

## The Clinical, Psychosocial, and Pharmacoeconomic Ramifications of Remission

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### Summary

At an estimated cost of almost \$50 billion a year, the socioeconomic burden of major depressive disorder is enormous. Although remission has been identified as the key goal of treatment, such treatment must be highly acceptable to patients, predictably effective, and carry minimal adverse effects. The cornerstone of depression management, remission can improve clinical status, functional ability, and quality of life for the patient while lowering utilization costs related to the disease and its comorbidities. Initially, the goals of therapy are to: (1) reduce and ultimately remove all signs and symptoms of the depressive syndrome; (2) restore occupational and psychosocial function to the asymptomatic state; and (3) achieve and maintain remission. Most patients can achieve these goals with the help of antidepressant medications, problem-focused psychotherapy, or a combination of the 2 methods. Following an initial assessment of the patient, treatment of depression has 3 phases: acute, continuation, and maintenance. Although adherence to treatment is crucial to successful treatment of depression, only about 25% to 35% of patients will achieve remission after 6 to 8 weeks of treatment; another 15% to 20% may remain depressed for months or years. Patients who achieve remission are much less likely to relapse than those who do not. Much debate has focused on the relative merits of prescribing selective serotonin reuptake inhibitors or venlafaxine. Results of a pooled analysis of 8 such comparative studies are presented.

ability with regard to functional status and quality of life. Furthermore, the socioeconomic burden associated with major depressive disorder is enormous, with total depression-related costs in the United States approaching \$50 billion annually.<sup>1,2</sup>

Numerous regulatory organizations have identified remission as a key treatment goal for patients with major depression. The Agency for Health Care Policy and Research recognizes 3 initial objectives of treatment: (1) to reduce and, ultimately, remove all signs and symptoms of the depressive syndrome; (2) to restore occupational and psychosocial function to that of the asymptomatic state; and (3) to reduce the likelihood of relapse and recurrence.<sup>3,4</sup> The American Psychiatric Association treatment recommendations for patients with major depressive disorder emphasize maintenance-phase treatment to prevent relapse.<sup>5</sup> In 2000, the guidelines of the British Association for Psychopharmacology for treating depressive disorders were revised such that remission is recognized as a key treatment goal.<sup>6</sup>

The optimal treatment for depression is one that is highly acceptable to patients, predictably effective, affordable, and associated with minimal adverse effects. It results in complete removal of symptoms and restoration of psychosocial and occupational functioning, a level of improvement known as remission. Remission, therefore, is the cornerstone of management. Achieving and maintain-

**D**epression is one of the most prevalent and debilitating disorders today. People who suffer from depression may experience profound dis-

ing remission not only improves clinical status, functional ability, and quality of life for the patient with depression, but also lowers the enormous utilization costs associated with depression and its comorbidities.

**Treatment of Major Depression**

Once major depressive disorder is diagnosed, relatively straightforward interventions that predictably decrease symptoms and morbidity and hasten recovery (ie, faster than would naturally occur during the course of the illness) are tried first. The key initial goals of therapy, in order of priority, are: (1) to reduce and ultimately to remove all signs and symptoms of the depressive syndrome; (2) to restore occupational and psychosocial function to that of the asymptomatic state; and (3) to achieve and maintain remission.<sup>4</sup> For most patients, these goals can be achieved with antidepressant medications, problem-focused psychotherapy, or a combination of both. However, the term *remission* is not synonymous with *cure*. From a longitudinal perspective, the acute phase should be followed by a continuation phase (intended to protect against relapse) and, if necessary, a maintenance phase, which aims to prevent recurrence of major depressive episodes (Table 1).<sup>5</sup>

**Acute Phase.** During the acute phase of treatment, the initial therapeutic regimen may consist of psychotherapy, pharmacotherapy, a combination of both, or less commonly, electroconvulsive therapy (ECT). The choice of therapeutic regimen

is based on treatment history, clinical factors, and patient preference. ECT is usually reserved for patients who are incapacitated by the severity of the episode and/or have not responded to multiple antidepressant trials. Either psychotherapy or pharmacotherapy may be opted for when the depression is mild to moderate in severity. Antidepressant medications are often chosen as the initial treatment modality for moderate-to-severe depression. Combined treatment (ie, the addition of psychotherapy to pharmacotherapy) may be useful for patients with chronic depression, ongoing interpersonal problems, or psychologically significant comorbid disorders (eg, panic disorder or social phobia). The selected antidepressant medication usually is initiated at the minimum effective dose, which is suggested in the product labeling.

