Major depressive disorder (MDD) has a devastating impact on individuals and society because of its high prevalence, its recurrent nature, its frequent comorbidity with other disorders, and the functional impairment it causes. Compared with other chronic diseases, such as arthritis, asthma, and diabetes, MDD produces the greatest decrement in health worldwide. The goals in treating MDD should be not just to reduce symptom severity but also to achieve continuing remission and lower the risk for relapse.

Antidepressants are the most common treatment for depression. Among psychotherapies used to treat MDD, cognitive-behavioral therapy (CBT) has been identified as an effective treatment. Collaborative care models have been reported to manage MDD more effectively. In this article, we review the evidence supporting the use of CBT as monotherapy and in combination with antidepressants for acute and long-term treatment of MDD.

### Acute treatment: Not too soon for CBT

**Mild to moderate depression**

Research has indicated that for the treatment of mild MDD, antidepressants are unlikely to be more effective than placebo. Studies also have reported that response to antidepressants begins to outpace response to placebo only when symptoms are no longer mild. Using antidepressants for patients with mild depression could therefore...
place them at risk of overtreatment. In keeping with these findings, the American Psychiatric Association (APA) has recommended the use of evidence-based psychotherapies, such as CBT, as an initial treatment choice for patients with mild to moderate MDD.

Two recent studies have suggested that the combination of CBT plus antidepressants could boost improvement in psychosocial functioning for patients with mild MDD. However, neither study included a group of patients who received only CBT to evaluate if CBT alone could have also produced similar effects. Other limitations include the lack of a control group in one study and small sample sizes in both studies. However, both studies had a long follow-up period and specifically studied the impact on psychosocial functioning.

**Moderate to severe depression**

Earlier depression treatment guidelines suggested that antidepressants should be used to treat more severe depression, while psychotherapy should be used mainly for mild depression. This recommendation was influenced by the well-known National Institute of Mental Health (NIMH) Treatment of Depression Collaborative Research Program, a multicenter randomized controlled trial (RCT) that used a placebo control. In this study, CBT was compared with antidepressants and found to be no more effective than placebo for more severely depressed patients. However, this finding was not consistent across the 3 sites where the study was conducted; at the site where CBT was provided by more experienced CBT therapists, patients with more severe depression who received CBT fared as well as patients treated with antidepressants. A later double-blind RCT that used experienced therapists found that CBT was as effective as antidepressants (monoamine oxidase inhibitors), and both treatments were superior to placebo in reducing symptoms of atypical depression.

Another placebo-controlled RCT conducted at 2 sites found that CBT was as effective as antidepressants in the treatment of moderately to severely depressed patients. As in the NIMH Treatment of Depression Collaborative Research Program trial, in this study, there were indications that the results were dependent on therapist experience. These findings suggest that the experience of the therapist is an important factor.

A recent meta-analysis of treatments of the acute phase of MDD compared 11 RCTs of CBT and second-generation antidepressants (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and other medications with related mechanisms of action). It found that as a first-step treatment, CBT and antidepressants had a similar impact on symptom relief in patients with moderate to severe depression. Patients treated with antidepressants also had a higher risk of experiencing adverse events or discontinuing treatment because of adverse events. However, this meta-analysis included trials that had methodological shortcomings, which reduces the strength of these conclusions.

Patients with MDD and comorbid personality disorders have been reported to have poorer outcomes, regardless of the treatment used. Fournier et al examined the impact of antidepressants and CBT in moderately to severely depressed patients with and without a personality disorder. They found that a combination of antidepressants and CBT was suitable for patients with personality disorders because antidepressants would boost the initial response and CBT would help sustain improvement in the long term.

Presently, the APA suggests that the combination of psychotherapy and antidepressants may be used as an initial treatment for patients with moderate to severe MDD. As research brings to light other factors that affect treatment outcomes, these guidelines could change.

