotherapeutic visits. Similar to pharmacotherapy, reliable and robust predictors of remission with psychosocial interventions are required in order to assemble a coherent evidence-based treatment algorithm that optimally sequences interventions with the highest probability of achieving remission.

### CONCLUSION

The goals of depression treatment are sustained symptomatic remission and functional recovery. Response and remission need to be defined at the initiation of treatment, and various measurement tools can be used to assess progress toward remission such as the patient-administered PHQ-9, which is feasible in busy clinical practices. Evidence suggests that all of the antidepressant agents currently available offer clinically significant symptomatic relief, but no evidence indicates whether one agent has a faster onset of action than another. Taken together, pharmacotherapy may have a slightly faster onset of action than psychotherapy. If the patient has not responded, the point at which to make a decision about a change in treatment seems to be approximately week 4 to week 6. As demonstrated by the STAR\*D trial, a subgroup of patients may respond beyond week 6, but in practice, patients with no sign of response may not be prepared to wait 8 to 12 weeks to achieve response or remission. Strategies such as using adjunctive pharmacotherapy/psychotherapy or more than one medication from the outset of treatment may be effective in more complex cases of depression, but more research is needed before definitive recommendations can be made. Future research vistas include determining whether or not the use of biomarkers, eg, frontal quantitative electroencephalography can be used



to identify individuals within 1 to 2 weeks of medication exposure who will ultimately remit with antidepressant therapy.<sup>40</sup>

**Drug names:** bupropion (Aplenzin, Wellbutrin, and others), citalopram (Celexa and others), fluoxetine (Prozac and others), lithium (Lithobid and others), mirtazapine (Remeron and others), venlafaxine (Effexor and others).

**Disclosure of off-label usage:** The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside US Food and Drug Administration–approved labeling has been presented in this article.

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