Patients who begin antidepressant therapy should be monitored carefully in order to assess response and safety. If the minimum effective dose is not beneficial, most newer antidepressants can be subsequently titrated, as tolerated, at every-other-week intervals. Generally, it takes 6 to 8 weeks to conduct an adequate trial if patients are able to tolerate maximal approved doses. Factors to consider in determining the frequency of patient monitoring include the severity of depression (including suicidality), degree of adherence to treatment, availability of social support, and presence of comorbid medical and/or psychiatric problems. Follow-up visits should be frequent enough to offset demoralization and to promote adherence to treatment. Psychotherapists treating depressed people should similarly assess symptom levels at each scheduled visit.

If remission is not obtained after the first 6 to 8 weeks of therapy, the treatment regimen should be reassessed. If there has been no response whatsoever, a major change is typically needed (eg, switching to a different class of antidepressant or adding an antidepressant to ongoing psychotherapy). In the case of partial or incomplete remission, the addition of psychotherapy to ongoing pharma-

**Table 1.** Phases of Antidepressant Therapy

Treatment Phase	Primary Therapeutic Goal
Acute phase	Induction of remission
Continuation phase	Stabilization and short-term preservation of remission
Maintenance phase	Long-term preservation of remission

cotherapy or one of several augmentation strategies might be considered.

**Continuation Phase.** All patients who respond to acute-phase antidepressant therapy should receive 6 to 9 months of continuation-phase therapy to protect against relapse. In general, the antidepressant dose used during the acute phase is also used in the continuation phase. Although the use of psychotherapy during the continuation phase to prevent relapse has not been extensively studied, growing evidence supports the use of a specific effective psychotherapy during a continuation phase if remission has been slow or incomplete.<sup>7</sup> Continuation-phase pharmacotherapy is also necessary to prevent relapse for patients who have responded to ECT. When this strategy fails, a longer-term model of continuation ECT (eg, weekly treatments followed by every-other-week and monthly treatments, as indicated) may be considered.

Patient education is an important component of adherence. Well-informed patients should be knowledgeable about the expected time course of response, the likelihood of certain side effects, and the availability of alternatives. Patients should also understand a personally relevant explanation about how the selected treatment will help relieve their suffering. Most people also require some assurance that the antidepressant will not be habit-forming and that taking medication is not a crutch or “cop-out.” Recently, a study of a comprehensive patient educational initiative in a primary care setting demonstrated significantly improved adherence.<sup>8</sup> Specifically, these patients were given information about: (1) when and how often to take the medicine; (2) the expected 2- to 4-week delay before beneficial effects may be noticed; (3) the need to take the medication even after feeling better; (4) the need to consult with the doctor before discontinuing the medication; and (5) what to do if problems or questions arise.<sup>8</sup> Some patients, particularly elders, may have improved adherence when both the complexity of the medication regimen and the associated costs are minimized.<sup>4</sup>

**Maintenance Phase.** Following the continuation phase, maintenance-phase treatment should be considered for patients at high risk for recurrent depressive episodes. Considerations for recommending maintenance treatment are listed in **Table 2**. The same full antidepressant doses used in prior phases of treatment should be employed in the maintenance phase whenever possible. The efficacy of lower doses has not been established, and some evidence indicates a greater chance of recurrence if lower doses are used. Maintenance-phase treatment usually involves a decreased frequency of visits (eg, monthly or quarterly).

Some experts consider the maintenance phase to be lifelong, whereas others speak of an indefinite duration of preventive therapy. The distinction here pertains partly to the possibility that a prolonged period of recovery (ie, >5 years) may be associated with a reduced risk of recurrence if medication is discontinued. It is also possible that truly curative treatments may possibly be available in the future, with more enduring effects after the treatment is discontinued. Until these issues are resolved, physicians and patients planning to stop an effective medication need to be informed they face up to a 50% risk of recurrent depression with-

**Table 2.** Considerations in the Decision to Use Maintenance Treatment

Factor	Component(s)
Remission induction	Ease of achieving remission in acute phase; ability to preserve remission in continuation phase
Risk of recurrence	Number of prior episodes; presence of comorbid conditions; residual symptoms between episodes
Severity of episodes	Suicidality; psychotic features; severe functional impairment
Drug side effects	Tolerability, safety, adherence to prescribed regimen
Patient preferences	Adherence to prescribed regimen

in the first 6 months of stopping treatment, regardless of the duration of successful pharmacotherapy.

