

Long-Term Management of Depression: Tips for Adjusting the Treatment Plan as the Patient's Needs Change

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Depression is a difficult-to-treat condition. Most individuals with depression do not achieve remission with any single treatment, and, when they do achieve remission, the majority will have residual symptoms. Therefore, clinicians must be prepared to aggressively manage relapse and recurrence throughout all phases of treatment. The ultimate goals for the long-term treatment of depression are to (1) help the patient achieve remission, (2) keep the patient as asymptomatic as possible, and (3) manage risk factors for subsequent episodes. Psychotherapies and pharmacotherapies appear to have dissimilar mechanisms of action and produce different effects in depression; psychotherapy, particularly cognitive-behavioral therapy and behavioral activation therapy, may have more of a relapse prevention effect than pharmacotherapy. Because chronicity and recurrence are the rule rather than the exception, clinicians should choose treatments that have shown efficacy for protecting against future episodes. In addition, factors such as comorbidities and stressful life events increase the likelihood of depressive relapse; thus, these problems must be addressed to prevent a full relapse. By anticipating and adjusting treatment to meet patients' changing needs over time, clinicians can help them achieve and maintain remission from depression.

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In most patients, major depressive disorder (MDD) is a highly recurrent illness¹ that has the potential to cause lifelong disability. More than half of individuals who experience a single depressive episode will experience further episodes,² and the majority of cases of depression are classified as moderate to very severe; relatively few (approximately 10%) are classified as mild.³

To effectively manage relapse and recurrence when treating MDD, clinicians should be proactive rather than reactive—that is, anticipate and immediately address factors that will increase the likelihood of depressive relapse rather than wait for impending relapse. By adapting therapies over time to meet the patient's changing needs, clinicians may help him or her achieve and maintain remission from depression.

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CHALLENGES OF TREATING DEPRESSION

Treatment Resistance

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study⁴ demonstrated that depression is a difficult condition to treat. Even with an algorithmic format for treatment, patients had a difficult time achieving remission. The percentage of patients who achieved remission dropped with each treatment step. Approximately 37% of patients remitted at step 1 and 31% at step 2, and then the remission rate decreased dramatically to 14% and 13% at steps 3 and 4, respectively.⁵ The majority of symptom improvement occurred early in treatment (at step 1). Although a subset of patients experienced symptom improvement and remission in the later levels of treatment, overall, only modest improvement was seen on the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16) following step 1 (Figure 1).⁵ The cumulative remission rate was 67%; thus, many patients do not achieve full remission of their depressive symptoms.

Residual Symptoms

Most patients who do experience remission of their depressive symptoms continue to be symptomatic, even if they appear to be feeling much better. For instance, Nierenberg et al⁶ measured the prevalence of threshold or subthreshold residual depressive symptoms in patients with remitted MDD; remission was defined as a score of ≤ 7 on the 17-item Hamilton Depression Rating Scale (HDRS-17). The study reported that the majority of patients in remission remained symptomatic; fewer than 20% of patients had no residual

FOR CLINICAL USE

- ◆ Devise a long-term strategy before beginning to treat depression, keeping in mind that most patients are at high risk of relapse.
- ◆ Choose a therapy that is effective not only during the acute phase but also for preventing relapse and recurrence over time (eg, cognitive therapy).
- ◆ Aggressively manage modifiable risk factors that increase the likelihood of subsequent depressive episodes, adjusting the treatment plan as necessary.

MDD symptoms (Figure 2). The residual threshold and subthreshold symptoms included sleep disturbances (44%), fatigue (38%), and diminished interest (27%).

The presence of residual symptoms means that patients continue to have an active illness, which increases their risk of relapse. The more symptomatic the individual is, the more likely he or she is to experience a relapse over the next year. Paykel and colleagues⁷ examined the effect of residual symptoms on relapse rates in patients with MDD (predominantly inpatients) for up to 15 months. Compared with fully remitted patients, those with residual symptoms after remission had significantly higher relapse rates (25% vs 76%, respectively; $P < .001$). Also, the results from STAR*D⁵ showed that relapse was more likely among patients who required more treatment steps to reach remission than among those who remitted after the first step. Thus, the long-term management of the patient's MDD should begin in the acute phase with aggressive treatment to get him or her as well as possible, as early as possible.

