ABSTRACT

INTRODUCTION: Major depressive disorder is a complex and frequent psychiatric condition that poses significant challenges to both the patients who experience it and the physicians who treat them. The goal of therapy is for patients to achieve remission, which requires identifying and measuring symptoms at the outset and throughout treatment to document both response and resistance to treatment. A number of validated instruments are available both for diagnosis of and response to treatment. Many factors affect a patient’s ability to achieve remission, but although many patients do achieve remission, a significant number continue to have residual symptoms that cause functional impairment.

METHODS: Review of the literature for treatment of major depression, including mechanisms of action, individualized treatment optimization, residual symptom reduction, and minimization of side effects.

RESULTS: For sustained remission, all symptoms must be treated until they are undetectable. Patients who do not achieve remission after adequate treatment trials should be evaluated for adherence to treatment, as well as comorbid psychiatric and medical disorders. In these cases, consideration should be given to changing therapy by switching, combining, or augmenting initial therapy, as well as referring some patients to a psychiatrist for treatment with specialized modalities. Linking symptoms with malfunctioning brain circuits and neurotransmitters provides a targeted approach for achieving sustained remission. Neurobiology also provides a rational basis for combination therapy in patients with treatment-resistant depression, because it can aid selection of different drugs with different mechanisms of action or of multifunctional/multimodal antidepressant drugs that target more than 1 molecular mechanism.

DISCUSSION: Recent advances and better understanding of neurobiology provide a rational basis for individualized treatment of patients with major depression.

KEYWORDS: Efficacy; Individualized Treatment; Major depression; Measurement based care; Multimodal antidepressants; Residual Symptoms

Major depressive disorder is widespread, with an estimated 12-month prevalence of 6.7%. It is associated with significant costs in quality of life and lost work productivity largely due to absenteeism/sick days, short-term disability, and performance deficits. The estimated economic burden of depression in 2000 was 83.1 billion dollars, of which 51.5 billion dollars were workplace costs. Treating depression is cost-effective because the cost of treatment is offset by increased work productivity associated with symptom remission.

Major depressive disorder is complex. If one considers the diagnostic criteria—depressed mood or apathy/loss of interest plus ≥4 additional symptoms (Figure 1)—there are >60 forms of major depressive disorder given the various
possible unique combinations of symptoms.\(^5\) Effectively treating patients with major depressive disorder to complete resolution of all symptoms presents a challenge to physicians. All antidepressant drugs have similar efficacy rates, but response among patients varies.

As our understanding of the neurobiology of major depressive disorder has increased, individualizing treatment to improve outcomes has improved. It is now recognized that psychiatric symptoms correlate with malfunctioning brain circuits. An understanding of a patient’s symptom profile is key to individualizing treatment because different symptoms may reflect differences in underlying neuropathology, including differences in neurotransmitter-related abnormalities. Such understanding supports the selection of medications or other treatments that have the mechanisms of action appropriate for the patient. Applying neurobiology principles provides a rationale for individualized treatment selection.

### DEFINING TREATMENT OUTCOMES: IMPORTANCE OF RESIDUAL SYMPTOMS

Over the last 3 decades, the desired outcome for the treatment of major depressive disorder has shifted from response to remission (Table 1).\(^6\) The definition of response—≥50% reduction in total symptom severity—allows for the presence of significant residual symptoms, which may predispose patients to recurrence, chronicity, and suicidality. The optimal outcome for patients with major depressive disorder is now considered to be symptomatic remission, a marker of wellness that is critical to return to premorbid level of functioning. It may be defined as minimal residual symptoms as measured by a ≥80% reduction in symptomatology using one of the accepted rating scales or as an absolute cutoff score, such as ≤7 on the 17-item Hamilton Rating Scale for Depression (HAM-D).

The concept of remission more closely matches, but falls short of, what patients are trying to achieve with treatment. The factors most frequently identified by patients as being very important for achieving remission with treatment are listed in Table 2.\(^7\) These factors relate to the concept of well-being, which is defined as having achieved at least 1 item in each of 6 dimensions, including environmental mastery, personal growth, purpose in life, autonomy, self-acceptance, and positive relations with others.\(^8\) Recovery from a major depressive episode also is suggested as a desirable treatment outcome. However, the definition of recovery includes the criterion that the patient remains in full remission despite discontinuation of treatment, which may not be reasonable given the chronicity of and biological basis for major depression in many patients.\(^8\)

Patients who achieve full remission are more likely to return to normal psychosocial functioning.\(^9\) Thus, the consequences of not achieving remission are many, affecting both the course of the disease and the healthcare and societal costs (Table 3).\(^10-12\) Patients who achieve remission but have residual symptoms are more likely to relapse than those without residual symptoms (Figure 2).\(^13,14\) A literature review that assessed the burden of treatment-resistant depression in the United States concluded that up to 20% of patients with depression are treatment resistant and that annual added societal costs related to treatment-resistant depression are in the range of $29 to $48 billion.\(^15\)

Patients who respond to treatment—≥50% reduction in symptoms—are more likely to have significant functional impairment than those who achieve remission.\(^9,17\) Nonetheless, some patients who attain symptomatic remission also experience significant functional impairment after treatment.\(^9,17-19\) Although a criterion for major depressive episodes is functional impairment, clinical studies almost universally have relied on symptoms or symptom profiles as outcome measures.\(^18\) Patients may report improvement in global functioning measures with treatment, but changes in specific functional domains (eg, social, occupational, physical) generally have not been studied. An analysis of the literature concluded that functional outcomes tend to be less responsive to treatment than are symptom outcomes.\(^18\) The presence of some residual symptoms, such as core mood symptoms, correlate more strongly with functional impairment in patients who achieved remission than do other residual symptoms.\(^19\)