### **Enhancing Treatment Adherence**

One of the major causes of treatment failure is poor adherence to the prescribed treatment regimen. Some symptomatic patients may be poorly motivated, misinformed, or pessimistic about their chances of recovery with treatment. Furthermore, side effects or the complexity of the treatment regimen may provoke poor adherence. Clinicians should emphasize the importance of adherence for successful treatment, and they should individualize the treatment regimen to achieve the best possible chance of adherence. Asking (in a matter-of-fact way) at each visit about the number of doses missed is one simple way to enhance compliance.

If medication is discontinued, it is important that the patient and his or her loved ones can recognize and address the early signs of relapse. Recurrences may occur "out of the blue," or they may be triggered by stressors encountered in day-to-day living. In either case, however, prodromal or early warning signs usually herald an impending recurrence, such as insomnia, worrying, or a decrease in recreational or leisure activities. Patients should also be encouraged to seek adequate treatment as early in the course of the new episode as possible to lessen the amount of time "lost" to the illness.

### **Assessing Remission in Major Depression**

The typical depressive episode is composed of 6 to 9 symptoms of moderate severity. In clinical trials, a commonly used measure of antidepressant efficacy is a 50% reduction in symptom burden using a measure such as the Hamilton Rating Scale for Depression (HAM-D) total score (Table 3).<sup>9</sup> The original HAM-D includes a core of 17 separately scored items that assess various depression-related parameters including mood, feelings of guilt, suicidal ideation, insomnia (3 items), work and interest, weight and appetite, psychomotor disturbances (2 items), energy,

anxiety (2 items), and other somatic symptoms. In an ambulatory population, the typical mean score on the HAM-D ranges from 18 to 22 with a standard deviation of about 4. A total HAM-D score of 7 or less has been chosen as an operational definition of remission (ie, >3 standard deviations below the mean).<sup>10</sup> In the clinical practice setting, remission is more likely to be gauged by the patient's report of being "well" or "nearly 100%," as well as the ability to resume normal daily activities in the home and at work.

### **Hypotheses for Low Remission Rates in Major Depression**

Only about 25% to 35% of patients treated with conventional antidepressants or psychotherapy are remitted after 6 to 8 weeks of treatment. Moreover, 15% to 20% are not responsive to therapy and may remain depressed for months or even years. Numerous hypotheses have been put forward to explain why some individuals who suffer from depression never fully recover. With respect to incomplete remission, physicians and patients are sometimes satisfied with the partial relief of target symptoms such as sleep and appetite disturbances and may not pursue treatment adjustments necessary to achieve remission. In addition, patients may not tolerate or may be unwilling to accept the side effects of higher doses of their medication, remaining on doses considered to be suboptimal. Sometimes a compromise occurs between physician and patient expectations, treatment risks and benefits, and hope and discouragement. Finally, the physician or psychotherapist may not collect sufficient information about residual difficulties to determine that the remission is incomplete. Patients and physicians alike may be setting their goals too low by merely accepting response as the end point of treatment rather than striving for remission.

### **The Importance of Remission**

Beyond the commonsense notion that people with fewer symptoms are better off than those with more numerous difficulties, there are several clear-cut risk factors

**Table 3.** Hamilton Rating Scale for Depression (HAM-D)

Most clinical trials are designed to enter patients with scores of at least 18. A typical interpretation of the HAM-D is as follows:

- 0-7 . . . . . None/minimal depression
- 8-17 . . . . . Mild depression
- 18-25 . . . . . Moderate depression
- 26+ . . . . . Severe depression

Note: Improvement is measured by a decrease in HAM-D score. (The lower the score, the better the outcome.)

FOR EACH ITEM, CIRCLE THE NUMBER NEXT TO THE PHRASE THAT BEST CHARACTERIZES THE PATIENT DURING THE PAST WEEK.

