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The Long-Term Management of Major Depressive Disorders

Abstract: In recent years, depression has been reconceptualized from a short, self-limiting condition to longer time frames as a result of the observation that most depressed persons will have a recurrent or chronic course. Similarly, antidepressant therapy, either with drugs or psychotherapy, has been recast in longer time periods. The best current evidence indicates that ongoing treatment with medications and certain types of psychotherapy (with interpersonal psychotherapy [IPT] and cognitive behavioral psychotherapy [CBT] and related approaches being the most widely tested) reduce risk for relapse (defined as the return of the original episode of depression) and recurrence (the occurrence of a new episode). IPT, CBT, and medications reduce risk while they are continued, but only CBT seems to have an enduring effect after it is discontinued. Significantly, combining CBT with antidepressant medications initially may reduce the preventive effect of CBT on relapse and recurrence. Therefore, the choice of initial treatment determines the need for longer-term continuation of therapy.

The treatment of depression is often conceptualized in relatively short time periods; for example, the median duration of an untreated depressive episode is about 23 weeks (1). This type of observation led to the common recommendation of continuing antidepressant treatment for 6-9 (or 12) months (2–4), followed by a slow taper (5). However, these recommendations are inconsistent with the longer-term outcome in most depressed people (6). About 80% of people with depression will experience a recurrence, and approximately 15% will be chronically ill (7). The probability of recurrence of depression is a function of the number of previous episodes: recurrence occurs in <60% after one episode of depression, 60%–90% after two, and > 95% for three or more episodes (6). Therefore, the majority of depressed people will need maintenance management of some kind. However, as discussed in greater detail below, maintenance *management* is not the same thing as maintenance *treatment.*

Treatment of depression is often conceptualized to occur in three phases: acute (typically the first 8-16 weeks of care or until remission occurs), continuation (usually an additional 6 months of treatment, representing the time to the end of the current episode), and maintenance (focused on prevention of a return of a new depressive episode) (8). These conventions are based on the observed short-term rates of relapse of previously effective antidepressant treatment for depression, which is highest if the treatment is withdrawn in the first 16 weeks, declines somewhat in the next 6 months, and is lowest thereafter (9, 10). Relapse is then defined as a return to the original episode of depression, within the acute and continuation treatment periods. Recurrence is described as the occurrence of a wholly new episode of depression (8). This review will focus on strategies to manage relapse and recurrence of depression.

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NATURALISTIC OUTCOMES

The good news about depression is that the broad majority of people with the condition will eventually improve (11, 12). More than 90% of people with depression will eventually recover (13). Better still is that treatment does influence longer-term outcome; for example, Leon and colleagues (14) assessed 285 people with an index episode of major depression in the National Institute of Mental Health Collaborative Depression Study over periods of up to 20 years in a naturalistic follow-up design. Those who received higher levels of somatic antidepressant treatment over the follow-up period tended to have more prior episodes and had more severe depression at baseline compared with those who received less treatment. In spite of this, those with higher levels of somatic treatment were significantly more likely to recover from depression than those receiving lower levels of treatment. Therefore, treatment appears to be effective in both short- and long-term care. Moreover, even chronically ill people may still experience recovery. Mueller et al. (13) found that of people depressed over an initial 5 years of observation, 38% recovered over the next 5 years. This means that the overall prognosis of recovery of depression is generally good.

The bad news, by contrast, is that most people will eventually relapse. For example, in a continuation follow-up study of 380 subjects who recovered from an index episode of major depressive disorder, including 105 who remained well for at least 5 years, Mueller et al. (12) observed relapse or recurrence in 85% of the whole sample, including 58% of those who remained well for at least 5 years. They found several factors that predicted relapse, including being female, never married, and having a longer index depressive episode and more prior episodes. Given that most depressed people have a recurrence after an initial episode, therapy should be reconceptualized as long-term management, much like current concepts of the treatment of diabetes or depression. Note that this may not mean long-term medication management; as described below, certain psychotherapies like cognitive behavioral therapy, behavioral activation therapy, maintenance management with interpersonal psychotherapy, and perhaps other forms of therapy appear to reduce relapse and recurrence as well (15).