The degree of remission appears to influence the improvement in the level of functionality. The accepted definition of remission on the 17-item HAM-D, a cutoff of ≤7, is now considered too high, because global psychosocial functioning and quality of life are still impaired.\(^20-22\) Scores of ≤5\(^20\) and even 0 to 2\(^22\) are suggested as better target scores for identifying normal levels of functionality. Even patients who scored ≤7 on the HAM-D did not consider themselves to be in remission.\(^21\)
Measuring Residual Symptoms and Functional Impairment

Assessment of treatment response using measurement-based assessment and rating scales is necessary to determine when to adjust therapy. Among the tools to measure the severity of major depressive disorder are the 16-item Quick Inventory of Depressive Symptomatology (QIDS), which has both patient self-report and clinician-rated versions, the 9-item Patient Health Questionnaire (PHQ-9), the HAM-D, the Montgomery Asberg Depression Rating Scale, and specific symptom scales (eg, Epworth Sleepiness, insomnia, and pain severity scales). To enable full recovery in patients with major depressive disorder, physicians must be aware of functional impairments that the patient is experiencing. Because the QIDS, HAM-D, and Montgomery Asberg Depression Rating Scale do not directly assess functional impairments, they often are coupled with validated instruments that can identify impairments and measure the change in impairments over time with treatment.

One instrument that is feasible for use in routine clinical practice is the Sheehan Disability Scale, a brief patient-rated measure of functional disability in work, social, and family life. A total score (the sum of the 3 domain scores ranging from 0 [no disability] to 10 [total disability]) is used to assess functional impairments.

### Table 1: Treatment Outcomes in Major Depressive Disorder

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>≥50% reduction in total symptom severity</td>
</tr>
<tr>
<td>Remission</td>
<td>Minimal residual symptoms as measured by ≥80% reduction in symptoms using an accepted rating scale or Absolute cutoff score, such as ≤7 on the 17-item HAM-D or &lt;5 on the PHQ-9</td>
</tr>
<tr>
<td>Recovery</td>
<td>Includes criterion that the patient remains in full remission despite discontinuation of treatment</td>
</tr>
</tbody>
</table>

HAM-D = Hamilton Rating Scale for Depression; PHQ-9 = 9-Item Patient Health Questionnaire.

### Table 2: Outcomes Important to Patients with Depression in Determining Remission

- Absence of symptoms of depression
- Presence of positive mental health (eg, optimism, vigor, self-confidence)
- Feeling like your usual, normal self
- Return to usual level of functioning at work, home, or school
- Feeling in emotional control
- Participating in, and enjoying, relationships with family and friends
Proportion of patients with and without residual symptoms: relapse after remission. The PHQ-9 asks patients about problems experienced over the last 2 weeks and how difficult those problems made it to do work, take care of things at home, or get along with other people on a 4-point scale ranging from not difficult to extremely difficult. The level of functional impairment on the PHQ-9 was shown to significantly correlate with severity of depression and with remission in a retrospective logistic regression analysis of 1083 patients enrolled in collaborative care management for depression. Severe depression was more common in patients with the highest levels of functional impairment (PHQ-9 score ≥20): 6.4% of patients in the somewhat difficult group, 22.3% of patients in the very difficult group, and 52.3% of patients in the extremely difficult group. In addition, the odds of achieving normal functional status at 6 months correlated highly with clinical remission (PHQ-9 score ≤5) with an odds ratio of 218.53 (P < .001) or with improvement to mild depressive symptoms (PHQ-9 score 5–9) with an odds ratio of 12.301 (P < .001).

The Work and Social Adjustment Scale (WSAS) is a 5-item self-report measure that assesses the ability to work, to manage home and social affairs, and to form and maintain close relationships rated on a 0 to 8 Likert scale. Scores <10 on the WSAS are associated with subclinical disease, and scores >20 suggest at least moderately severe functional impairment. In an analysis of the Sequenced Treatment Alternatives to Relieve Depression trial, higher WSAS scores were associated with greater risk for poorer quality of life. The WSAS was shown to be a reliable and valid measure of impaired functioning.

The Quality of Life Enjoyment and Satisfaction Questionnaire is a 16-item instrument that asks how satisfied patients have been during the past week with such things as physical health, mood, work, social and family relationships, and ability to function in daily life on a scale of 1 to 5 (numeric score corresponds to descriptive terms from very poor to very good). Fourteen of the 16 items are summed for a total score ranging from 14 to 70. The last 2 questions are stand-alone ones that relate to medication and a rating of overall life satisfaction and contentment during the past week. The scale scores are reliable, valid, and related to quality of life measures.

### Residual Symptoms and Functional Impairment

Studies have shown consistently that a high proportion of patients with major depressive disorder who experience full symptomatic remission still have at least 1 (median, 2–4) residual symptom after treatment. The most commonly reported residual symptoms are sleep disturbances, appetite/weight disturbances, cognitive problems, and lack of energy. Symptoms that were present during the course of the depressive episode also were present approximately half of the time during periods of remission. A higher proportion of patients who do not experience remission have residual symptoms compared with those who achieve remission.

Recent work confirms that individual depressive symptoms have differential effects on impairments. Among the symptoms shown to have strong associations with impairment were sadness, concentration problems, fatigue, and interest loss, whereas hypersomnia had little association. Patients’ characteristics, including age and sex, also had little association with impairment. Overall, sad mood and concentration problems had the highest associations with impairment and were among the most debilitating symptoms in each of the 5 domains (work impairment, home management, close relationships, social activities, and private activities). The 3 most debilitating symptoms included...
1 affective (sad mood), 1 cognitive (concentration problems), and 1 somatic (fatigue) symptom, which suggest the need to monitor all kinds of symptoms of depression rather than focusing on 1 domain or factor score.

Another factor that affects the chance of remission is concomitant medical conditions. Patients with ≤1 concomitant medical condition are likely to achieve remission at 6 months, whereas the odds of achieving remission for patients with ≥4 concomitant conditions is <0.5.

