Evidence-Based Applications of Combination Psychotherapy and Pharmacotherapy for Depression

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Combination treatment with psychotherapy and antidepressant medication can be provided from the initiation of treatment, sequentially after nonremission with a single-modality treatment or sequentially after remission to buttress the patient's recovery to prevent recurrence. Combination treatment from the initiation of care is best reserved for patients with high depression severity. Sequential addition of treatments, particularly psychotherapy after nonremission to antidepressant medication, is the best supported method of combination, improving remission rates and reducing relapse and recurrence in the long term. However, uncertainty persists around the optimal form of psychotherapy to combine with antidepressant medication for maximizing long-term gains. Better outcomes from combination treatment have been strongest in clinical trials that limited pharmacotherapy to a single antidepressant; benefits of combination treatment have been substantially smaller in trials that allowed flexible use of multiple antidepressant classes. Patients with recurrent major depressive disorder who benefit from combination treatment have better long-term outcomes if an active treatment component is maintained during recovery.

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CLINICAL CONTEXT

Depressive disorders are common, disabling, and strongly associated with risk for suicide (1). Patients treated with either antidepressant medication or an evidence-based psychotherapy are equally likely to benefit, on average, from either of these forms of treatment (2). However, for most patients the initial treatment produces inadequate benefit, with only about one-third achieving full remission. Most patients eventually experience recurrent depressive episodes, even when an effective treatment is maintained (1). As awareness of the limitations of single-modality treatments has increased, a growing number of clinical trials have evaluated the value of combinations of psychotherapy and antidepressant medication for achieving better acute and long-term outcomes. Today, all the major treatment guidelines for depression assert that combination treatments are superior to single-modality treatments, at least for some patients (1–7) (Table 1). However, the overall superiority of combination treatments over monotherapy between groups of patients in clinical trials does not imply that all patients with depression require combination treatment to achieve full recovery. Because of its greater cost and inconvenience compared with single-modality treatments, combination treatment is best reserved for those patients likely to benefit from the higher treatment intensity.

Structure of Major Depressive Disorder Treatment

Treatment of major depressive disorder is typically structured into three phases, with three different goals. *Acute phase* treatment, typically six to 12 weeks, is focused on reducing symptoms, improving functioning, and achieving *remission* from the major depressive episode. *Continuation phase* treatment occurs after acute response (preferably remission) has been achieved, and it lasts four to nine months to prevent *relapse* back into the major depressive episode. *Maintenance phase* treatment begins at the end of the combination phase and involves ongoing provision of care or active monitoring of symptoms to prevent *recurrence* of a new major depressive episode (8, 9). In studies where the acute treatment is not followed by a period of continuation treatment, patients who experience subsequent major depressive episodes may be classified under the single outcome of *relapse-recurrence*. Combination treatment with psychotherapy and antidepressant medication can be initiated or continued at any of these three phases of treatment.

Benefits of Combination Treatment

Combination treatment during acute and continuation phases may increase the likelihood of achieving remission, shorten the time required to achieve remission, and enhance adherence to treatment. Potential maintenance phase benefits of combination treatment include reduced risk for depressive recurrence and improvements in role function and quality of life.

Meta-analyses have concluded that the combination of pharmacotherapy with psychotherapy produces small