Another piece of bad news is that residual depression, conceptualized as continued depression even after an initial treatment, is the common outcome of depression treatment. In the NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR*D) program (16), only about a third of patients with major depression experienced remission with an initial period of optimized treatment with the SSRI citalopram (17). Even after four levels of treatment (i.e., treatment trials), the cumulative remission rate was only 67% (16). Moreover, many patients relapse and even patients considered "remitted" (typically defined as a Hamilton Rating Scale for Depression [HRSD] score of $\leq$7) may not actually think of themselves as well (18). For example, Zimmerman et al. (18) assessed 274 outpatients with major depression in ongoing psychiatric treatment, including 174 who performed a self-assessment of outcome. Of those meeting the standard definition of remission (HRSD $\leq$7), half did not consider themselves as truly remitted as assessed by the Remission of Depression Questionnaire (19). These data are consistent with the previous findings by Zimmerman and colleagues, which showed that depressed patients in treatment who scored 0-2 on the HRSD had significantly less impaired psychosocial functioning and better quality of life than those scoring 3-7. This indicates that even mild residual depression is associated with significant life impairment, and that depression severity must be driven down to very low levels to achieve normal functioning.

THE INFLUENCE OF THE INITIAL QUALITY OF RECOVERY AND RELAPSE OF DEPRESSION

There is a considerable range of outcomes with initial treatment of depression, with the majority of people experiencing only partial improvement (16, 20). There is now strong evidence indicating that the quality of initial improvement in depression is a strong predictor of long-term depression outcome (20, 21). Ramana et al. reported an early observation of this problem in a study in 1995 (22); overall, 40% of people treated initially for depression experienced relapse over a 15-month follow-up period. However, when divided into initial remission or nonremission, the remitted participants (i.e., those with an end-of-treatment HRSD score of $<$7) had a relapse rate of 25%, while those not remitted had a 76% chance of subsequent return of major depression. These findings have been supported by subsequent studies over short-term follow-up periods (e.g., 1 year) (23, 24). However, relapse and recurrence in much longer-term follow-up does not seem to be affected by initial quality of response (25–27). For example, Kennedy et al. (26, 27) found over a period of 10 years of follow-up that those with and without initial remission of depression did not differ in the likelihood of experiencing a recurrence, mean number of recurrences,

readmissions to hospital, the development of chronic depression, or clinical global outcome, although those with initial nonremission did spend more time with significant depressive symptoms (although not necessarily in episode) and greater overall impairment of social functioning. These data indicate that the initial quality of improvement affects short-term relapse and recurrence rates over the first 18 months, persistence of depressive symptoms, and impairment, but it does not influence the ultimate likelihood of the recurrence of full episode of depression (20, 28).

CONTINUATION AND MAINTENANCE TREATMENT OF DEPRESSION: MEDICATIONS

There is now overwhelming evidence that longer-term treatment with antidepressants after initial adequate response dramatically reduces risk of relapse and recurrence of depression (6, 29). This is true, given the caveat of adequate initial response described above; unfortunately, many depressed people do not recover even after multiple rounds of adequate treatment. Therefore, many follow-up studies are actually enrichment designs—only those who did reasonably well initially were taken into follow-up treatment. As a result, the benefits of continuation and maintenance treatments may be somewhat inflated over what might be expected with a full sample.

One of the earliest long-term follow-up trials after initial treatment of depression was that of Prien, Klett, and Caffey in 1984 (30). In this study, both bipolar and unipolar depressed patients were randomly assigned to treatment with lithium, imipramine, and placebo for up to 2 years. Not surprisingly, those with bipolar depression did better on a regimen of lithium than either imipramine or placebo, with more treatment-emergent mania seen with imipramine treatment. By contrast, continuation treatment with either lithium or imipramine was equally effective and more so than placebo in preventing depression for unipolar patients. This study highlights the effectiveness of continuation treatment with an antidepressant medication, which now has been confirmed with many subsequent studies (for reviews see Keller [6, 29, 31], Paykel [5], and Kaymaz et al. [32]). In a meta-analysis of 30 trials with 4,890 participants (32), the odds ratio of relapse in continuation treatment versus withdrawal from treatment (typically to placebo) was highly significant for both SSRIs (OR=0.24, 95% CI=0.20 to 0.29) and tricyclics (OR=0.29, 95% CI=0.23 to 0.38) over 1 year of follow-up. Interestingly, recurrent patients experienced somewhat less protection from a return of depression by antidepressant treatment over the maintenance phase (OR=0.37, 95% CI=0.31 to 0.44) than single-episode patients (OR=0.12, 95% CI=0.06 to 0.26). However, continuation treatment clearly reduces relapse, at least in people who have a good initial response.

There have been relatively few long-term controlled follow-up studies greater than 1 year in duration. In one study of maintenance therapy in 128 patients, the rates of recurrence over 3 years were 22% for patients treated with imipramine, 78% with placebo, 24% with interpersonal psychotherapy (IPT) plus imipramine, 65% with IPT plus placebo, and 62% with IPT alone, indicating that imipramine reduced rates of recurrence more that either placebo or IPT, while IPT alone had modest effects (33). In a follow-up from that same study, participants who were treated with imipramine were randomly assigned to continuation imipramine or placebo (34). Rates of relapse were dramatically lower with imipramine (10%) than placebo (60%), indicating that continuation treatment with an antidepressant (at least with a tricyclic) beyond 3 years was beneficial. The bulk of evidence then indicates that longer-term treatment with antidepressants produces sustained benefits.