Relapse Risk

Certain patient characteristics predict relapse risk in MDD; these can be separated into 4 general categories: (1) chronicity and recurrence, (2) severe baseline depression, (3) neurovegetative symptoms and melancholic features, and (4) comorbid disorders.

Chronic depression (ie, a current episode lasting 2 years or more) and recurrence (ie, presence of prior episodes) are strong predictors of relapse in continuation treatment. In a large, placebo-controlled study, McGrath et al⁸ examined predictors of relapse in patients with MDD. Although this study did not find an association between comorbidities and increased relapse risk, results showed that chronic depression, symptom severity, and a neurovegetative symptom profile significantly increased the risk of relapse. Regarding recurrence, a meta-analysis of randomized placebo-controlled trials⁹ revealed that patients who had experienced 1 or more prior depressive episodes were more likely to relapse after initial treatment. Patients with chronic or recurrent MDD are the rule rather than the exception in clinical practice. In fact, almost 80% of participants in STAR*D had chronic or recurrent depression,¹⁰ and these individuals were typical "real-world" patients from both psychiatry specialty clinics and primary care environments. Hence, psychiatrists must

be prepared to thoroughly manage relapse in most patients with depression.

Patients with the melancholic subtype of depression (ie, a neurovegetative symptom pattern) tend to have severe baseline depression, and these 2 predictors of relapse (severity and neurovegetative symptoms) are related to each other. Melancholic features include physiologic hyperarousal,¹¹ such as early morning awakening, loss of appetite with weight loss, and worse mood in the morning. Individuals with melancholic depression may be more sensitive to minor stressful life events than those with nonmelancholic depression¹²; this may be caused by hyperreactivity of locus ceruleus-norepinephrine systems¹¹ and an associated activation of the hypothalamic-pituitary-adrenal axis.

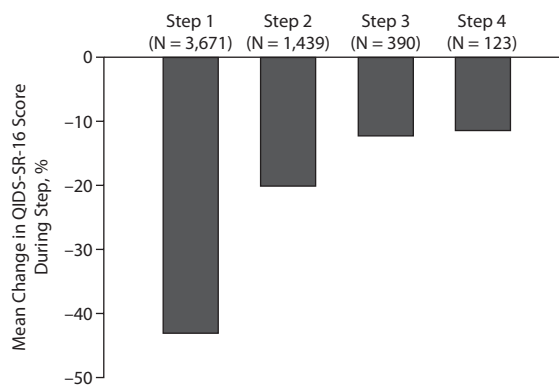
The presence of comorbid disorders (eg, personality disorders, substance use disorders, and anxiety disorders) also increases the risk of relapse in patients with depression. Fournier et al¹³ demonstrated that the presence of a comorbid personality disorder affects both acute and sustained response to depression treatment. Persons with a comorbid personality disorder were more likely to respond to the antidepressant paroxetine (66%) versus cognitive-behavioral therapy (CBT; 44%). Individuals with personality disorders who were discontinued from antidepressant medication during the continuation phase had extremely high relapse rates; only 6% of these patients did not relapse into depression, while 23% of those without personality disorders had no relapse during the 12-month follow-up. Also, a prospective, naturalistic cohort study¹⁴ examined the influence of comorbidity and psychosocial factors on treatment outcomes in patients with MDD. After remitting from the current depressive episode, patients participated in an 18-month follow-up phase. Severity of illness and a higher number of comorbid psychiatric disorders (eg, personality disorders) significantly predicted recurrence ($P = .002$ and $P = .04$, respectively). Thus, both comorbidities and depressive symptoms must be addressed to prevent relapse and recurrence.

PREVENTING RELAPSE AND RECURRENCE WITH LONG-TERM TREATMENT

Adjusting the Treatment Plan

The long-term management of depression requires the clinician to adjust the treatment plan over time according to

Figure 1. STAR*D: Acute Treatment Outcomes for Depressive Symptoms by Treatment Step^a



^aData from Rush et al.⁵

Abbreviations: QIDS-SR-16 = Quick Inventory of Depressive Symptomatology–Self-Report, STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

the patient's changing needs. Any negative events that occur in the person's life warrant attention. For example, cerebrovascular disease must be managed, as this condition may lead to vascular depression (ie, small vessel disease in the brain) in later life. In addition, stressful life events such as marital and family problems require vigorous management, because these issues may contribute to relapse of depressive symptoms.

