Clinician Perspective on Achieving and Maintaining Remission in Depression

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The majority of large-scale clinical trials of depression focus on response, typically defined as a 50% reduction in symptoms, as the endpoint. Response in the absence of remission places patients at greater risk for relapse, decreases their level of functioning, and erodes quality of life. Most importantly, both research and our clinical experience suggest that remission, or "getting well," is an attainable goal for patients with major depressive disorders. Pharmacotherapy, psychotherapy, and combination regimens are all treatment options. Recent studies across a range of patient populations have demonstrated the benefit of affecting multiple transmitter systems over a single antidepressant mechanism. Pooled data from more than 2000 patients comparing venlafaxine, a serotonin-norepinephrine reuptake inhibitor, and selective serotonin reuptake inhibitors suggest that the dual mechanism of action of venlafaxine provides significantly greater efficacy in achieving remission. Ultimately, achieving a good clinical outcome is desirable, but sustaining the mood state is, perhaps, more important. Studies of venlafaxine show it is possible to prevent more relapses and recurrences of depression with dual-mechanism treatment than with placebo. These data highlight the need for setting appropriately aggressive goals and working closely with our patients to achieve them. By doing so, we create the best opportunity for restoring patients to "wellness" and, ultimately, a normal and fulfilling life.

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Major depressive disorder (MDD) is a common disorder routinely encountered in general and psychiatric practice. In urban settings, the prevalence of MDD may be as high as 19%.[1] Patients with depression often experience substantial disability in addition to core symptoms. Depression-associated disability negatively impacts the patients' quality of life and contributes to the overall burden of the disorder.[2] The burden of depression is rooted in 2 main issues: (1) a substantial number of individuals with depression do not seek or receive appropriate mental health services, and (2) individuals who do receive appropriate mental health services fail to benefit from optimal use of efficacious treatment.[3]

In a cross-sectional survey of a nationwide U.S. sample of adults (N = 1636) with probable 12-month (1997–1998) depressive or anxiety disorders,[4] about 81% saw a primary care physician for their symptoms. Of these, 80% received suboptimal care, including insufficient dosing or inadequate duration of treatment, despite the availability of newer, effective antidepressants; this was primarily because, overall, members of this population were much less likely to perceive a need for mental health care. Of the 80% who received suboptimal care, only about 30% received at least 1 appropriate treatment for their disorder.[4]

Underrecognition of MDD in the primary care setting, inaccurate or missed diagnosis, and inadequate or suboptimal treatment lead to significant disability rates, functional impairment, increased suicidal tendencies, and greater risk of relapse and recurrence[2,5,6]—undermining the patients' attainment of a state of health.[7,8] Many cases of mild depression pass unrecognized and untreated. The depressive symptoms that are recognized and treated tend to be more severe.[9] The high frequency of underrecognition of depression strongly indicates the need for better physician education and the routine screening of primary care patients to detect the milder cases. However, because greater illness severity is associated with a higher risk of relapse and recurrence, the burden of preventive measures in depression hinges on optimizing treatment to prevent the occurrence of relapse.

CONSEQUENCES OF PERSISTENT SUBTHRESHOLD SYMPTOMS

The Collaborative Depression Study,[10] a prospective 10-year follow-up study, found that patients with depression

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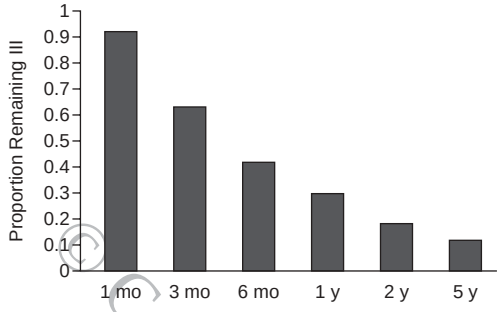
Figure 1. Proportion of Patients Remaining Ill After a Second Recurrent Episode of Depression[a]



[a]Data from Solomon et al.[10] Proportions represent Kaplan-Meier product limit estimates.