CONTINUATION AND MAINTENANCE MANAGEMENT OF DEPRESSION: PSYCHOTHERAPY

We know less about extended treatment with psychotherapy but what we do know suggests that keeping patients in treatment longer reduces risk for relapse and recurrence. Continuation treatment with IPT was superior to withdrawal onto pill-placebo or no pill (35), so long as IPT was not combined with pill-placebo (36). Moreover, continuation IPT had a delayed effect on the quality of patients' interpersonal relationships not found for medications (37). As previously noted, maintenance IPT was less efficacious than maintenance medication in the prevention of recurrence in normal aged adults, but still more efficacious than pill-placebo (33). It should be noted that that maintenance IPT was provided only monthly (whereas acute IPT is usually provided weekly) so that the lesser efficacy of IPT in this study may have been a consequence of its reduced "dose." Moreover, process studies indicate that when IPT was conducted in an adherent fashion it had a considerably larger prophylactic effect than when it was not (38). Maintenance IPT was as efficacious as maintenance medication and their combination better still (with each superior to pill-placebo) in the prevention of recurrence in a

"young" geriatric sample up to 75 years of age (39). However, a subsequent replication in an older geriatric sample aged 70 or above found maintenance IPT no more efficacious than pill-placebo and less efficacious than maintenance medications (40), although maintenance IPT was protective of cognitively impaired elders (41).

Cognitive behavior therapy (CBT) has been less often tested as a continuation or maintenance treatment than IPT, although it has generally performed well when it has. Continued treatment with CBT reduces relapse relative to treatment discontinuation; the duration of follow-up in studies suggests that the benefits of continued treatment may extend into the maintenance period. This means that CBT may be effective for the prevention of both relapse and recurrence (42). Maintenance treatment with a Cognitive Behavioral Analytic System of Psychotherapy (CBASP) was found to reduce risk for recurrence in patients with chronic depressions (43). Although the studies are few, their results are positive.

One of the reasons that such continuation or maintenance treatment studies are so scarce with respect to this approach is that CBT appears to have an enduring effect that lasts beyond the end of treatment (44). Patients treated with prior CBT during acute treatment are only about half as likely to relapse following treatment termination as patients withdrawn from antidepressant medications (45–50) and the magnitude of that preventive effect is at least as great as keeping patients on continuation medication (48–51). Even the more purely behavioral treatment Behavioral Activation Therapy evidenced an enduring effect following treatment termination that was as efficacious as keeping patients on continuation antidepressant (50). The only study in the literature that did not show such an enduring effect for prior CBT was the NIMH Treatment of Depression Collaborative Research Program and such differences as were evident favored prior CBT over discontinuation of medications (52). There are even indications that this enduring effect extends to the prevention of recurrence (49, 50). It would appear that there are at least two ways to protect patients against subsequent symptom return: either keep them on medications or provide them with prior exposure to CBT during acute treatment (53).

What is not so clear is whether CBT still has an enduring effect when combined with medications. Curiously enough, only two studies have compared prior exposure to CBT when it was provided in combination with as opposed to without medication and the findings from those two trials run in opposite directions. One trial found that combining CBT with medications eliminated its enduring effect (47) whereas the other found that its enduring effect was just as robust regardless of whether it was combined with medications or not (48). Both studies had small samples in their follow-ups (about a dozen patients per condition) and therefore the question remains unanswered. There are indications that combining CBT with medications undercuts its enduring effect in panic and anxiety disorders and the possibility exists that it does so in depression (44). Given the relative lack of efficacy of our current treatments with more chronic and refractory patients, this is an issue that will have to be resolved.

CBT does appear to have an enduring effect when it is introduced after patients are already in remission or recovery, either following acute treatment with medications or spontaneous remission. Providing 3 months of a modified version of CBT called Well-being Therapy prevented recurrence for up to 3 years (54), and providing a similar duration of CBT for patients who showed only partial response to ongoing medication treatment reduced rates of relapse (55) and subsequent recurrence for up to 5 years (56). Providing 8 weeks of group CBT for patients who had already remitted prevented relapse and recurrence for up to 5 years following treatment termination, with the strongest differential effects for patients with three or more prior episodes (57). A similar moderated effect was found for acute CBT followed by brief psychoeducation (but not psychoeducation alone) for patients with four or more prior episodes (58). The only studies that failed to find an enduring effect for CBT provided following remission involved comparisons to continuation medication (59, 60).