**1. DEPRESSED MOOD**

- 0. Absent
- 1. These feelings indicated only on questioning
- 2. These feelings spontaneously reported verbally
- 3. Communicates feeling nonverbally (ie, facial expression, posture, voice, and tendency to weep)
- 4. Reports *virtually only* these feelings in spontaneous verbal and nonverbal communication

**2. FEELINGS OF GUILT**

- 0. Absent
- 1. Self-reproach; feels has let people down
- 2. Ideas of guilt or rumination over past errors or sinful deeds
- 3. Present illness is a punishment; delusions of guilt
- 4. Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

**3. SUICIDE**

- 0. Absent
- 1. Feels life is not worth living
- 2. Wishes were dead; thoughts of possible death to self
- 3. Suicide ideas or gesture
- 4. Attempts at suicide (any serious attempt rates 4)

**4. INSOMNIA, INITIAL**

- 0. No difficulty falling asleep
- 1. Occasional difficulty falling asleep (ie, more than 1/2 hour)
- 2. Nightly difficulty falling asleep

**5. INSOMNIA, MIDDLE**

- 0. No difficulty
- 1. Complains of being restless and disturbed during the night
- 2. Walking during the night (any getting out of bed, except for purposes of voiding, rates 2)

**6. INSOMNIA, DELAYED**

- 0. No difficulty
- 1. Waking in early hours of morning but goes back to sleep
- 2. Unable to fall asleep again if gets out of bed

**7. WORK AND INTEREST**

- 0. No difficulty
- 1. Thoughts and feelings of incapacity, fatigue, or weakness related to activities, work, or hobbies
- 2. Loss of interest in activities, hobbies, or work, either directly reported by patient or indirectly as listlessness, indecision, and/or vacillation (feels has to push self to work or activities)
- 3. Decrease in actual time spent in activities or decrease in productivity (inpatients—rate 3 if patient does not spend at least 3 hours per day in activities exclusive of ward chores)
- 4. Stopped working because of present illness (inpatients—rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted)

**8. RETARDATION** (slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

- 0. Normal speech and thought
- 1. Slight retardation at interview
- 2. Obvious retardation at interview
- 3. Interview difficult
- 4. Complete stupor

**9. AGITATION**

- 0. None
- 1. "Playing with" hands, hair, etc
- 2. Hand-wringing, nail-biting, hair-pulling, biting of lips

**10. ANXIETY, PSYCHIC**

- 0. No difficulty
- 1. Subjective tension and irritability
- 2. Worrying about minor matters
- 3. Apprehensive attitude apparent in face or speech
- 4. Fears expressed without questioning

**11. ANXIETY, SOMATIC**

- (Physiological concomitants of anxiety, including: gastrointestinal [dry mouth, wind, indigestion, diarrhea, cramps, belching]; cardiovascular [palpitations, headaches]; respiratory [hyperventilation, sighing]; urinary frequency; sweating)
- 0. Absent
  - 1. Mild
  - 2. Moderate
  - 3. Severe
  - 4. Incapacitating

**12. SOMATIC SYMPTOMS (GASTROINTESTINAL)**

- 0. None
- 1. Loss of appetite but eats without staff encouragement; "heavy" feelings in abdomen
- 2. Difficulty eating without staff urging; requests or requires laxatives or medication for bowels or gastrointestinal symptoms

(Continued)