The goal of treatment for major depressive disorder is for patients to achieve sustained remission. A number of validated instruments are available both for diagnosis of and response to treatment for major depressive disorder. Many factors affect a patient’s ability to achieve remission, and a significant number of patients continue to have residual symptoms that cause functional impairment. For sustained remission, all symptoms must be treated until they are gone. Attaining remission is key to patients returning to full functioning in their premorbid roles, including at work and in their family and social networks.

**CLINICAL ROLE OF MULTIMODAL NEUROTRANSMITTER MODULATION**

The diagnosis of major depressive disorder is composed of many forms because of the numerous unique symptom profiles that patients may exhibit. Psychiatric symptoms correlate somewhat with malfunctioning brain circuits, but psychiatric disorders do not correlate well with genotypes, biosignatures, or brain circuits. Genes do not code for psychiatric behaviors or symptoms. Rather, they code for subtle molecular abnormalities, which if they exist in a specific circuit have the potential to change the efficiency of information processing. Psychiatric research is attempting to link maladaptive brain circuits to treatment response and to regulatory genes (Figure 4). Downstream from inefficient circuits in the brain that can be visualized with a functional magnetic resonance imaging scanner are the epigenetic and genetic forces that change gene expression. Both normal and abnormal genes can lead to molecular abnormalities in a circuit or abnormal information processing, which can cause symptoms. Some symptoms can be clustered into diagnostic syndromes, and others may predict treatment response. DSM = Diagnostic and Statistical Manual of Mental Disorders. From Stahl SM. Stahl’s Essential Psychopharmacology: Neuroscience, Basis, and Practical Applications. 4th ed. New York, NY: Cambridge University Press; 2013.

![Figure 3](image) Prevalence of residual symptoms by symptom type in patients with major depressive disorder. A higher proportion of patients who do not experience remission have residual symptoms compared with those who achieve remission.

![Figure 4](image) Hypothetical path linking circuits to symptom domains and biomarkers. Downstream from inefficient brain circuits are the epigenetic and genetic forces that change gene expression. Both normal and abnormal genes can lead to molecular abnormalities in a circuit or abnormal information processing, which can cause symptoms. Some symptoms can be clustered into diagnostic syndromes, and others may predict treatment response. DSM = Diagnostic and Statistical Manual of Mental Disorders. From Stahl SM. Stahl’s Essential Psychopharmacology: Neuroscience, Basis, and Practical Applications. 4th ed. New York, NY: Cambridge University Press; 2013.
Figure 5 Match each diagnostic symptom for a major depressive episode to hypothetically malfunctioning brain circuits. The same topographic area or circuit of the brain is responsible for specific symptoms regardless of the psychiatric disorder. For example, sleep and appetite disturbances involve the hypothalamus, and mood disturbances involve another area of the brain. A = Amygdala; BF = Basal forebrain; C = Cerebellum; H = Hippocampus; Hy = Hypothalamus; NA = nucleus accumbens; NT = brainstem neurotransmitter centers; PFC = Prefrontal cortex; S = Striatum; T = Thalamus. From Stahl’s Essential Psychopharmacology, 4th ed. 2013, copyright Neuroscience Education Institute, with permission.

Table 4

<table>
<thead>
<tr>
<th>Neurotransmitter Related</th>
<th>Common Residual Symptoms by Neurotransmitter Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Guilt and lowered self-esteem</td>
</tr>
<tr>
<td>Inhibited communication</td>
<td>Hopelessness</td>
</tr>
<tr>
<td>Dysfunctional attitude</td>
<td>Impaired work and interests</td>
</tr>
<tr>
<td>High neuroticism</td>
<td>Psychosocial disability</td>
</tr>
<tr>
<td>Social maladjustment</td>
<td>Sexual symptoms</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Anhedonia</td>
</tr>
<tr>
<td>Psychotic and somatic anxiety</td>
<td>Lack of motivation</td>
</tr>
</tbody>
</table>

Molecular Targets

There are 5 potential molecular targets for psychotropic drugs. Approximately 30% of psychotropic drugs and 90% of antidepressants target the 12-transmembrane region transporter (Figure 6). Serotonin, dopamine, and norepinephrine reuptake inhibitors all target the 12-transmembrane region transporter. Psychotropic drugs that act at G-protein linked receptors often are added to antidepressant drugs. Psychotropic drugs acting on ligand-gated and voltage-gated ion channels are sometimes used to treat anxiety and bipolar disorder.

Psychotropic drugs may have a single mode of action, may be multifunctional, or may be multimodal. Examples of antidepressants with a single or selective mode of action include the selective serotonin reuptake inhibitors, which selectively inhibit the 12-transmembrane region transporter, and the monoamine oxidase inhibitors, which target an enzyme. Although they have a single mode of action, they also may have downstream effects that increase all 3 neurotransmitters.

Multifunctional and multimodal psychotropic drugs have more than 1 mode of action. A multifunctional antidepressant class is the serotonin-norepinephrine reuptake inhibitors, which block 2 neurotransmitter pumps. Several atypical antipsychotic drugs block numerous G-protein linked receptors, including aripiprazole and quetiapine, and are approved for augmentation of antidepressant drugs. Multimodal psychotropic drugs affect 2 different molecular targets, such as a neurotransmitter pump and a G-protein linked receptor. Examples of multimodal antidepressants are the serotonin partial agonist reuptake inhibitor vilazodone, vortioxetine (which targets 5 different receptors with 3 modes of action), and agomelatine, which is a melatonergic agonist and serotonin antagonist. The benefit of using a drug with multimodal action is to administer 1 drug with 2 modes of action rather than 2 drugs.