experienced an average of 3 recurrent episodes in a span of 10 years. After the second recurrence of MDD, a significant proportion of patients remained ill for prolonged periods of time.[10] Six months after the onset of the second depressive episode, more than 42% of patients remained ill (Longitudinal Interval Follow-Up Evaluation). Thereafter, the rate of recovery declined substantially, with 30% of patients still suffering from depression 1 year, and 12% still suffering from depression 5 years, after the onset of the second depressive episode (Figure 1).[10]

A history of 2 or more episodes of MDD and chronic mood symptoms for 2 years are major risk factors associated with relapse. Another prominent risk factor is the persistence of subthreshold depressive symptoms 7 months after the initiation of antidepressant treatment.[11] A 2-year prospective follow-up study indicated that of the one third of patients who relapse 1 year after remission (i.e., Hamilton Rating Scale for Depression [HAM-D] score ≤ 7), 40% received inadequate treatment.[12] The common occurrence of subtherapeutic treatment with antidepressants has also been reported in other studies.[13–15] Such therapeutic shortcomings have a direct bearing on negative patient outcomes.

Achieving a treatment response (i.e., ≥ 50% symptom reduction from baseline) without complete remission profoundly affects the patient's long-term prognosis—persistence of subthreshold symptoms prolongs the illness and decreases the chance of a complete recovery.[12,16] Hence, in recent years, the treatment goal for depression and anxiety has shifted from attaining treatment response to achieving remission, a virtually asymptomatic state that is functionally akin to the premorbid state.[17–20]

TREATMENT CONSIDERATIONS

The most common therapeutic strategies used in treating depression are pharmacotherapy, psychotherapy, multidrug therapy, and the combination of drugs and psychotherapy.[21] Each modality and therapeutic agent is associated with specific advantages and disadvantages; the most appropriate treatment choice should balance the likelihood of treatment success with the potential risk of adverse effects, always keeping in mind the patient's characteristics.

Table 1. Achieving Mixed Serotonin-Norepinephrine Activity With Antidepressant Therapy

Mixed-activity drugs for monotherapy
Monoamine oxidase inhibitors (MAOIs)
Clomipramine, imipramine, amitriptyline
Mirtazapine/mirtazapine SolTab
Venlafaxine/venlafaxine XR
Combination therapy
Serotonin reuptake inhibitor or mixed-activity drug (caution with MAOIs) plus
Tricyclic antidepressant
Bupropion
Stimulants
Reboxetine

Pharmacotherapy

Antidepressant treatment is the most extensively evaluated treatment modality in clinical trials. It is the treatment of choice for patients with moderate-to-severe depression[21] and those with concomitant symptoms of anxiety. Antidepressants modify neurotransmitter function by acting primarily on the serotonergic, noradrenergic, or dopaminergic systems, or any combination thereof.[22]

The outcome of studies of depressed inpatients and outpatients using response[23] or remission[24–26] as a treatment endpoint suggests that the activation of multiple monoaminergic neurotransmitter systems is associated with enhanced efficacy in comparison to the activation of only 1 monoamine neurotransmitter. As shown in Table 1, mixed neurotransmitter activity can be achieved with a number of monotherapies, including the serotonergic-noradrenergic tricyclic antidepressants (TCAs) clomipramine, imipramine, and amitriptyline and newer-generation agents venlafaxine/venlafaxine extended release (XR) and mirtazapine/mirtazapine orally disintegrating tablets (SolTab).[27,28] Mirtazapine enhances noradrenergic transmission by blocking presynaptic α_2 autoreceptors and increases serotonin release by blocking α_2 heteroreceptors; in addition, it antagonizes both 5-HT_2 and 5-HT_3 receptors.[29] Venlafaxine enhances presynaptic levels of serotonin and norepinephrine by inhibiting their reuptake.[28,30] Higher doses of venlafaxine further enhance norepinephrine activity, which may underlie the dose-response relationship associated with this agent.[31]

Psychotherapy

Psychotherapy is frequently used to target psychological, social, and occupational dysfunction in patients with mild depression.[21] Used alone, this approach has the