**Table 1** summarizes the findings of select studies evaluating the use of CBT for the acute treatment of depression.

**CBT’s role in long-term treatment**

Recurrence and relapse are major problems associated with MDD. The large majority of individuals who experience an episode of depression go on to experience more episodes of depression, and the risk
of recurrence increases after each successive episode.21

To reduce the risk of relapse and the return of symptoms, it is recommended that patients treated with antidepressants continue pharmacotherapy for 4 to 9 months after remission.9 Maintenance pharmacotherapy, which involves keeping patients on antidepressants beyond the point of recovery, is intended to reduce the risk of recurrence, and is standard treatment for patients with chronic or recurrent MDD.22 However, this preventive effect exists only while the patient continues to take the medication. Rates of symptom recurrence following medication withdrawal are often high regardless of how long patients have taken medications.23

Studies examining CBT as a maintenance treatment—provided alone or in combination with or sequentially with antidepressants—have found it has an enduring effect that extends beyond the end of treatment and equals the impact of continuing antidepressants.24-27 A recent meta-analysis of 10 trials where CBT had been provided to patients after acute treatment found that the risk of relapse was reduced by 21% in the first year and by 28% in the first 2 years.28

Studies have compared the prophylactic impact of maintenance CBT and antidepressants. In an early study, 40 patients who had been successfully treated with antidepressants but had residual symptoms were randomly assigned to 20 weeks of CBT or to clinical management.29 By the continued on page 20

### Table 1
Cognitive-behavioral therapy during acute treatment of depression

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>CBT</th>
<th>Results</th>
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<tbody>
<tr>
<td>Zhang et al.</td>
<td>Outpatients with mild depression received ADM only (n = 30) or ADM plus weekly CBT (n = 32) for 12 weeks. ADM was continued for 12 months</td>
<td>Group format; cognitive restructuring; emotion regulation</td>
<td>12 weeks: CBT plus ADM group had significantly better scores than ADM-only group on HAM-D. CBT plus ADM group had significantly better scores than ADM-only group on measures of social functioning. 12 months: CBT plus ADM group had significantly better scores than ADM-only group on HAM-D and measures of social functioning.</td>
</tr>
<tr>
<td>Matsunaga et al.</td>
<td>43 patients with treatment-resistant mild depression received 12 weeks of ADM plus CBT. ADM was continued for 12 months</td>
<td>Group format; psychoeducation on depression; cognitive restructuring; psychoeducation on relapse prevention</td>
<td>12 weeks: Significant improvement on HAM-D. Significant improvement on GAF measure of social functioning. 12 months: Significant improvement on HAM-D and GAF measure of social functioning was maintained</td>
</tr>
<tr>
<td>Jarrett et al.</td>
<td>Patients with moderate, atypical depression received 10 weeks of CBT only (n = 36) or ADM only (n = 36). A control group (n = 36) received placebo</td>
<td>Individual format; 20 sessions in 10 weeks</td>
<td>Both ADM and CBT produced significant improvement at end of treatment as measured on HAM-D. No significant difference in outcomes noted between ADM and CBT.</td>
</tr>
<tr>
<td>DeRubeis et al.</td>
<td>Patients with moderate to severe depression received 16 weeks of ADM only (n = 120) or CBT only (n = 60). A control group (n = 60) received placebo</td>
<td>Individual format; 20 sessions in 16 weeks</td>
<td>CBT and ADM produced similar, significant improvement as measured on HAM-D.</td>
</tr>
</tbody>
</table>

ADM: antidepressants; CBT: cognitive-behavioral therapy; GAF: Global Assessment of Functioning scale; HAM-D: Hamilton Depression Rating Scale
Weaknesses of this study include a small sample size, and the fact that a single therapist provided the CBT.

This study was extended to a 6-year follow-up; antidepressants were prescribed only to patients who relapsed. The CBT group continued to have a significantly lower relapse rate (40%) compared with the antidepressant group (90%). This study was extended to a 6-year follow-up; antidepressants were prescribed only to patients who relapsed. The CBT group continued to have a significantly lower relapse rate (40%) compared with the antidepressant group (90%).