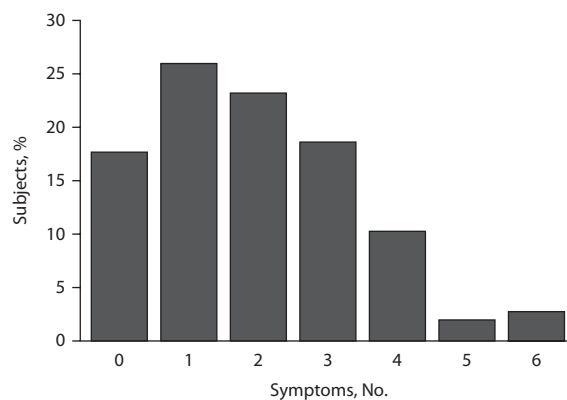
Clinicians should begin to devise a long-term strategy before beginning treatment, keeping in mind that most patients will fall into the category of high relapse risk and that the majority will remain actively symptomatic. Therefore, the focus of treatment should be aggressive management of depression during both the acute and maintenance phases. The ultimate goals of therapy are to (1) get the patient as well as possible, (2) keep the patient as well as possible, and (3) manage risk factors for subsequent relapse, or "causal factors."

The management of causal factors involves continuous communication between the physician and the patient about the patient's changing needs. He or she should let us know if symptoms have increased, since even a mild increase in symptoms may signal that a person is at high risk for relapse. For instance, if someone who has been treated for a year or 2 is suddenly having difficulty sleeping, is feeling more anxious, or is experiencing a loss of interest or motivation, the clinician needs to address these problems as early as possible to prevent a full relapse into depression. By rigorously dealing with core causal factors, physicians are likely to be able to sustain long-term wellness without a significant return of symptoms.

Long-Term Efficacy of Therapies for Depression

An effective treatment for depression not only reduces symptoms acutely but also protects against relapse over

Figure 2. Distribution of Total Subthreshold and Threshold Residual Depressive Symptoms After Remission (N = 108)^a



^aReprinted with permission from Nierenberg et al.⁶

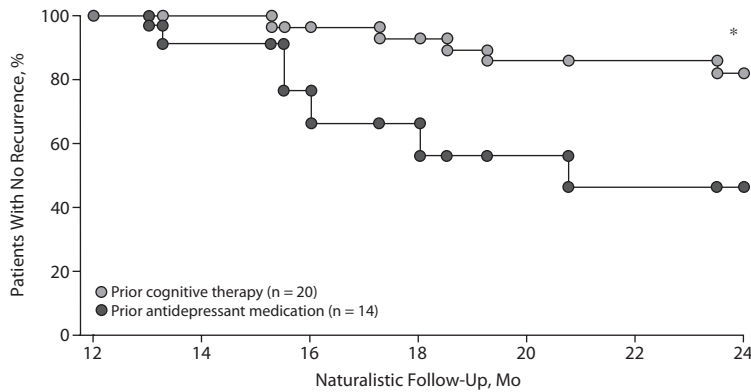
time. For that reason, a long-term, multicenter study^{15,16} compared the acute and preventive efficacy of 2 therapies—antidepressant medication and cognitive therapy—in patients with moderate to severe depression.

For the initial 16-week treatment phase, participants were randomly assigned to receive one of the following treatments: paroxetine, which could be augmented with lithium or desipramine or switched to another antidepressant if necessary after 8 weeks ($n = 120$); cognitive therapy ($n = 60$); or placebo ($n = 60$).¹⁵ After 16 weeks, the medication remission rate was 46% and the cognitive therapy remission rate was 40%. At this point, cognitive therapy was discontinued (although patients could have up to 3 booster sessions over the next 12 months), and the antidepressant-treated patients were randomly assigned to either medication continuation or treatment with placebo for 12 months.¹⁶ After 12 months, sustained response (that is, lack of relapse) was found in 23.8% of those who took medication for the first 16 weeks followed by placebo, 52.8% of those who continued the medication, and 69.2% of those who had prior cognitive therapy.

All therapies were discontinued at the completion of 12 months, and patients who had not relapsed during the 12-month continuation phase were observed for an additional 12 months.¹⁶ At 24 months, the cognitive therapy group had had significantly fewer recurrences than the group who had continued antidepressant treatment (Figure 3). Thus, the risk of recurrence after treatment discontinuation was 85% lower with cognitive therapy than with antidepressant therapy.