Mindfulness based cognitive therapy (MBCT) adds meditation to conventional CBT and also has been shown to prevent relapse and recurrence in remitted patients (61–63). Curiously, MBCT appears to have its largest differential effects for patients with three or more prior episodes. Prior exposure to MBCT appears to be about as efficacious as keeping patients on medications such that most of the patients exposed to MBCT were able to discontinue medications (63). MBCT has yet to be used as an acute intervention but its capacity to prevent relapse and recurrence clearly has been established.

There are indications that CBT can prevent onset of first episode of depression in at-risk adolescents (64) and the same might be true for IPT (65). These preventive interventions can be applied universally to unselected populations (for example as part of the school curriculum) but have their greatest effect in at-risk samples (66). If psychosocial interventions

can be used to reduce risk for initial onset it might prove possible to alter the trajectory of the life-course of depression. It might prove that the best way to deal with the long-term management of depression is to provide the skills to high-risk individuals that enable them to not fall victim to depression in the first place.

CONTINUATION AND MAINTENANCE MANAGEMENT OF DEPRESSION: MAINTENANCE ELECTROCONVULSIVE THERAPY

Electroconvulsive therapy (ECT) is a highly effective treatment for depression, including treatment resistant MDD (67). For example, one study found that, overall, 73% of people with MDD who received ECT achieved remission; of those who had at least one adequate prior antidepressant trial, 63% responded, compared with 91% of people without an adequate prior treatment (67). Most studies have found that approximately 60% of treatment-resistant patients achieve response (68). However, a relatively high proportion of people who achieve adequate initial response eventually relapse (69). Sackeim and colleagues (69) found that 84% of ECT-treated patients who continue on placebo relapse within 6 months. This rate was reduced to 60% if people continued on the tricyclic antidepressant nortriptyline. However, only 39% of people treated with a combination of lithium and nortriptyline relapsed, indicating that this combination may be the most effective means of preventing relapse with pharmacotherapy.

An alternative approach for the prevention of relapse after initial response to ECT is continuation (C-ECT) and maintenance (M-ECT) ECT therapy, in which ECT is continued on a weekly basis or less frequently (70, 71). C-ECT is typically defined as a continuation of ECT for 6 months following the initial period of ECT, while M-ECT is ECT that continues beyond 6 months. There has been relatively little systematic study of C-ECT or M-ECT; this led the National Institute for Clinical Excellence (NICE) Technology Appraisal, "Guidance on the Use of Electroconvulsive Therapy," to come to the following conclusion regarding continuing ECT following initial response: ECT is "not recommended as a maintenance therapy in depressive illness [since] longer-term benefits and risks of ECT have not been clearly established." The report goes on to say, "There was no conclusive evidence to support the effectiveness of ECT beyond the short term or that it is more beneficial as a maintenance therapy in depressive illness than currently available pharmacological alternatives." One randomized prospective study compared C-ECT given weekly for 4 weeks, biweekly for 8 weeks, and monthly for 2 months, for a total of 10 ECT treatments over 6 months with a nortriptyline-plus-lithium combination in participants who experienced remission with initial ECT (72). Those in the ECT condition had no psychotropic medications other than lorazepam or diphenhydramine as needed. In the C-ECT condition, 37.1% experienced relapse, 16.8% dropped out, and 46.1% continued to have remission. In the comparison nortriptyline plus lithium condition, 31.6% experienced relapse, 22.1% dropped out of the study, and 46.3% continued to experience remission. While maintenance ECT did appear to reduce relapse as compared with placebo-treated patients in previous studies, it was not more effective than continuation treatment with the tricyclic-plus-lithium combination, at least when delivered on the schedule described.

Only one relatively small, randomized trial compared combined nortriptyline and ECT against nortriptyline alone in elderly depressed over a 2-year period and found the combination superior (73). However, there have been no other published studies on the relative benefits of combined medications and C-ECT or M-ECT. In addition, whether C-ECT or M-ECT given on a more frequent schedule would work better is unknown.

EXTENDED TREATMENT FOR COMPLICATED PATIENTS

Finally, not everyone gets better with initial treatment, and patients with chronic depression or depressions superimposed upon axis II personality disorders are particularly likely to need treatment to be extended. IPT has developed a strategy for dealing with such patients that encourages patients to reconceptualize what they consider to be lifelong character flaws as chronic but treatable "states" rather than immutable "traits" (74). Therapy itself is defined as a process of "role transition" from seeing oneself as flawed to recognizing and treating the affective disorder. CBT deals with such patients by adopting a "schema-focused" approach in which great emphasis is put upon identifying and changing the core beliefs and dysfunctional assumptions that underlie the specific negative automatic thoughts that drive mood and problematic behavior in everyday situations. Therapists adopt what is called the "three-legged stool" in which attention is paid to childhood antecedents and aspects of the therapeutic relationship in equal measure to current concerns in the patient's life (75). Schema-focused CBT recognizes that change is harder to produce in some patients and starts from the assumption that

efforts to deal with current life concerns will have to take place in a broader context than typically is the case for less complicated patients.