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advantage of being devoid of the physiologic side effects associated with drug therapy. The longer time to onset of improvement with psychotherapy compared with pharmacotherapy is disadvantageous because it is conducive to a prolongation of the illness and therapeutic noncompliance.[21]

Although placebo-controlled data on the efficacy of different types of psychotherapy (interpersonal, cognitive, behavioral, brief dynamic, and marital) are limited, accumulating evidence affirms that psychotherapeutic interventions contribute to the reduction in the incidence of relapse[21,32] and also enhance compliance.[33] Cognitive-behavioral therapy (CBT) has been shown to reduce the likelihood of a relapse within a 4-year follow-up period by as much as 40%.[32] Because individuals who have "recovered" from depression may be unaware of maladaptive lifestyles and behavior, CBT can deter the progression of residual symptoms to relapse by training them to modify ineffective and harmful behavior.[34]

The most successful psychotherapeutic interventions are integrated into comprehensive medical/psychological disease management programs for patients with specific medical diseases. The prevalence of MDD and subsyndromal depression in patients with active medical illnesses far exceeds that in the general population.[35] Psychosocial treatment may prolong survival among patients with coronary artery disease; in those with human immunodeficiency virus (HIV), psychotherapy may improve coping and quality of life.[35]

Combination Therapy

Pharmacotherapeutic combinations or pharmacotherapy-psychotherapy combinations may be useful in certain clinical scenarios, especially in treatment-refractory depression. Patients who do not respond adequately to 1 antidepressant may benefit from the addition to their regimen of a second agent from a different antidepressant class.[21] Examples of augmentation/combination strategies include 2 or more antidepressant medications,[36–39] antidepressant-antipsychotic tandem,[40] antidepressant-lithium combination,[41–43] and augmentation of an antidepressant with folate,[44] tryptophan,[45] pindolol,[46] or estrogen.[47]

Dual-neurotransmitter activity can be achieved by combining 2 agents with different mechanisms of action. For instance, a selective serotonin reuptake inhibitor (SSRI) or a mixed-activity agent can be combined with a TCA with potent norepinephrine activity (e.g., desipramine, nortriptyline),[48] bupropion,[49] stimulants,[50] or reboxetine.[51] Bupropion's mechanism of action appears related to its inhibition of dopamine and norepinephrine reuptake.[52] Reboxetine exerts its antidepressant effects by selectively inhibiting norepinephrine reuptake without appreciable effects on dopamine or serotonin.[28]

Safety issues should be taken into consideration when combining antidepressants for dual-neurotransmitter action therapy. Care must be exercised, especially when using TCAs, to prevent untoward electrocardiographic events. Seizures, although rare, have been reported with the use of bupropion; hence, patients should be screened for seizure risk factors before being prescribed this agent. The risk of drug-drug interactions is also an important safety factor when combining antidepressants, particularly in older patients. Blood levels of TCAs should be monitored when TCAs are used in combination with agents that inhibit the CYP2D6 isoenzyme such as fluoxetine and paroxetine.[53,54] Similarly, drugs that inhibit the CYP3A4 isoenzyme can increase blood levels of reboxetine, thus increasing drug exposure, and reboxetine may alter levels of—and exposure to—drugs metabolized by the CYP2D6 and CYP3A4 isoenzymes.[55] In the case of bupropion, coadministration with drugs that alter the profile of its hepatic metabolizing enzymes may affect blood levels of this antidepressant.[56]

Neither venlafaxine nor mirtazapine exerts any clinically relevant inhibition of the major cytochrome P450 isoenzymes, and therefore the risk of inducing drug-drug interactions is minimal.[29,57] Mirtazapine, however, may exacerbate the cognitive and motor impairment induced by alcohol or diazepam, and patients who are prescribed this antidepressant should be advised to avoid the concomitant use of those agents.[29]

Many patients with severe depression use some form of herbal alternative or complementary therapy,[58] which may not necessarily be clinically prescribed; hence, patients should be carefully questioned about food supplements, vitamins, herbal products, and other medications, particularly those available over the counter.