In another RCT, patients with depression who had recovered with CBT or medication continued with the same treatment dosage not allowed to fall below half of maximum active treatment dosage.

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Continuation treatments</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al (1992)</td>
<td>Patients with moderate depression received ADM only (n = 21), CBT only (n = 10), or ADM plus CBT (n = 13). All had at least partial response to 12 weeks of active treatments. 24-month follow-up</td>
<td>ADM continued for 12 months for half of ADM-only group ADM discontinued for half of ADM-only group ADM discontinued for ADM plus CBT group CBT discontinued for CBT-only and CBT plus ADM group</td>
<td>ADM dosage not allowed to fall below half of maximum active treatment dosage</td>
</tr>
<tr>
<td>Fava et al (1998)</td>
<td>40 patients with moderate to severe recurrent depression who had been successfully treated with ADM and had residual symptoms. 24-month follow-up</td>
<td>ADM continued for 20 weeks (n = 20) 10 sessions of CBT for residual symptoms over 20 weeks (n = 20)</td>
<td>Conventional clinical management with ADM was continued for 20 weeks during continuation phase. By the end of this period ADM was tapered and stopped</td>
</tr>
<tr>
<td>Fava et al (2004)</td>
<td>40 patients with moderate to severe recurrent depression who had been successfully treated with ADM and had residual symptoms. 6-year follow-up</td>
<td>ADM continued for 20 weeks (n = 20) 10 sessions of CBT for residual symptoms over 20 weeks (n = 20)</td>
<td>Conventional clinical management with ADM was continued for 20 weeks during continuation phase. By the end of this period ADM was tapered and stopped</td>
</tr>
<tr>
<td>Hollon et al (2005)</td>
<td>Patients with moderate to severe depression who were responders to 16 weeks of active treatment. 12-month continuation phase followed by 12-month naturalistic follow-up (no ADM or CBT)</td>
<td>CBT for responders to 16 weeks of treatment with CBT (n = 35) ADM for responders to 16 weeks of ADM (n = 34) Pill placebo withdrawal for pill placebo group (n = 35)</td>
<td>ADM: Biweekly clinical management sessions followed by monthly sessions until end of 12 months CBT: 3 booster sessions in 12 months</td>
</tr>
<tr>
<td>Hollon et al (2014)</td>
<td>Adult outpatients with moderate to severe depression</td>
<td>Patients were randomly assigned to ADM only (n = 225) or ADM plus CBT (n = 227). Treatment was continued for up to 42 weeks until recovery was achieved</td>
<td>ADM: Monthly clinical management sessions CBT: Monthly session</td>
</tr>
<tr>
<td>Bockting et al (2015)</td>
<td>172 patients with a history of recurrent depression who were in remission. 10-year follow-up</td>
<td>TAU, which could include ADM (n = 84) PCT plus TAU as usual (n = 88)</td>
<td>PCT: 8 weekly, 2-hour group sessions. PCT focused on identification of dysfunctional attitudes and schemas and teaching patients to challenge these, enhancing specific memories of positive experiences and formulating specific prevention strategies TAU: Included ADM</td>
</tr>
</tbody>
</table>

ADM: antidepressants; CBT: cognitive-behavioral therapy; MDD: major depressive disorder; PCT: preventive cognitive therapy; TAU: treatment as usual
Results

Patients in the ADM without continuation group had the highest relapse rate of 50%
Patients in the ADM continuation group had a relapse rate of 32%
CBT-only group had a relapse rate of 21%
CBT and ADM group had the lowest relapse rate (15%)

Patients in the ADM group had a relapse rate of 80%
Patients in the CBT group had a relapse rate of 25%

Patients in the ADM group had a relapse rate of 90%
Patients in the CBT group had a relapse rate of 40%

Continuation phase: Sustained response in 16.4% of placebo group, 26.9% of ADM group, and 37.3% of CBT group
Naturalistic follow-up: Recurrence rates 17.3% in CBT group, 53.6% in ADM group