Combination Treatment Based on Neurobiology

It is notable that all antidepressants are similarly effective. Approximately one third of patients get better with their first-line therapy. The challenge is what to do for those patients who do not respond to initial therapy. It is important to treat the residual symptoms by switching to a drug with a different mechanism of action or by adding a second drug with a different mechanism of action based on the potential molecular targets discussed earlier.

Brain circuits are regulated by more than 1 neurotransmitter, suggesting that perhaps combination treatment for major depressive disorder is justified on the basis of neurobiology. There is evidence that combining drugs with different mechanisms is effective when a single mechanism fails. It is not so much about which drug to add, but more about when to initiate combination therapy. Any of the antidepressant drugs are more effective earlier in the course of depression, and no drug works well after several failed treatments. Interest has shifted to giving the most effective treatments first, either alone or in combination, which is analogous to the treatment of tuberculosis, human immunodeficiency virus infection, or cancer for which multiple drugs may be given early.
A double-blind trial of 105 patients who met the Diagnostic and Statistical Manual of Mental Disorders IV criteria for major depressive disorder assessed whether combination therapy from initiation of treatment was superior to single-drug therapy. Patients were randomized to 6 weeks of treatment with fluoxetine (20 mg/d) alone or mirtazapine (30 mg/d) in combination with fluoxetine (20 mg/d) or bupropion (150 mg/d) or venlafaxine (225 mg/d titrated in 14 days). The reduction in the HAM-D score was significantly (P = .011) greater with the combination regimens than with fluoxetine monotherapy. The proportion of patients achieving sustained remission (HAM-D score, ≤7) was significantly greater for the mirtazapine/fluoxetine (52%) and mirtazapine/venlafaxine (58%) combinations but not for the mirtazapine/bupropion (46%) compared with fluoxetine monotherapy (25%). Combination regimens were as well tolerated as fluoxetine monotherapy. This study demonstrates the benefit of targeting multiple molecular targets at the initiation of treatment for major depressive disorder: Fluoxetine targets the serotonin pump, whereas mirtazapine targets G-protein linked receptors and venlafaxine targets both serotonin and norepinephrine pumps.

A second single-blind randomized study evaluated acute (12 weeks) and long-term (7 months) outcomes with escitalopram (≤20 mg/d) plus placebo monotherapy compared with those of combination regimens of escitalopram (≤20 mg/d) and sustained-release bupropion (≤400 mg/d) or mirtazapine (≤45 mg/d) and venlafaxine (≤300 mg/d). Remission rates at both 12 weeks and 7 months were similar among the groups: 12 weeks, 38.8% for escitalopram-placebo vs 38.9% for escitalopram-bupropion vs 37.7% for mirtazapine-venlafaxine. At 7 months, remission rates ranged from 41.8% to 46.6%. Unlike in the previous study, combination regimens were not as well tolerated as escitalopram monotherapy. Severe or intolerable adverse events were reported by 4.2% of patients treated with escitalopram vs 10.0% of patients treated with escitalopram-bupropion and 15.2% of patients treated with mirtazapine-venlafaxine.

Therefore, clinical trial results are mixed regarding the use of combination therapy in treatment-naïve patients and do not support its use at initiation of therapy because the risk–benefit ratio tends to favor monotherapy. However, combination therapy is becoming more common practice in patients with prior treatment failures. Combining mechanisms of action provides a synergistic effect particularly for those patients who have failed on 1 or 2 drugs. Combining psychotherapy or cognitive behavioral therapy with antidepressant medication may improve response rate and tolerability.
therapy with psychopharmacology also may be effective because it combines different mechanisms.\textsuperscript{45,50,51} Another way to target several mechanisms yet prescribe only 1 drug is to use multifunctional or multimodal antidepressant drugs.

Neurobiology provides a rational basis for individualizing treatment of patients with major depressive disorder. Linking symptoms with malfunctioning brain circuits and neurotransmitters provides a targeted approach for achieving sustained remission. Neurobiology also provides a rational basis for combination therapy by prescribing 2 different drugs with different mechanisms of action or by using multifunctional/multimodal antidepressant drugs because they target different molecular target mechanisms.

**IMPROVING OUTCOMES**

Despite advances in our understanding of the science of major depressive disorder and its treatment, 75% to 90% of patients experience 1 episode of depression. As the number of recurrences increase, there is a tendency for episodes to increase in frequency and become less responsive to treatment.\textsuperscript{52} Table 3 lists the consequences of not achieving remission in major depressive disorder.\textsuperscript{10-12} Obstacles to attaining remission include both physicians and patients settling for a treatment response although the patients may still be experiencing residual symptoms, poor tolerance to drug treatment, medication dose or length of therapy, or the failure to recognize residual symptoms.\textsuperscript{52,53} In addition to antidepressant drugs, nonpharmacologic approaches such as support, exercise, informal counseling, and psychotherapy are beneficial in patients with a major depressive episode.\textsuperscript{54,55}

Because all antidepressant drugs have similar efficacy rates and mechanisms of action, other factors affect treatment choices (Table 5).\textsuperscript{54} The perceptions of the patient or family and friends regarding a specific antidepressant they have received may influence the patient’s comfort level with taking that medication. Comorbidities and other drugs that the patient is taking affect treatment decisions for a depressive episode. After selecting therapy, frequent follow-up is necessary for managing both efficacy and tolerability of the drug (Table 6).\textsuperscript{56} It is important to provide education and occasionally provide educational materials at the initial visit. This aids in ensuring that the patient recognizes that depression is a biological illness, that the drugs to treat depression can increase suicidality, and that they have the potential to cause adverse effects before a therapeutic effect. At 2 to 3 weeks, after an initial response to therapy, patients may realize that troublesome side effects are not going away. It may be necessary to consider changing drug therapy. At 3 to 6 weeks, patients should be noticeably improved, but there may be a need to change the drug or adjust dosing. Continued monitoring should continue out to 12 weeks with considerations for changing therapy or adding nonpharmacologic therapies such as psychotherapy if there is only a partial response. If the patient achieves a full response, the patient enters the continuation phase of treatment.