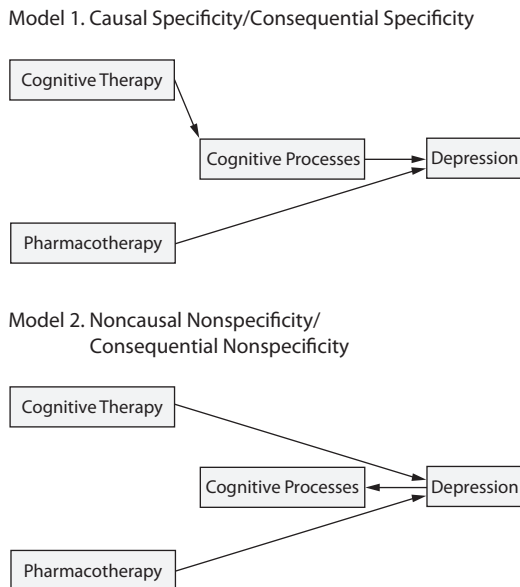
Dobson et al¹⁷ compared the preventive efficacy of cognitive therapy, behavioral activation, and medication in patients with major depression. The study showed that, like cognitive therapy, behavioral activation had a relapse prevention effect superior to medication 12 months after discontinuation of all 3 treatments. The higher relapse rate

Figure 3. Cumulative Proportion of Patients Who Remained Well After Discontinuing Cognitive Therapy or Antidepressant Medication^a



^aReprinted with permission from Hollon et al.¹⁶
**P* = .009.

Figure 4. Models of Change in Depression^a



^aAdapted with permission from Hollon et al.¹⁹

in those who were discontinued from medication was likely due to fundamental differences in the mechanisms by which psychotherapy and pharmacotherapy produce change in depression.¹⁸

Mechanisms of Treatment Response

When a treatment is applied, changes may be produced through response mechanisms that directly affect the structures in the brain that are generating depressive symptoms, thus reducing these symptoms, or they may be produced

through causal mechanisms that alter vulnerability factors. Psychotherapy and pharmacotherapy may differentially produce response in individuals with depression.

Models of depression remediation.

Hollon and colleagues¹⁹ proposed 2 models by which specific treatments produce changes in depression (Figure 4)—causal specificity/consequential specificity (Model 1) and noncausal nonspecificity/consequential nonspecificity (Model 2). Model 1 states that, although cognitive therapy and medication are both effective for treating depression, cognitive therapy, but not medication, produces response by directly changing fundamental cognitive processes. Model 2 asserts that both cognitive therapy and medication (if effective) change depressive symptoms

directly, and, as a result, cognitive processes are changed indirectly. If Model 1 is correct, then the direct change in cognitive processes should not only reduce depression in acute treatment but also produce reductions in relapse or recurrence over time.

Effects of antidepressants versus cognitive therapy.

Serotonin reuptake inhibitors (SRIs) have been found to produce changes in the activity of specific brain regions that are thought to generate depressive symptoms. The amygdala, for example, has been studied for its role in responding to anxiety-inducing stimuli. One study²⁰ in animal models found that injecting citalopram directly into the amygdala before exposure to conditioned fear stress substantially reduced freezing or anxiety-related behavior. Another study²¹ enrolled patients with MDD to examine amygdala activation in response to masked emotional faces. In this study, functional magnetic resonance imaging was used to measure amygdala reactivity before and after treatment with an SRI. In participants with MDD, amygdala reactivity was reduced after receiving the antidepressant. This evidence supports the notion that medications—particularly SRIs—directly constrain reactivity of the amygdala and, therefore, produce symptomatic change through physiologic inhibition of the brain region thought to underlie anxiety and depressive symptoms. However, these medications probably will not reduce subsequent risk, as opposed to treatments that may target potential causal mechanisms or vulnerability factors for relapse or recurrence.