SUMMARY

Depression has proven to be a much more difficult condition to treat than previously thought, with a large majority of patients having either recurrent or chronic depression. Depression treatment has moved from a predominant focus on acute management toward conceptualizing treatment in longer timeframes—that is, managing acutely but also preventing relapse and recurrence long-term. Both antidepressants and some psychotherapies (e.g., IPT and CBT and its variants) have both acute and enduring benefits in depressed patients. However, the enduring effects of IPT seem to occur primarily in the face of ongoing treatment. By contrast, a prior course of CBT seems to reduce the risk for relapse and, possibly, recurrence of depression. Interestingly, combining CBT initially with a medication may reduce the relapse and recurrence prevention effect. Therefore, based on the best current information, whenever possible CBT should be provided in the absence of medication at least initially. There are clearly some situations in which CBT should probably not be provided without initial medication management because of the delay in effect of CBT relative to medications (e.g., patients with serious suicidal potential, psychotic depression, or severe impairment). Antidepressants reduce risk for relapse and recurrence but, like IPT, antidepressants reduce risk only while they are continued. Therefore, an initial choice of an antidepressant medication entails the need for ongoing drug treatment to achieve the objective of relapse and recurrence prevention.

Once relapse or recurrence occurs, the possibility of the development of an intercurrent medical condition such as hypothyroidism or inflammatory disease that may be contributing should be considered. This should parallel the assessment of possible medical contributors as would be done in an initial evaluation. In face of a significant return of depressive symptoms in the absence of a known contributing medical condition, more advanced therapies, including combined CBT plus medication (if not done) or an augmentation (76) or other advanced treatment strategy may be given.

REFERENCES

1. Posternak MA, Solomon DA, Leon AC, Mueller TI, Shea MT, Endicott J, et al: The naturalistic course of unipolar major depression in the absence of somatic therapy. J Nerv Ment Dis 2006; 194:324–329
2. National Collaborating Center for Mental Health: Depression: The Treatment and Management of Depression in Adults (NICE Clinical Guideline 90). UK, NCCMH, 2009
3. American Psychiatric Association: Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition. Arlington, Va, APA, 2010
4. Lam RW, Kennedy SH, Grigoriadis S, McIntyre RS, Milev R, Ramasubbu R, Parikh SV, Patten SB, Ravindran AV; Canadian Network for Mood and Anxiety Treatments (CANMAT): Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults, III: Pharmacotherapy. J Affect Disord 2009; 117(Suppl 1):S26–S43
5. Paykel ES: Continuation and maintenance therapy in depression. Br Med Bull 2001; 57:145–159
6. Keller MB: The long-term treatment of depression. J Clin Psychiatry 1999; 60(Suppl 17):41–45, discussion 46–48
7. Eaton WWS, Shao H, Nestadt G, Lee HB, Bienvenu OJ, Zandi P: Population-based study of first onset and chronicity in major depressive disorder. Arch Gen Psychiatry 2008; 65:513–520
8. Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM: Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. Arch Gen Psychiatry 1991; 48:851–855
9. Prien RF, Caffey EM Jr: Long-term maintenance drug therapy in recurrent affective illness: current status and issues. Dis Nerv Syst 1977; 38:981–992
10. Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE: Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry 1984; 41:1096–1104
11. Solomon DA, Keller MB, Leon AC, Mueller TI, Shea MT, Warshaw M, Maser JD, Coryell W, Endicott J: Recovery from major depression. A 10-year prospective follow-up across multiple episodes. Arch Gen Psychiatry 1997; 54: 1001–1006
12. Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, Warshaw M, Maser JD: Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. Am J Psychiatry 1999; 156: 1000–1006
13. Mueller TI, Keller MB, Leon AC, Solomon DA, Shea MT, Coryell W, Endicott J: Recovery after 5 years of unremitting major depressive disorder. Arch Gen Psychiatry 1996; 53:794–799
14. Leon AC, Solomon DA, Mueller TI, Endicott J, Rice JP, Maser JD, Coryell W, Keller MB: A 20-year longitudinal observational study of somatic antidepressant treatment effectiveness. Am J Psychiatry 2003; 160:727–733
15. Hollon SD, Ponniah K: A review of empirically supported psychological therapies for mood disorders in adults. Depress Anxiety 2010; 27:891–932
16. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M: Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163:1905–1917
17. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, Shores-Wilson K, Biggs MM, Balasubramani GK, Fava M; STAR*D Study Team: Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006; 163:28–40
18. Zimmerman M, Martinez JA, Attiullah N, Friedman M, Toba C, Boerescu DA, Rahgeb M: Why do some depressed outpatients who are in remission according to the Hamilton Depression Rating Scale not consider themselves to be in remission? J Clin Psychiatry 2012; 73:790–795
19. Zimmerman M, Galione JN, Attiullah N, Friedman M, Toba C, Boerescu DA, Rahgeb M: Depressed patients' perspectives of 2 measures of outcome: the Quick Inventory of Depressive Symptomatology (QIDS) and the Remission from Depression Questionnaire (RDQ). Ann Clin Psychiatry 2011; 23:208–212
20. Paykel ES: Partial remission, residual symptoms, and relapse in depression. Dialogues Clin Neurosci 2008; 10:431–437
21. Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A: Residual symptoms after partial remission: an important outcome in depression. Psychol Med 1995; 25:1171–1180
22. Ramana R, Paykel ES, Cooper Z, Hayhurst H, Saxty M, Surtees PG: Remission and relapse in major depression: a two-year prospective follow-up study. Psychol Med 1995; 25:1161–1170
23. Nierenberg AA, Husain MM, Trivedi MH, Fava M, Warden D, Wisniewski SR, Miyahara S, Rush AJ: Residual symptoms after remission of major