Approximately two thirds of patients have residual symptoms after 12 weeks of treatment, and as much as 20% will have severe or very severe symptoms.\textsuperscript{39,57} Many patients have 1 symptom and will meet criteria for minor or subsyndromal depression. Residual symptoms of fatigue or mood and sleep disturbances represent dysfunctional changes that patients do not consider normal and add to the economic burden of depression.\textsuperscript{39,57,58} In addition, comorbid anxiety is a predictor of lower remission rates.\textsuperscript{59} The most common reasons for an inadequate response are misdiagnosis, inappropriate treatment, or failure to address concurrent disorders (Table 7).\textsuperscript{60,61}

### Table 5: Factors to Consider in Antidepressant Drug Selection\textsuperscript{54}

<table>
<thead>
<tr>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient comfort level with use of medication</td>
</tr>
<tr>
<td>Efficacy of prior treatments or treatment of family members</td>
</tr>
<tr>
<td>Insurance coverage, cost to patient</td>
</tr>
<tr>
<td>Medical comorbidities</td>
</tr>
<tr>
<td>Psychiatric comorbidities</td>
</tr>
<tr>
<td>Drug–drug interactions</td>
</tr>
<tr>
<td>Side effects</td>
</tr>
<tr>
<td>Tolerability, both early and long term</td>
</tr>
<tr>
<td>Dosing and cost potential of using higher than FDA-approved doses</td>
</tr>
</tbody>
</table>

**Table 6: Active Management Guide After Initiation of Therapy**

- **Initial presentation**
  - Provide education/durable material
  - 48- to 72-h assessment for adverse effects and suicidality

- **2-3 wks**
  - Assess initial response, side effects, suicidality
  - Consider dose or treatment (same class or different mechanism of action) change if necessary

- **3-6 wks**
  - Assess response trajectory
  - Consider dose or treatment (same class or different mechanism of action) change if necessary

- **6-12 wks**
  - Further monitoring

**Therapeutic Options for Patients with Residual Symptoms**

Difficult-to-treat or refractory depression can be treated successfully with many patients achieving remission.\textsuperscript{62} For patients who do not achieve remission after 12 weeks of initial therapy, there are several therapeutic options from changing to another antidepressant drug, to combination antidepressant therapy, to augmentation therapies and special treatment programs (Table 8).\textsuperscript{56} It is necessary to first evaluate those factors that may contribute to lack of treatment response, such as comorbid medical or psychiatric
conditions. After this evaluation, one could begin using the 4 classic strategies for enhancing antidepressant efficacy: optimization, augmentation, combination therapy, and switching agents.\textsuperscript{54,63} Table 9 provides an overview of the efficacy of the pharmacologic options for treatment-resistant depression.\textsuperscript{11,54,64} Selected strategies with data for their use in major depressive disorder are discussed next.

**Strategies with Clear Efficacy.** Monoamine oxidase inhibitors. The monoamine oxidase inhibitors were the first antidepressant drugs and block monoamine oxidase-A or monoamine oxidase-B isoenzymes. The A isoenzyme is found in the brain but also is found throughout the body, including the intestines. The B isoenzyme is found in the brain, lymphocytes, platelets, and norepinephrine neurons.\textsuperscript{65,66} Inhibition of monoamine oxidase-A in the brain is necessary for an antidepressant effect; however, inhibition of monoamine oxidase-A in the intestinal tract can result in extensive absorption of tyramine, which can lead to hypertensive crisis.\textsuperscript{54,67,69} Older monoamine oxidase inhibitors are irreversible nonselective blockers (inhibit both A and B) and metabolize serotonin, dopamine, norepinephrine, and tyramine. Primary care physicians do not commonly prescribe them, in large part because of their drug and food interactions. Nevertheless, monoamine oxidase inhibitors are useful drugs for patients with difficult-to-treat depression and can be used safely because many of the interactions are overstated.\textsuperscript{69,70}

Inhibiting monoamine oxidase-B, which primarily metabolizes dopamine, has anti-Parkinson effects. The selective monoamine oxidase-B inhibitor selegiline is prescribed for Parkinson’s disease, and it is the first drug approved as a transdermal patch for the treatment of depression.\textsuperscript{66,68} The area under the 24-hour concentration time curve is approximately the same for the 6-mg patch (dose delivered over 24 hours) and a 10-mg oral dose.\textsuperscript{66} Because transdermal delivery bypasses the gastrointestinal tract and the hepatic first-pass metabolism that occurs with orally administered drugs, the 6 mg/24-hour selegiline patch can be used without the dietary restrictions common for monoamine oxidase inhibitors; at higher doses, the dietary restrictions for monoamine oxidase inhibitors are recommended.\textsuperscript{68} It is important to keep in mind that selegiline shares the same drug—drug interactions and medication contraindications as the other monoamine oxidase inhibitors (Table 10).\textsuperscript{68,69}

**Atypical antipsychotics.** The atypical antipsychotic agents, quetiapine and aripiprazole, have been shown in clinical trials to augment the response to initial antidepressant treatment.\textsuperscript{54,63} Remission rates with quetiapine extended-release 300 mg per day as adjunctive therapy were 42.5% compared with 24.5% with placebo adjunctive therapy ($P < .01$),\textsuperscript{71} whereas those for aripiprazole (mean dose, $\sim 11$ mg/d) were approximately 25% to 26% compared with 15% to 16% for placebo adjunctive therapy.\textsuperscript{72,73} The addition of these drugs to preexisting therapy increases the risk of adverse effects. Common adverse effects with quetiapine include dry mouth, somnolence, dizziness, gastrointestinal symptoms, insomnia, headache, and fatigue. Aripiprazole can cause akathisia, headache, insomnia, and fatigue. The medications are also associated with an increased risk of tardive dyskinesia, weight gain, and adverse metabolic, endocrine, and electrocardiographic effects.