**Table 3.** Hamilton Rating Scale for Depression (HAM-D) (Continued)

<p><b>13. SOMATIC SYMPTOMS (GENERAL)</b>                      0. None                      1. Heaviness in limbs, back, or head; backache, headache, muscle ache; loss of energy; fatigability                      2. Any clear-cut symptom rates 2</p>	<p><b>17. INSIGHT</b>                      0. Acknowledges being depressed and ill                      1. Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc                      2. Denies being ill at all</p>
<p><b>14. GENITAL SYMPTOMS</b> (symptoms such as loss of libido, menstrual disturbances)                      0. Absent                      1. Mild                      2. Severe</p>	<p><b>18. DIURNAL VARIATION</b> (if present, circle severity and check whether symptoms are worse in the morning or evening: <span style="margin-left: 2em;">AM</span> <span style="margin-left: 2em;">PM</span>)                      0. Absent                      1. Mild                      2. Severe</p>
<p><b>15. HYPOCHONDRIASIS</b>                      0. Absent                      1. Self-absorption (bodily)                      2. Preoccupation with health                      3. Frequent complaints, requests for help, etc                      4. Hypochondriacal delusions</p>	<p><b>19. DEPERSONALIZATION AND DEREALIZATION</b> (eg, feelings of unreality; nihilistic ideas)                      0. Absent                      1. Mild                      2. Moderate                      3. Severe                      4. Incapacitating</p>
<p><b>16. LOSS OF WEIGHT</b> (rate according to "A" at initial visit; "B" at all other visits)                      A. When rating by history:                      0. No weight loss                      1. Probable weight loss associated with present illness                      2. Definite (according to patient) weight loss                      B. On weekly ratings by ward psychiatrist, when actual weight changes are measured:                      0. &lt;1 lb weight loss in a week                      1. &gt;1 lb weight loss in a week                      2. &gt;2 lb weight loss in a week</p>	<p><b>20. PARANOID SYMPTOMS</b>                      0. None                      1. Suspicious                      2. Ideas of reference                      3. Delusions of reference and persecution</p>
	<p><b>21. OBSESSIVE AND COMPULSIVE SYMPTOMS</b>                      0. Absent                      1. Mild                      2. Severe</p>

Source: Hamilton M. Rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-61. Adapted with permission.

that validate using remission as the standard of antidepressant efficacy. For example, data from both controlled and naturalistic studies indicate patients who achieve remission are significantly less likely to relapse than those who do not.<sup>10-12</sup> Moreover, fully remitted patients were found to be significantly more likely to have normal occupational and psychosocial functioning.<sup>13</sup> Other potential consequences of incomplete remission include increased utilization of medical services, increased healthcare costs, and a sustained elevation of suicide and substance-abuse risks.

**Remission Rates During Antidepressant Treatment**

The 5 most commonly used antidepressants in the United States in 2000 were

either members of the class called selective serotonin reuptake inhibitors (SSRIs), including fluoxetine, sertraline, paroxetine, and citalopram; or the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine. The widespread use of these particular medications is accounted for by a number of factors over and above commercial marketing. The SSRIs and extended release venlafaxine (venlafaxine XR) are better tolerated than the older tricyclic antidepressants—an advantage obtained without a reduction in efficacy for the typical ambulatory patient.

Because of both commercial and conceptual issues, the relative merits of the SSRIs and venlafaxine have been debated extensively. Initially, the immediate-release formulation of venlafaxine was viewed as more difficult to prescribe and

somewhat less well tolerated than the SSRIs. This tended to force the issue of greater efficacy presumed to result from a second putative mechanism of action (norepinephrine reuptake inhibition). Some studies using the immediate-release formulation of venlafaxine supported this hypothesis<sup>14-17</sup> and others did not.<sup>18,19</sup> However, no one study can be said to be truly definitive, and a number of methodological factors limit the “power” of clinical trials to detect modest yet clinically important differences between effective antidepressants.<sup>20</sup>

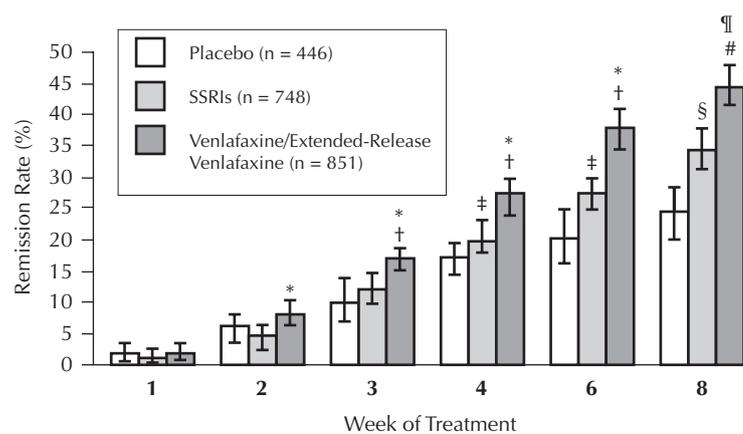
Thase et al<sup>21</sup> performed the first pooled analysis of remission rates comparing venlafaxine and SSRIs. This intent-to-treat analysis includes data from 2045 patients with major depression who participated in 8 randomized, double-blind, controlled trials.<sup>14,15,21-25</sup> Antidepressant doses were: venlafaxine (immediate-release), 75 to 375 mg/day; venlafaxine XR, 75 to 225 mg/day; fluoxetine (5 studies), 20 to 80 mg/day; paroxetine (2 studies), 20 to 40 mg/day; and fluvoxamine (1 study), 100 to 200 mg/day. Four of the 7 outpatient studies included a placebo-controlled group; the single inpatient study did not. Efficacy assessments included the HAM-D, the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Clinical Global Impression—Improvement scale (CGI-I) across 6 to 8 weeks of double-blind therapy.<sup>21</sup> Safety and tolerability were evaluated based on recorded adverse events.