depressive disorder with citalopram and risk of relapse: a STAR*D report. Psychol Med 2010; 40:41–50
24. Fava GA, Ruini C, Belaise C: The concept of recovery in major depression. Psychol Med 2007; 37:307–317
25. Kennedy N, Abbott R, Paykel ES: Remission and recurrence of depression in the maintenance era: long-term outcome in a Cambridge cohort. Psychol Med 2003; 33:827–838
26. Kennedy N, Abbott R, Paykel ES: Longitudinal syndromal and subsyndromal symptoms after severe depression: 10-year follow-up study. Br J Psychiatry 2004; 184:330–336
27. Kennedy N, Paykel ES: Residual symptoms at remission from depression: impact on long-term outcome. J Affect Disord 2004; 80:135–144
28. Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A: Residual symptoms after partial remission: an important outcome in depression. Psychol Med 1995; 25:1171–1180
29. Keller MB. Long-term treatment of recurrent and chronic depression. J Clin Psychiatry 2001; 62(suppl 24):3–5
30. Prien RF, Klett CJ, Caffey EM Jr: Lithium carbonate and imipramine in prevention of affective episodes: a comparison in recurrent affective illness. Arch Gen Psychiatry 1973; 29:420–425
31. Keller MB: Long-term treatment strategies in affective disorders. Psychopharmacol Bull 2002; 36(Suppl 2):36–48
32. Kaymaz N, van Os J, Loonen AJ, Nolen WA: Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials. J Clin Psychiatry 2008; 69:1423–1436
33. Frank E, Kupfer DJ, Perel JM, Cornes C, Jarrett DB, Mallinger AG, Thase ME, McEachran AB, Grochocinski VJ: Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990; 47:1093–1099
34. Kupfer DJ, Frank E, Perel JM, Cornes C, Mallinger AG, Thase ME, McEachran AB, Grochocinski VJ: Five-year outcome for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1992; 49:769–773
35. Klerman GL, Dimascio A, Weissman M, Prusoff B, Paykel ES: Treatment of depression by drugs and psychotherapy. Am J Psychiatry 1974; 131:186–191
36. Hollon SD, DeRubeis RJ: Placebo-psychotherapy combinations: inappropriate representations of psychotherapy in drug psychotherapy comparative trails. Psychol Bull 1990; 90:467–477
37. Weissman MM, Klerman GL, Paykel ES, Prusoff B, Hanson B: Treatment effects on the social adjustment of depressed patients. Arch Gen Psychiatry 1974; 30:771–778
38. Frank E, Kupfer DJ, Wagner EF, McEachran AB, Cornes C: Efficacy of interpersonal psychotherapy as a maintenance treatment of recurrent depression: contributing factors. Arch Gen Psychiatry 1991; 48:1053–1059
39. Reynolds CF 3rd, Frank E, Perel JM, Imber SD, Cornes C, Miller MD, Mazumdar S, Houck PR, Dew MA, Stack JA, Pollock BG, Kupfer DJ: Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. JAMA 1999; 281:39–45
40. Reynolds CF 3rd, Dew MA, Pollock BG, Mulsant BH, Frank E, Miller MD, Houck PR, Mazumdar S, Butters MA, Stack JA, Schlernitzauer MA, Whyte EM, Gildengers A, Karp J, Lenze E, Szanto K, Bensasi S, Kupfer DJ: Maintenance treatment of major depression in old age. N Engl J Med 2006; 354:1130–1138
41. Carreira K, Miller MD, Frank E, Houck PR, Morse JQ, Dew MA, Butters' MA, Reynolds CF 3rd: A controlled evaluation of monthly maintenance interpersonal psychotherapy in late-life depression with varying levels of cognitive function. Int J Geriatr Psychiatry 2008; 23:1110–1113
42. Jarrett RB, Kraft D, Doyle J, Foster BM, Eaves GG, Silver PC: Preventing recurrent depression using cognitive therapy with and without a continuation phase: a randomized clinical trial. Arch Gen Psychiatry 2001; 58:381–388
43. Klein DN, Santiago NJ, Vivian D, Blalock JA, Kocsis JH, Markowitz JC, McCullough JP Jr, Rush AJ, Trivedi MH, Arnow BA, Dunner DL, Manber R, Rothbaum B, Thase ME, Keitner GI, Miller IW, Keller MB: Cognitive-behavioral analysis system of psychotherapy as a maintenance treatment for chronic depression. J Consult Clin Psychol 2004; 72:681–688
44. Hollon SD, Stewart MO, Strunk D: Enduring effects for cognitive behavior therapy in the treatment of depression and anxiety. Annu Rev Psychol 2006; 57:285–315
45. Kovacs M, Rush AJ, Beck AT, Hollon SD: Depressed outpatients treated with cognitive therapy or pharmacotherapy: a one-year follow-up. Arch Gen Psychiatry 1981; 38:33–39
46. Blackburn IM, Eunson KM, Bishop S: A two-year naturalistic follow-up of depressed patients treated with cognitive therapy, pharmacotherapy and a combination of both. J Affect Disord 1986; 10:67–75
47. Simons AD, Murphy GE, Levine JL, Wetzel RD: Cognitive therapy and pharmacotherapy for depression: sustained improvement over one year. Arch Gen Psychiatry 1986; 43:43–48