**Mirtazapine.** Mirtazapine is a multifunctional antidepressant drug in that it enhances release of norepinephrine and serotonin.\textsuperscript{54} It has been used as an across-class switch from selective serotonin reuptake inhibitor therapy and to augment selective serotonin reuptake inhibitor therapy, although it is not Food and Drug Administration approved for this use.\textsuperscript{75,77} Common adverse effects are sedation and weight gain, but it is less likely to cause sexual and sleep-related side effects than are selective serotonin reuptake inhibitors.\textsuperscript{54}

### Table 7 Reasons for Inadequate Treatment Response\textsuperscript{60,61}

- Misdiagnosis resulting in inappropriate treatment
  - Unipolar vs bipolar depression
  - Substance abuse
  - Undiagnosed medical disorder
- Inadequate treatment
  - Duration and dose
  - Poor adherence and adverse effects
  - Combination antidepressant use at subtherapeutic doses
- Failure to address known concurrent disorders
  - Alcohol or substance use disorders
  - General medical conditions
  - Other psychiatric disorders

### Table 8 Possible Next Therapeutic Options for the Treatment of Major Depressive Disorder\textsuperscript{56,63}

- Switch antidepressants
  - Within class
  - Across class
- Combination/augmentation therapy
  - Add-on antidepressants
    - Bupropion
    - Tricyclic antidepressants
  - Combination antidepressants
- Referral for special treatments
  - Inpatient care
  - Day treatment programs
  - Crisis team approaches
- Augmentation
  - Atypical antipsychotics
    - (aripiprazole, quetiapine)
  - Mirtazapine
  - Cognitive behavioral therapy
  - Omega-3 fatty acids
  - Modafinil
  - SAMe, T3, L-methylfolate
  - Miscellaneous drugs: buspirone, lithium, pindolol
  - Methylphenidate

SAMe = S-adenosyl-L-methionine.
Within-class vs across-class switch. A meta-analysis comparing within- vs across-class switches of selective serotonin reuptake inhibitor therapy found that pooled remission rates for across-class switches (to bupropion, mirtazapine, or venlafaxine) were greater compared with a within selective serotonin reuptake inhibitor class switch (28% vs 23.5%; \( P = .007 \)).\(^\text{75}\) Another review concluded that an across-class switch may offer greater benefits than a within-class switch.\(^\text{76}\)

Strategies with Suggested Efficacy. \( S \)-adenosylmethionine. The nutraceutical \( S \)-adenosylmethionine works by adding a methyl group to neurotransmitters.\(^\text{77}\) It has shown promise in studies of patients with mild-to-moderate and moderate-to-severe depression, with most studies reporting a positive effect with doses of 400 to 1600 mg per day.\(^\text{79}\) The studies do have methodological flaws (eg, small size, short-term analyses). Although many of the studies did not report adverse events, psychomotor excitation, mania, and insomnia are among the reported behavioral-related adverse events with \( S \)-adenosylmethionine. Because \( S \)-adenosylmethionine readily interacts with oxygen, only containers of foil-wrapped tablets should be purchased.

**Table 9** Overview of Pharmacologic Options for Treatment-Resistant Depression\(^\text{11,54,64}\)

<table>
<thead>
<tr>
<th>Clear Efficacy +++</th>
<th>Suggested Efficacy ++</th>
<th>Unclear Efficacy +/-</th>
<th>Inadequate Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirtazapine</td>
<td>Omega-3 fatty acids†</td>
<td>Buspironet†</td>
<td>Opiates†</td>
</tr>
<tr>
<td>Atypical antipsychotics*</td>
<td>Modafinil†</td>
<td>Pindolol†</td>
<td>Inositol†</td>
</tr>
<tr>
<td>SSRI to SSRI</td>
<td>SAMe†</td>
<td>Methylphenidate†</td>
<td>Anticonvulsant†</td>
</tr>
<tr>
<td>SSRI to SNRI, bupropion, mirtazapine</td>
<td>L-methylfolatet†</td>
<td>Lithium†</td>
<td>Benzodiazepinet†</td>
</tr>
<tr>
<td></td>
<td>Testosteronet†</td>
<td>T3†</td>
<td>Antipsychotic†</td>
</tr>
<tr>
<td></td>
<td>Switch to MAOIt</td>
<td>Switch to TCA</td>
<td>Estrogen†</td>
</tr>
</tbody>
</table>

MAOI = monoamine oxidase inhibitor; SAMe = \( S \)-adenyl-L-methionine; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

*Not approved by the Food and Drug Administration for the treatment of major depressive disorder, either as monotherapy or in combination.

**Table 10** Medications Contraindicated with Monoamine Oxidase Inhibitors Because of Drug—Drug Interactions\(^\text{68}\)

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>Meperidine, methadone, tramadol, propoxyphene</td>
</tr>
<tr>
<td>Cold preparations</td>
<td>Dextromethorphan, ephedrine, phenylephrine, phenylpropanolamine, pseudoephedrine</td>
</tr>
<tr>
<td>Sympathomimetic amines</td>
<td>Amphetamines</td>
</tr>
<tr>
<td>MAOIs</td>
<td>Isocarboxazid, phenelzine, rasagiline, selegiline, tranylcypromine</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Fluoxetine, paroxetine, sertraline</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Duloxetine, venlafaxine</td>
</tr>
<tr>
<td>TCAs</td>
<td>Amitriptyline, imipramine</td>
</tr>
<tr>
<td>Tetracyclic antidepressants</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Other</td>
<td>Bupropion, buspirone, ziprasidone</td>
</tr>
</tbody>
</table>

MAOI = monoamine oxidase inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

\( L \)-methylfolate. Patients treated for depression who cannot convert folate to \( L \)-methylfolate may have worse outcomes than those without this abnormality. A study of 75 patients who had an inadequate response to selective serotonin reuptake inhibitors found that those with a genomic biomarker associated with an abnormality in \( L \)-methylfolate synthesis and metabolism treated with \( L \)-methylfolate supplementation had significantly greater improvement in both HAM-D scores and the Clinical Global Impressions Severity of Illness Scale compared with patients treated with placebo.\(^\text{85}\) \( L \)-methylfolate is classified as a medical food and therefore does not require the same Food and Drug Administration review and approval as antidepressants. Additional studies are necessary to confirm the link between depression and \( L \)-methylfolate.