TABLE 1. Guideline Recommendations for Combination Treatment of Depression

Organization	Source	Summary of Guideline Recommendations
American Psychiatric Association	American Psychiatric Association (1)	Combination treatment is recommended for patients with severe major depressive disorder, and it may be used for patients with mild to moderate depression severity and psychosocial or interpersonal problems, a personality disorder, or intrapsychic conflict. Psychotherapy and antidepressant medication may be used as an initial treatment for patients with moderate to severe major depressive disorder. In addition, combining psychotherapy and medication may be a useful initial treatment even in milder cases for patients with psychosocial or interpersonal problems, intrapsychic conflict, or co-occurring axis II disorder.
British Association for Psychopharmacology	Cleare et al. (3)	Combination of psychological treatment and antidepressant medication may be superior to psychotherapy alone when treating moderate-to-severe major depressive disorder. Combination treatment is more effective than antidepressant treatment alone, most likely on the basis of greater effects among patients with at least moderate depression severity.
Canadian Network for Mood and Anxiety Treatments	Parikh et al. (4)	Combination treatment is superior to either modality alone, with the greatest support for use in special populations, such as elderly patients or women. Sequential addition of cognitive-behavioral therapy (CBT) or interpersonal therapy for patients with partial response to antidepressant medication should be considered. Discontinuing an antidepressant with crossover to CBT, mindfulness-based cognitive therapy, or interpersonal therapy provides relapse prevention that is generally comparable with that achieved with maintenance antidepressant medication.
National Institute for Health and Clinical Excellence	National Institute for Health and Clinical Excellence (5)	A combination of pharmacotherapy and high-intensity psychotherapy (interpersonal therapy, CBT) should be provided for patients with moderate-to-severe depression.
Department of Veterans Affairs and Department of Defense	Management of MDD Working Group (6)	Combination treatment of antidepressant medication and psychotherapy should be used for moderate-to-severe major depressive disorder or as a potential strategy for treating patients who have had partial or nonresponse to monotherapy. Chronic patients can be considered for combination treatment regardless of severity level.
World Federation of Societies for Biological Psychiatry	Bauer et al. (7)	Psychotherapy is recommended in combination with antidepressants for patients with moderate to severe depression and for patients who have had only partial response to antidepressant medications or who have had problems with adherence to antidepressant medications.

effect sizes for improvement over either modality alone (10). Meta-analyses of studies evaluating a broad array of patient samples have found similar small effect sizes in favor of combination treatment over pharmacotherapy alone (11) or psychotherapy alone (12). However, the summary conclusions provided by meta-analyses obscure the variability of effects across studies, which emerge from differences in design features, sample characteristics, and the type of psychotherapy or pharmacotherapy used.

Challenges of Combination Treatment

Beyond the obvious issues of time and cost, perhaps the greatest challenge in providing combination treatment is communication between the psychotherapist and pharmacotherapist. Today, receiving both components of combination treatment by the same clinician occurs only in expensive private practice settings. More commonly the treatment components are split between two clinicians. The ideal of coordinated care between pharmacotherapist and psychotherapist is undermined by crowded schedules and lack of insurance reimbursement for the time required to coordinate treatment. Nevertheless, understanding of the patient's difficulties, appropriate goal-setting, treatment adherence, prevention of defensive splitting, and identification of comorbid psychiatric conditions and medication side effects are enhanced when treating clinicians communicate. Clinicians engaging in split treatment should prioritize communication with each other early in the acute treatment phase and periodically thereafter to maximize the benefits of combination treatment.

An important ongoing uncertainty about combination treatment is identifying the optimal timing of delivery of the treatment components. In general practice, it is probably most often the case that patients receive a single modality of treatment initially, moving on to combination treatment only if they fail to achieve adequate benefit from the initial treatment. The main drawback of this sequential combination strategy is the delay in time to remission compared with combination provided at the beginning of treatment. Both treatment strategies, combination from initiation and combination sequentially, suffer from the uncertainty of knowing whether the patient's improvement is simply due to the effect of a single modality or whether the combination truly provides synergistic effects. This concern is most pronounced during the maintenance phase, when the question of treatment discontinuation arises. When patients have received and benefited from combination treatment, which treatment should be discontinued, if any?

Treatments Used in Combination

Pharmacotherapy treatments used in studies of combination treatment may be a single antidepressant or a medication algorithm that allows switching or combining medications over the acute treatment phase. Antidepressant medication is typically provided via clinical management (CM) visits, typically 20- to 30-minute sessions involving education, support, encouragement of adherence, and monitoring for adverse events (13). Only a few combination trials have used placebo controls in the acute treatment phase. When the control arm of a combination study is treatment as usual, patients may not be required to take medication, the duration and class of pharmacotherapy are not limited, and the structure and frequency of visits with the prescribing clinician are not specified.