48. Evans MD, Hollon SD, DeRubeis RJ, Piasecki JM, Grove WM, Garvey MJ, Tuason VB: Differential relapse following cognitive therapy and pharmacotherapy for depression. Arch Gen Psychiatry 1992; 49:802–808
49. Hollon SD, DeRubeis RJ, Shelton RC, Amsterdam JD, Salomon RM, O'Reardon JP, Lovett ML, Young PR, Haman KL, Freeman BB, Gallop R: Prevention of relapse following cognitive therapy vs medications in moderate to severe depression. Arch Gen Psychiatry 2005; 62:417–422
50. Dobson KS, Hollon SD, Dimidjian S, Schmaling KB, Kohlenberg RJ, Gallop RJ, Rizvi SL, Gollan JK, Dunner DL, Jacobson NS: Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the prevention of relapse and recurrence in major depression. J Consult Clin Psychol 2008; 76:468–477
51. David D, Szentagotai A, Lupu V, Cosman D: Rational emotive behavior therapy, cognitive therapy, and medication in the treatment of major depressive disorder: a randomized clinical trial, posttreatment outcomes, and six-month follow-up. J Clin Psychol 2008; 64:728–746
52. Shea MT, Elkin I, Imber SD, Sotsky SM, Watkins JT, Collins JF, Pilkonis PA, Beckham E, Glass DR, Dolan RT, et al: Findings from the National Institute of Mental Health Treatment of Depression Collaborative Research Program: course of depressive symptoms over follow-up. Arch Gen Psychiatry 1992; 49:782–787
53. Hollon SD: Cognitive and behavior therapy in the treatment and prevention of depression. Depress Anxiety 2011; 28:263–266
54. Fava GA, Rafanelli C, Grandi S, Conti S, Belluardo P: Prevention of recurrent depression with cognitive behavioral therapy: preliminary findings. Arch Gen Psychiatry 1998; 55:816–820
55. Paykel ES, Scott J, Teasdale JD, Johnson AL, Garland A, Moore R, Jenaway A, Cornwall PL, Hayhurst H, Abbott R, Pope M: Prevention of relapse in residual depression by cognitive therapy: a controlled trial. Arch Gen Psychiatry 1999; 56:829–835
56. Paykel ES, Scott J, Cornwall PL, Abbott R, Crane C, Pope M, Johnson AL: Duration of relapse prevention after cognitive therapy in residual depression: follow-up of controlled trial. Psychol Med 2005; 35:59–68
57. Bockting CL, Schene AH, Spinhoven P, Koeter MW, Wouters LF, Huyser J, Kamphuis JH: Preventing relapse/recurrence in recurrent depression with cognitive therapy: a randomized controlled trial. J Consult Clin Psychol 2005; 73:647–657
58. Conradi HJ, de Jonge P, Ormel J: Cognitive-behavioural therapy v. usual care in recurrent depression. Br J Psychiatry 2008; 193:505–506
59. Perlis RH, Nierenberg AA, Alpert JE, Pava J, Matthews JD, Buchin J, Sickinger AH, Fava M: Effects of adding cognitive therapy to fluoxetine dose increase on risk of relapse and residual depressive symptoms in continuation treatment of major depressive disorder. J Clin Psychopharmacol 2002; 22:474–480
60. Wilkinson P, Alder N, Juszczak E, Matthews H, Merritt C, Montgomery H, Howard R, Macdonald A, Jacoby R: A pilot randomised controlled trial of a brief cognitive behavioural group intervention to reduce recurrence rates in late life depression. Int J Geriatr Psychiatry 2009; 24:68–75
61. Teasdale JD, Segal ZV, Williams JMG, Ridgeway VA, Soulsby JM, Lau MA: Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. J Consult Clin Psychol 2000; 68:615–623
62. Ma SH, Teasdale JD: Mindfulness-based cognitive therapy for depression: replication and exploration of differential relapse prevention effects. J Consult Clin Psychol 2004; 72:31–40
63. Kuyken W, Byford S, Taylor RS, Watkins E, Holden E, White K, Barrett B, Byng R, Evans A, Mullan E, Teasdale JD: Mindfulness-based cognitive therapy to prevent relapse in recurrent depression. J Consult Clin Psychol 2008; 76:966–978
64. Garber J, Clarke GN, Weersing VR, Beardslee WR, Brent DA, Gladstone TRG, DeBar LL, Lynch FL, D'Angelo E, Hollon SD, Shamseddeen W, Iyengar S: Prevention of depression in at-risk adolescents: a randomized controlled trial. JAMA 2009; 301:2215–2224
65. Horowitz JL, Garber J, Ciesla JA, Young JF, Mufson L: Prevention of depressive symptoms in adolescents: a randomized trial of cognitive-behavioral and interpersonal prevention programs. J Consult Clin Psychol 2007; 75:693–706
66. Horowitz JL, Garber J: The prevention of depressive symptoms in children and adolescents: a meta-analytic review. J Consult Clin Psychol 2006; 74:401–415
67. Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, Greenberg R, Rifas SL, Sackeim HA: Resistance to antidepressant medications and short-term clinical response to ECT. Am J Psychiatry 1996; 153:985–992
68. Kennedy SH, Milev R, Giacobbe P, Ramasubbu R, Lam RW, Parikh SV, Patten SB, Ravindran AV; Canadian Network for Mood and Anxiety