**Modafinil.** Modafinil, a mood enhancer and wakefulness drug, is used in some patients with major depressive disorder as an adjunct treatment, but it is a nonapproved use. When added to existing treatment, modafinil may resolve
symptoms of depression in patients with residual symptoms of somnolence and fatigue.\textsuperscript{11,64,86}

\textit{Bupropion and buspirone.} Both bupropion and buspirone were evaluated as augmentation therapy to citalopram in the Sequenced Treatment Alternatives to Relieve Depression study.\textsuperscript{87} Remission rates based on HAM-D scores were approximately 30\% for both drugs. The higher remission rates based on the self-reported QIDS scores for bupropion (39\% and 33\%, bupropion and buspirone) and the lower QIDS total scores at the end of the study suggest that bupropion use may be more advantageous. Neither drug is approved for augmentation therapy of major depression.

\textbf{Strategies with Unclear Efficacy.} \textit{Pindolol.} The results are mixed for pindolol, a serotonin receptor antagonist, as an augmentation strategy for patients receiving selective serotonin reuptake inhibitor therapy.\textsuperscript{88,89} A meta-analysis of pindolol plus selective serotonin reuptake inhibitor therapy found that outcomes favored pindolol early (at 2 weeks) in the treatment but not at 4 to 6 weeks.\textsuperscript{90} Efficacy and safety outcomes do not suggest a role for pindolol as augmentation therapy, and it is not approved for this use.

\textit{Switch antidepressants.} Switching within or to a different antidepressant class may increase remission rates and minimize the risks associated with polypharmacy.\textsuperscript{54} Patients who switch from one selective serotonin reuptake inhibitor to another have a 40\% to 70\% chance of responding to a second selective serotonin reuptake inhibitor.\textsuperscript{91} In one study of a switch from tricyclic antidepressant to selective serotonin reuptake inhibitor therapy and vice versa after 12 weeks of initial treatment, a further 12 weeks of crossover drug therapy benefited more than 50\% of chronically depressed patients who had not responded to their initial treatment.\textsuperscript{92} A switch to selective serotonin reuptake inhibitor therapy resulted in a higher proportion of responders than a switch to tricyclic antidepressant therapy (60\% vs 44\%), and the selective serotonin reuptake inhibitor was better tolerated. Only approximately one half of the responders achieved full remission after the switch, that is, had half significant residual symptoms after an additional 12 weeks of antidepressant therapy. Switching antidepressant drug classes may provide additional benefit in some patients, but adverse effects may limit patient acceptance.\textsuperscript{11}

\textit{Lithium.} Lithium is an older drug used to treat mania and bipolar disorder and as a mood stabilizer to prevent suicide in bipolar depression.\textsuperscript{54,93} It has been studied as an augmentation strategy in treatment-resistant depression, but it is not approved for this use. A meta-analysis of placebo-controlled studies found that, with a minimum treatment duration of 2 weeks, the absolute improvement in response rate was 27\% with lithium augmentation therapy.\textsuperscript{94} Lithium therapy has disadvantages, including adverse effects (cognitive effects, weight gain, tremor), need for monitoring of blood levels to prevent lithium toxicity, and drug–drug interactions that may lead to increased lithium levels and toxicity.\textsuperscript{93} The studies for lithium augmentation therapy are older and often studied tricyclic antidepressants, which are not used commonly today. Lithium is recommended by some clinicians\textsuperscript{64,94} but not others\textsuperscript{11} as a augmentation strategy for treatment-resistant depression.

\textit{T3.} There is an established link between thyroid function and depression: Patients with thyroid disorders are more prone to develop symptoms of depression, and depression may be accompanied by abnormalities in thyroid function.\textsuperscript{95} Augmentation with T3 has been studied, but T3 is not approved for this indication. A meta-analysis of 8 controlled clinical trials of tricyclic antidepressant augmentation with T3 found a 23\% absolute improvement in response rates with T3 augmentation; however, limiting the analysis to 4 double-blind controlled studies yielded no significant effect for T3 augmentation.\textsuperscript{96} An analysis of double-blind studies of selective serotonin reuptake inhibitor augmentation with T3 concluded that simultaneous initiation of T3 and selective serotonin reuptake inhibitor therapy is not significantly more likely to accelerate a clinical response in patients with depression compared with selective serotonin reuptake inhibitor monotherapy.\textsuperscript{97}

Studies comparing lithium and T3 as augmentation strategies show improvement over tricyclic antidepressant or selective serotonin reuptake inhibitor monotherapy. A small, 2-week, randomized controlled study of tricyclic antidepressant augmentation found similar improvement in response rates (HAM-D score <10 or \geq50\% reduction in HAM-D score) with T3 (10/17 patients) and lithium (9/17 patients).\textsuperscript{98} A 14-week study of selective serotonin reuptake inhibitor augmentation with T3 or lithium as a third-step treatment for major depressive disorder reported remission rates of 24.7\% with T3 and 15.9\% with lithium.\textsuperscript{99} A significantly higher proportion of patients randomized to lithium compared with T3 discontinued treatment because of adverse effects (23.2\% vs 9.6\%; \textit{P} = .027). Augmentation with lithium or T3 may be a useful strategy for some patients with treatment-resistant depression, but neither is approved for this indication.