Psychotherapy treatments studied in combination trials have most often used a manual-based version of the evidence-based psychotherapies: cognitive-behavioral therapy (CBT), or its variants, or interpersonal therapy (14–18; Table 2). Acute phase psychotherapy may be followed by less frequent continuation sessions of interpersonal therapy or CBT (*continuation cognitive therapy*) to solidify treatment gains and to reach recovery. Several trials have used versions of psychodynamic psychotherapy, which is currently not considered an evidence-based treatment for major depressive disorder (19). Few combination trials have used a comparator form of psychotherapy; when included, it has most often been a form of supportive therapy or education. Therapist experience and adherence to the treatment manual, as well as the number of sessions of therapy delivered, are major variables of concern across trials (20).

In the past 15 years, *third-wave* cognitive and behavior therapies have gained increasing traction as treatments for depressive disorders. Third-wave therapies include a diverse array of approaches that go beyond traditional directive and didactic interventions to incorporate change strategies emphasizing contextual and experiential processes (21). Included among third-wave therapies are mindfulness-based cognitive therapy (MBCT), dialectical behavior therapy, acceptance and commitment therapy, as well as others. Of these, MBCT has been the most extensively studied as a modality of treatment for major depressive disorder, primarily for the purpose of reducing relapse-recurrence risk among patients in remission. A standard course of MBCT involves eight 2.0- to 2.5-hour weekly sessions delivered by a therapist in groups of up to 12 patients.

COMBINATION TREATMENT FROM INITIATION OF CARE

Several large trials have compared the combination of antidepressant medication and psychotherapy from the beginning of treatment versus one or both of the components provided as a single-modality treatment. The greatest emphasis has been on assessing combination treatment among patients with chronic forms of depression because chronicity is often associated with poorer clinical outcomes (1). Results of these trials have been mixed, and conclusions about the value of combination treatment can only be tentative because of variations in design features across the trials.

Combination treatment may be superior to each component alone through either additive or synergistic effects. Additive effects simply reflect the possibility that certain patients can specifically respond to only one form of treatment (antidepressant medication or psychotherapy). In the synergistic model, benefits that can be obtained only when both treatments are present drive the greater benefit of combination treatment. For example, the relatively rapid antidepressant effects of medication may allow for greater patient engagement with the work of psychotherapy; alternatively, provision of psychotherapy may prevent dropout and may increase medication adherence compared with medication provided without psychotherapy (22). Furthermore, patients who experience only partial remission (i.e., obtain improvement but have residual symptoms) with one treatment may need the mechanisms activated by the alternative treatment to achieve full remission (23, 24).

CBT With Antidepressant Medication

The first study evaluating cognitive therapy combined with an antidepressant versus an antidepressant alone from the beginning of treatment found a large effect in favor of combination treatment among treatment completers, although the very poor response to the tricyclic antidepressants used and inconsistent effects across study sites presaged the challenges that would face future studies of combination treatments (25). Also foreshadowing findings from subsequent studies, the two-year naturalistic follow-up of these patients found greater relapse-recurrence rates among patients treated with medication alone versus cognitive therapy (26). Subsequent small-to-moderate-sized studies generally found similar, although more modest, benefits for combination (27, 28).