Treatments (CANMAT): Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults, IV: neurostimulation therapies. J Affect Disord 2009; 117(Suppl 1):S44–S53
69. Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, et al: Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. JAMA 2001; 285: 1299–1307
70. Frederikse M, Petrides G, Kellner C: Continuation and Maintenance Electroconvulsive Therapy for the Treatment of Depressive Illness: A Response to the National Institute for Clinical Excellence Report. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=ovfth&NEWS=N&AN=00124509-200603000-00003.
71. Petrides G, Tobias KG, Kellner CH, Rudorfer MV: Continuation and maintenance electroconvulsive therapy for mood disorders: review of the literature. Neuropsychobiology 2011; 64:129–140
72. Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM, Rasmussen K, Mueller M, Bernstein HJ, O'Connor K, Smith G, Biggs M, Bailine SH, Malur C, Yim E, McClintock S, Sampson S, Fink M: Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). Arch Gen Psychiatry 2006; 63:1337–1344
73. Navarro V, Gasto C, Torres X, Masana G, Penades R, Guarch J, et al Continuation/maintenance treatment with nortriptyline versus combined nortriptyline and ECT in late-life psychotic depression: a two-year randomized study. Am J Geriatr Psychiatry 2008; 16:498–505
74. Markowitz JC: Psychotherapy of dysthymia. Am J Psychiatry 1994; 151: 1114–1121
75. Beck AT, Freeman A, Davis DD: Cognitive Therapy of Personality Disorders, 2nd ed. New York, Guilford Press, 2004.
76. Shelton RC, Osuntokun O, Heinloth AN, Corya SA: Therapeutic options for treatment-resistant depression. CNS Drugs 2010; 24:131–161

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