The combination of drug therapy and psychotherapy may be particularly advantageous in patients with a history of chronic depression and those with continued psychosocial dysfunction despite resolution of other depressive symptoms with drug therapy.[21]

Clinical Management of Depression

Clinicians must strive to integrate the insight provided by research into clinical practice in order to develop practical and individualized treatment approaches that will ultimately restore the patient's state of wellness and quality of life. Independent of considering drug efficacy and safety profile, clinicians have no established means to suggest which medication will provide optimal treatment in a given patient. The selection of a therapeutic agent should largely be based on the consideration of the patient's characteristics: age, disease pathophysiology, medical and psychiatric history, current health status, and medical and psychiatric comorbidities, such as anxiety. Empirical evidence suggests that early and aggressive antidepressant treatment[59–61] that engages more than 1 neurotransmitter system can elicit complete remission[24] and reduce the risk of relapse[62] and recurrence in the greatest numbers of patients.[25,26]

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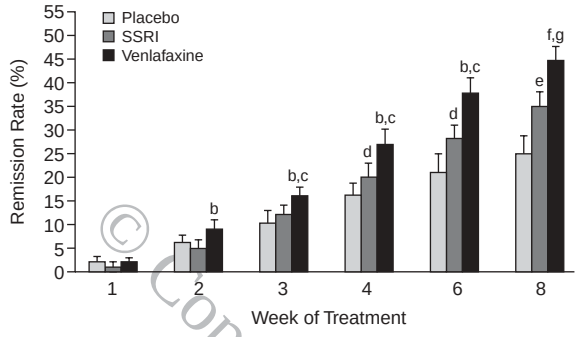
Figure 2. Remission Rates (HAM-D_{17} Score ≤ 7; Mean, 95% CI) for Pooled Studies Comparing Venlafaxine, SSRI, and Placebo Treatments[a]



[a]Adapted with permission from Thase et al.[63] Abbreviations: HAM-D_{17} = 17-item Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.
[b]p ≤ .001, venlafaxine vs. SSRI.
[c]p ≤ .05, venlafaxine vs. placebo.
[d]p ≤ .05, SSRI vs. placebo.
[e]p < .001, SSRI vs. placebo.
[f]p < .001, venlafaxine vs. SSRI.
[g]p < .001, venlafaxine vs. placebo.

VENLAFAXINE: A MODEL FOR REMISSION AND RELAPSE PREVENTION

The efficacy of the antidepressant venlafaxine, a dual-action agent, is supported by a growing body of evidence from studies that examined treatment remission rates relative to placebo and single-action active comparators. A meta-analysis of 8 randomized, double-blind studies included 851 patients treated with venlafaxine or venlafaxine XR, 748 treated with fluoxetine, paroxetine, or fluvoxamine, and 446 treated with placebo.[63] The demographic and clinical characteristics of the patients were similar to those typically seen in clinical practice: 66% were women, most with moderate-to-severe depression as indicated by a mean HAM-D total score of about 25. Based on the percentage of patients who achieved remission (HAM-D score ≤ 7), venlafaxine/venlafaxine XR was statistically significantly more effective than the SSRIs (p ≤ .05) from week 2 onward, and statistically significantly better than placebo (p ≤ .05) from week 3 onward (Figure 2).[63] Venlafaxine treatment was associated with a 50% greater chance of remission over SSRI treatment. Subgroup analyses (i.e., patients enrolled in placebo-controlled studies, hospitalized patients, and outpatients) also favored venlafaxine over SSRIs and placebo.[63] Tolerability profiles of venlafaxine and the SSRIs were comparable in this meta-analysis, and there were no significant differences between the 2 treatments in the proportions of patients discontinuing therapy due to adverse effects.[63]

Maintaining a state of wellness over the long term, with the lowest possible risk of relapse or recurrence of depression, is as important as achieving remission. Long-term treatment of depression, beyond the onset of symptomatic improvement and full remission of the acute episode, has been shown to improve the likelihood of maintaining the patient virtually asymptomatic and fully functional.