Although only 2 of the 8 studies yielded statistically significant results favoring venlafaxine over the particular SSRI to which it was compared, the results of this large-sample pooled analysis were striking. From week 2 onward, a significantly greater proportion of venlafaxine-treated patients achieved remission than did SSRI-treated patients (Figure).<sup>21</sup> The SSRI-treated group had significantly higher remission rates than the placebo-treated group from week 4 onward. By the end of week 8, remission was achieved by 283 (45%) of 851 venlafaxine-treated patients, 260 (35%) of 748 SSRI-treated patients, and 110 (25%) of 446 patients who

received placebo.<sup>21</sup> All differences were highly statistically significant ( $P < .001$ ). Moreover, the advantage was demonstrated consistently whether remission was defined as a HAM-D17 score of 7 or less, a HAM-D17 score of 10 or less, a HAM-D21 score of 7 or less, a HAM-D21 score of 8 or less, a HAM-D21 score of 10 or less, a 50% or greater decrease in HAM-D21 score, a MADRS score less than 10, or a HAM-D17 score of 10 or less and a CGI-I score of 1. Finally, because the results were based on a complete set of studies (specifically, no studies were left in the file drawer), there is no chance of selective bias.

The results of this pooled analysis are compelling for several reasons. First, although the analysis focused on remission, the results generalized to numerous other definitions of favorable outcome. Second, the patient pool was heterogeneous and included outpatients and inpatients of varying levels of disease severity and age, as well as patients with depres-

**Figure.** Remission Rates From Pooled Studies Comparing Venlafaxine, Selective Serotonin Reuptake Inhibitors (SSRIs), and Placebo



\*Venlafaxine versus SSRIs,  $P < .05$ .

†Venlafaxine versus placebo,  $P < .05$ .

‡SSRI versus placebo,  $P < .05$ .

§SSRI versus placebo,  $P < .001$ .

¶Venlafaxine versus SSRIs,  $P < .001$ .

#Venlafaxine versus placebo,  $P < .001$ .

Source: Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* 2001;178:234-241. Adapted with permission.

sion alone and those with comorbid anxiety. Third, the results were validated by subgroup analyses and a sensitivity analysis, which was performed by removing each individual study from the pooled analysis, one at a time.

The principal shortcomings of this pooled analysis are the relative predominance of studies using fluoxetine as the comparator, an absence of studies examining the comparative effectiveness of sertraline or citalopram, and the lack of data beyond the 8th week of treatment. For example, it is possible that the SSRI group may have “caught up” if the studies had lasted for 12 or 16 weeks. Another limitation is that all 8 studies were funded by the manufacturer of venlafaxine. Although this concern is mitigated by an “open file drawer” (ie, the studies represent a complete set and were not selected based on their finding), independent replication would be desirable. Additional pooled analyses are planned when comparative datasets from a number of other studies are available. The studies included an unknown number of patients who had failed to respond to other SSRIs, but no patients who had failed to respond to venlafaxine. Finally, as is the case with virtually all controlled clinical trials, the study group was selected according to various inclusion and exclusion criteria and is not fully seen in day-to-day practice.

### Conclusion

The primary objective of the acute phase of antidepressant therapy is to achieve remission. Achieving this goal reduces depressive symptoms to the level of the general population, quality of life is improved, and healthcare utilization and costs are reduced. Remission is also the most direct gateway to sustained recovery and prevention of chronicity and recurrent depression. Important factors to consider include adherence to treatment, the need for concomitant psychotherapy, and the selection of a particular type of antidepressant. Among the more widely used newer medications, the SNRI venlafaxine appears to have significant advantages in terms of remission rates.

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