Cognitive therapy may reduce predisposing psychological factors for depression. To examine the effect of treatments on cognitive factors related to depression, DeRubeis and colleagues²² randomly assigned outpatients with MDD to cognitive therapy (n = 32) or antidepressant therapy (n = 32) for 12 weeks. Four scales were used to measure cognitive change throughout treatment—the

Table 1. Brain Regions Where Glucose Metabolism Was Affected in Responders to Cognitive-Behavioral Therapy (CBT) or Antidepressant Therapy^a

Region	Left/Right	Brodmann's Area	Increase/Decrease	
			CBT	Antidepressant
Same regions, same direction				
Lateral orbital prefrontal	Left	11, 47	Decrease	Decrease
Lateral orbital prefrontal	Right	11, 47	Decrease	Decrease
Dorsomedial prefrontal	Left	8	Decrease	Decrease
Lateral inferior occipital	Right	19	Increase	Increase
Same regions, different direction				
Posterior cingulate	Left	29	Decrease	Increase
Inferior temporal	Left	20, 21	Increase	Decrease
Unique to each treatment				
Thalamus	Right	NA	Decrease	NA
Subgenual/ventromedial frontal	Right	32	Increase	NA
Postsubgenual cingulate	Right	25	NA	Decrease

^aAdapted with permission from Kennedy et al.²³
Abbreviation: NA = not applicable.

Attributional Styles Questionnaire (ASQ), the Automatic Thoughts Questionnaire (ATQ), the Dysfunctional Attitudes Scale (DAS), and the Hopelessness Scale (HS). The study found that in the cognitive therapy group, but not in the antidepressant group, improvements on the ASQ, DAS, and HS predicted change in depressive symptoms. Thus, while antidepressants may have a direct effect on brain structures that generate symptoms, cognitive therapy appears to be acting indirectly by modifying underlying psychological processes that increase the risk for depression. Although not every patient will experience relapse prevention with cognitive therapy, this psychotherapy, when well executed, can reduce the likelihood of subsequent depression.

Some effects of cognitive therapy and antidepressants may be the same. One study²³ compared the effects of CBT to those of antidepressant monotherapy (venlafaxine) in patients with depression over time, looking at the activation of brain regions using positron emission tomography. Certain brain regions were affected similarly with both CBT and the antidepressant (Table 1). Both treatments increased glucose metabolism in the right occipital-temporal cortex and decreased metabolism bilaterally in the left medial prefrontal cortex and the orbitofrontal cortex. However, other brain regions were differentially affected by each therapy.

THERAPEUTIC CANDOR IN PSYCHIATRIC PRACTICE

Starting at the beginning of treatment, clinicians should practice "therapeutic candor," which means not overselling therapies and managing patient expectations of a "silver bullet." As evidenced in the literature, the reality is that the majority of individuals will not reach remission quickly, and residual symptoms are common. Patients will often have a significant return of depressive symptoms, usually within 12 months of achieving remission. Therefore, clinicians must help their patients understand the importance of relapse prevention. In addition, evidence-based psychotherapies should be implemented, since these therapies are likely to

modify risk factors for the return of depression.

Patients are often vigorously treated acutely, and then, after the first few weeks of treatment, clinicians have a tendency to become less aggressive and less systematic. Frequently, when patients are significantly asymptomatic, clinicians do not actively make changes as time goes by. Psychiatrists should be aggressive in treatment over time and ask, "Have I done everything I can to help this patient?" If the patient is still symptomatic, try to get him or her as well as possible. Also, consider whether any

further change is realistic with the current treatment regimen; for example, if the patient has been taking medication but has residual symptoms, psychotherapy may be needed. Clinicians may need to refer patients to alternative providers. Many patients will benefit from regular contact with someone like a case manager or a therapist, because they offer ongoing support that will help maintain long-term wellness.

SUMMARY

Because depression is a highly recurrent illness, clinicians must identify and address modifiable risk factors for relapse or recurrence throughout all phases of treatment. While some individuals will become asymptomatic following initial treatment, these types of patients are the minority. Most patients are not going to reach full remission with any single treatment, and, for that reason, clinicians must focus on change in cognitive mediators of relapse and recurrence; these are likely to be changed either with cognitive therapy or behavioral activation. Although antidepressants, such as SRIs, reduce depressive symptoms and anxiety, they may not protect against relapse over time.

Another component of long-term treatment is actively managing comorbidity, including anxiety, personality, and substance use disorders as well as medical comorbidities. These comorbidities significantly increase the risk of relapse.

Residual depressive symptoms should be alleviated. However, often, too much focus is placed on symptom remission, and too little attention is given to psychosocial factors that may increase the risk for return of symptoms. Predictable stressors must be aggressively managed, both acutely and long-term, and the treatment plan should be adjusted when necessary to meet the patient's changing needs over time.

Drug names: citalopram (Celexa and others), desipramine (Norpramine and others), lithium (Lithobid, Eskalith, and others), paroxetine (Paxil, Pexeva, and others), venlafaxine (Effexor and others).

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

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