Recovery rate was significantly higher for ADM plus CBT group vs ADM-only group (75.2% vs 65.6%)
Recovery rate was significantly higher in the CBT plus ADM group for patients with high-severity MDD (76.9% vs 60.3%) and non-chronic MDD (79.5% vs 62.8%)
PCT was found to have a protective effect for patients who had >2 prior episodes of depression
The protective effect of PCT intensified with increasing number of prior episodes
Although PCT increased time to recurrence, it had no impact on number of recurrences
The mean severity of recurrences was lower in PCT patients with >3 prior episodes

An RCT that included 452 patients with severe depression used a long intervention period (up to 42 weeks) and a flexible treatment algorithm to more closely model the strategies used in clinical practice. Patients were randomly assigned to antidepressants only or in combination with CBT. At the end of 12 months, outcome assessment by blinded interviewers indicated that patients with more severe depression were more likely to benefit from the combination of antidepressants and CBT (76.9% vs 60.3%) and those with severe, non-chronic depression received the most benefit (79.5% vs 62.8%). The lack of a CBT-only group limits the generalizability of these findings. Neither patients nor clinicians were blinded to the treatment assignment, which is a common limitation in psychotherapy studies but could have contributed to the finding that combined treatment was more effective.

Some evidence suggests that augmenting treatment as usual (TAU) with CBT can have a resilient protective impact that also intensifies with the number of depressive episodes experienced. In an RCT, 172 patients with depression in remission were randomly assigned to TAU or to TAU augmented with CBT. The time to recurrence was assessed over the course of 10 years. Augmenting TAU with CBT had a significant protective impact that was greater for patients who had >3 previous episodes.

Another long-term study assessed the longitudinal course of 158 patients who received CBT, medication, and clinical management, or medication and clinical management alone. Patients were followed 6 years after randomization (4.5 years after completion of CBT). Researchers found the effects of CBT in preventing relapse and recurrence persisted for several years.

Table 2 summarizes the findings of select studies evaluating the use of CBT for the long-term treatment of depression.

**Clinical Point**

The expertise of the CBT therapist has an impact on outcomes

during a maintenance phase. The CBT group received 3 booster sessions during the next year and antidepressant group received medication. At the end of the second year (without CBT or medication) CBT patients were less likely to relapse compared with patients receiving antidepressants. The adjusted relapse rates were 17.3% for CBT and 53.6% for antidepressants.
delineated in all studies. This is important because recurrence rates tend to be lower, and long-term follow-up would be needed to detect multiple recurrences so that their incidence is not underestimated. In addition, the types of CBT interventions utilized has varied across studies. Some studies have employed standard interventions such as cognitive restructuring, while others have added strategies that focus on enhancing memories for positive experiences or interventions to encourage medication adherence. Despite these limitations, research has shown promising results and suggests that adding CBT to the maintenance treatment of patients with depression—with or without antidepressants—is likely to reduce the rate of relapse and recurrence.

Consider CBT for all depressed patients

Research indicates that CBT can be the preferred treatment for patients with mild to moderate MDD. Antidepressants significantly reduce depressive symptoms in patients with moderate to severe MDD. Some research suggests that CBT can be as effective as antidepressants for moderate and severe MDD. However, as the severity and chronicity of depression increase, other moderating factors need to be considered. The expertise of the CBT therapist has an impact on outcomes. Treatment protocols that utilize CBT plus antidepressants are likely to be more effective than CBT or antidepressants alone. Incorporating CBT in the acute phase of depression treatment, with or without antidepressants, can have a long-term impact. For maintenance treatment, CBT alone and CBT plus antidepressants have been found to help sustain remission.

References


Bottom Line

Cognitive-behavioral therapy (CBT) can be an effective treatment for patients with major depressive disorder, regardless of symptom severity. The expertise of the clinician who provides CBT has a substantial impact on outcomes. Combination treatment with CBT plus antidepressants is more likely to be effective than either treatment alone.