Effective treatment should signify a reduction in the risk of relapse and recurrence and a functional restoration to the premorbid state. Few controlled studies on the pharmacotherapy of depression have evaluated these endpoints. However, 2 recent studies[64,65] with venlafaxine demonstrate that these goals were achieved through dual serotonin-norepinephrine inhibition in a significant proportion of patients. In a double-blind study designed to evaluate relapse prevention with long-term (up to 6 months) treatment, patients with mild-to-moderate depression who had responded to an 8-week course of venlafaxine XR were randomized to either continue therapy with venlafaxine (75–225 mg/day) or switch to placebo.[64] Data from 138 patients assigned to placebo and 154 assigned to venlafaxine XR were included in the efficacy analysis. Mean HAM-D total scores were similar between the 2 groups at the start of the 6-month relapse-prevention phase, 6.4 for placebo and 6.5 for venlafaxine XR.[64] The results showed that continuation therapy with venlafaxine XR was significantly more effective than placebo in preventing relapse. At 1, 3, and 6 months, venlafaxine XR–treated patients had significantly higher rates of sustained remission (94.0%, 81.2%, and 71.8%, respectively) than placebo (82.0%, 56.4%, and 47.7%, respectively) (p = .003 at month 1, and p < .001 at months 3 and 6).[64]

In a double-blind open-label study, the efficacy and safety of prophylactic treatment was evaluated in patients with recurrent depression who responded to venlafaxine therapy (100–200 mg/day) and sustained remission during 6 months of open-label treatment.[65] Patients were randomly assigned to either continue therapy with venlafaxine (N = 109) or take a placebo substitute (N = 116) for 12 months. The time to recurrence was analyzed using the survival analysis procedure. Recurrence was defined as a score of ≥ 4 on the Clinical Global Impressions-Severity of Illness (CGI-S) scale. After 12 months, 22% of venlafaxine-treated patients and 55% of placebo-treated patients had a recurrence of MDD (p < .001).[65] Furthermore, the rate of discontinuations due to lack of efficacy was more than twice as high in the placebo group (48%) as in the venlafaxine group (21%; p < .001).[65] These data confirm the need for long-term treatment in patients with a history of depression and highlight the utility of the mixed-activity agent venlafaxine in providing durable antidepressant effects.

CONCLUSIONS

The persistence of subsyndromal depressive symptoms contributes to functional impairment and a reduction in quality of life. Moreover, the incomplete resolution of

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symptoms is a major risk factor for relapse. The definition of treatment efficacy has become more stringent in that the attainment of treatment response (i.e., ≥ 50% reduction in symptom rating relative to baseline) is no longer a sufficient goal, precisely because patients can still exhibit residual symptoms and functional impairment in spite of a treatment response. The treatment goal should be set toward attaining a virtually asymptomatic state (i.e., remission) and restoring function to the premorbid condition.

Helping our patients to become "well," not merely "better," is our responsibility as clinicians and patient advocates. In order to achieve this goal in the largest number of patients, treatment choices should be based on those therapies proven to achieve and sustain remission. A drug's pharmacokinetic profile and the patient's history of response to medications and tolerance of side effects also contribute important information to the decision-making process.

Pharmacotherapy, psychotherapy, and combination regimens are all options for treatment. The attainment of sustained remission especially in those with moderate-to-severe depression invariably implies long-term therapeutic strategies. Although there are numerous treatment options for depression, long-term studies of pharmacologic agents are lacking. The achievement of remission and relapse prevention, however, has been studied using venlafaxine. There is accumulating evidence that agents with dual serotonin-norepinephrine activity, such as venlafaxine XR, provide more rapid, robust, and sustained antidepressant effects than agents affecting a single neurotransmitter system.

A concerted effort by physicians toward the optimization of the treatment of depression is necessary in order to control the disabling effects of this treatable illness.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin and others), desipramine (Norpramin and others), diazepam (Valium and others), fluoxetine (Prozac and others), fluvoxamine (Luvox), mirtazapine (Remeron), nortriptyline (Pamelor and others), paroxetine (Paxil), reboxetine (Vestra), venlafaxine (Effexor).

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