\textbf{Nonpharmacologic Interventions.} Some patients initially treated by primary care physicians will require referral to a psychiatrist. Patients to consider for referral are those who have severe depression or are suicidal, have a history of treatment resistance, have comorbidities (eg, substance abuse, personality disorder, eating disorder), or need modalities not available to primary care physicians (inpatient or day hospital care, intensive community support team, specialized interventions).

New treatment modalities used by psychiatrists that may ameliorate treatment-resistant depression include repetitive transcranial magnetic stimulation, electroconvulsive therapy, magnetic seizure therapy, vagal nerve stimulation, and deep brain stimulation.\textsuperscript{100} Of these, repetitive transcranial magnetic stimulation is the least invasive and has been shown to provide significant benefit in short-term studies.\textsuperscript{101}
A meta-analysis of 24 studies reported pooled response and remission rates of 25% and 17%, respectively, with repetitive transcranial magnetic stimulation compared with 9% and 6% response and remission rates, respectively, for sham treatment. Discontinuations from treatment due to adverse events were low.

Continuation/Maintenance Treatment. After achieving remission, patients should continue therapy for an additional 6 to 9 months. Patients with multiple (≥3) lifetime episodes of depression, or 2 episodes if 1 was severe or difficult to treat, may require an even longer treatment period. Other factors that may necessitate a longer duration of maintenance therapy are brief remission periods between episodes, incomplete inter-episode recovery, treatment resistance during the current episode, and patient preference. The same drug at the same dose should be continued as maintenance treatment, and consideration may be given to adjunctive cognitive behavioral therapy or interpersonal psychotherapy. Patients should continue to be monitored and treated for adverse events, residual symptoms, and withdrawal symptoms, as well as other psychiatric and medical problems. Psychoeducation, including management of inter-current life events and recognition of recurrence of depression, adverse events, residual symptoms, and withdrawal symptoms, should be provided to patients during maintenance treatment.

Patient Adherence. Adherence to antidepressant treatment is not optimal. Studies report 25% to 42% of patients discontinue therapy within 1 month, and up to 72% discontinue therapy within 3 months. Use of newer antidepressants with improved adverse event profiles and education regarding antidepressant drug use (eg, take daily, require 2-4 weeks for noticeable effect, continue even if feel better, do not stop without consulting physician) help improve adherence with therapy. Adherence to antidepressant treatment in older adults may be affected by visual and auditory impairments, memory deficits, medication regimen complexity due to comorbid conditions, and a sense of hopelessness and despair.

Treatment beliefs and patient–physician communication influence patient adherence. One study identified the demographic and clinical characteristics that accounted for patient beliefs about antidepressants, characteristics that influence adherence to treatment (Figure 7). Younger patients are more likely to be at risk for poor adherence because of their harmful beliefs. Frequent physician contact (eg, ≥3 follow-up visits) was shown in one study to improve adherence with the initially prescribed antidepressant, as well as discussions about expected duration of therapy and patient willingness to discuss adverse effects. Multifaceted interventions that increase the intensity (medication monitoring, patient education) and frequency of

![Figure 7](image-url)
visits (2 with primary care physician, 2 with psychiatrist) during the initial 6 weeks of treatment improve adherence and outcome measures compared with usual care by a primary care physician.\textsuperscript{107}

Improving outcomes in patients with major depressive disorder requires identifying and measuring symptoms at the outset and throughout treatment to document remission or resistance to treatment. Adequate treatment trials of antidepressant therapy (sufficient dose and duration) are necessary to achieve remission. If patients do not achieve remission, they should be evaluated for adherence to treatment and comorbid psychiatric and medical disorders, and consideration should be given to changing therapy by switching, combining, or augmenting initial therapy. It may be necessary to refer some patients to a psychiatrist for treatment with specialized modalities. Once patients achieve remission, it is important to continue with maintenance therapy.

**CONCLUSIONS**

Major depressive disorder is complex, taking many forms because of the various possible unique symptom combinations. Although the desired outcome of treatment is remission of all symptoms, a high proportion of patients who achieve remission have at least 1 residual symptom. Symptoms of depression that have strong associations with functional impairments include sad mood, difficulty concentrating, fatigue, and loss of interest, and these add to the economic burden of depression. All antidepressant drugs have similar efficacy, although some may not be effective in a given patient. A better understanding of the neurobiology of depression now provides a rationale for how to individualize drug selection both initially and in patients with treatment-resistant depression to optimize outcomes. It is now known that symptom domains correlate somewhat with malfunctioning brain circuits and that restoring neurotransmitter activity in the circuits with impaired information processing restores function. Applying neurobiology principles to treatment selections may assist physicians in determining whether to switch antidepressants, add another antidepressant medication, or augment antidepressant therapy with another pharmacologic agent or a nonpharmacologic treatment such as psychotherapy. Throughout a treatment course for major depressive disorder, antidepressant medications must be given for a sufficient duration at a sufficient dose and patients monitored for response to and adverse events with treatment and psychiatric and medical comorbidities. Patients with residual symptoms or treatment-resistant depression can achieve complete remission of their symptoms and regain functionality.

**References**


20. Romera I, Pérez V, Menchon JM, Polavieja P, Gilaberte I. Optimal cutoff point of the Hamilton Rating Scale for Depression according to normal levels of social and occupational functioning. *Psychiatry Res*. 2011;186:133-137.


44. Pehrson AL, Sanchez C. Serotonergic modulation of glutamate neurotransmission as a strategy for treating depression and cognitive dysfunction. *CNS Spectrums*. 2014;19:121-123.


68. Culppepper L, Kovalick LJ. A review of the literature on the selegiline transdermal system: an effective and well-tolerated monoamine