Since these early findings, two large randomized trials have specifically evaluated the combination of a CBT-related therapy with antidepressant medication for patients with chronic forms of major depressive disorder. The most influential of these studies compared the cognitive-behavioral analysis system of psychotherapy (CBASP) and nefazodone (a serotonin type 2 receptor antagonist), each separately or in combination, among adults with a chronic major depressive episode or current major depressive episode with chronic depressive symptoms (29). In total, 681 patients were randomly assigned to one of the three treatment arms for a 12-week acute treatment phase. Responders to acute treatment entered a 16-week continuation phase (30), with sustained responders eligible to enter a one-year maintenance phase in which patients were randomly assigned to receive continued active treatment or placebo-observation only (31, 32). Furthermore, nonresponders to one of the monotherapy arms after acute treatment could be switched to the alternative monotherapy, with responders eligible to enter the continuation and maintenance phases (33). Combination treatment in this study emerged as clearly superior

TABLE 2. Psychotherapy Treatments Used in Combination Treatment Studies

Therapy Type	Source	Brief Description	Structure
Cognitive therapy and cognitive-behavioral therapy	Beck et al. (14)	Cognitive therapy targets dysfunctional beliefs or cognitions believed to contribute to depression and risk for future depressive episodes. Cognitive therapy uses methods of challenging automatic thoughts that reinforce depressed mood, with the aim of changing the underlying beliefs that negatively bias attention and thought processes. Behavioral components focus on the relationship between activity and mood, encouraging engagement in behaviors and contexts that are reinforcing and consistent with the patient's long-term goals. Activation strategies used include self-monitoring, scheduling daily activities, rating pleasure and accomplishment with activities, and role-playing.	16–24 individual 1-hour sessions
Cognitive-behavioral analysis system of psychotherapy (CBASP)	McCullough (15)	CBASP was developed specifically for chronic forms of depression that integrate behavioral, cognitive, interpersonal, and psychodynamic elements. CBASP uses situational analysis to identify recent, distressing, interpersonal events with the aim of improving social problem-solving skills and changing patterns of coping.	16–20 individual 1-hour sessions
Interpersonal psychotherapy	Klerman et al. (16)	Interpersonal psychotherapy links depressed mood to a problematic life event, such as complicated bereavement, role transition, or role dispute, or to more general interpersonal deficits. Expression and understanding of affect within the therapeutic alliance are pursued, along with analysis of the patient's communication patterns.	12–20 individual 1-hour sessions
Mindfulness-based cognitive therapy	Segal et al. (17)	This skills-training program integrates traditional cognitive-behavioral therapy techniques with mindfulness-based stress reduction; its aim is to reduce the likelihood of depressive relapse through changing the way patients relate to their thoughts, feelings, and bodily sensations—specifically how to break free from automatic, often ruminative, dysfunctional cognitive routines.	Eight group 2.50-hour sessions
Short psychodynamic supportive psychotherapy	de Jonhge (18)	This psychodynamic approach focuses initially on interpersonal aspects with subsequent focus on an intrapersonal perspective examining internalizations of relevant former relationships. Interventions vary from supportive mechanisms to enhancing insight as well as exploring affects and confrontation.	16 individual 1-hour sessions

to either treatment alone, with no significant difference in remission rates between the monotherapy arms (combination=48%, nefazodone=29%, CBASP=33%; $p<.001$).

In a second, more recent, large trial using traditional cognitive therapy, the combination of cognitive therapy with antidepressant medication versus medication alone from the beginning of treatment did not produce significantly higher remission rates (63% vs. 60%, respectively) after one year of treatment among 452 adults with chronic or recurrent major depressive disorder (34). This trial was remarkable in that cognitive therapy was provided weekly until a four-week period of remission was achieved, and the therapy could continue for up to 19 months. Applying a nonstandard definition of recovery (partial or full remission sustained for 30 weeks), resulted in a 10% higher recovery rate in the combination arm compared with medication alone (72.6% vs. 62.5%, respectively; p=.01). Addition of cognitive therapy had a significant impact on recovery rates among patients with greater depressive symptom severity (73% vs. 54%, respectively; p=.001) or with nonchronic episodes (77% vs. 59%, respectively; p=.001). However, among the patients with a chronic current depressive episode, recovery rates were actually lower in combination than medication alone, although the difference was not statistically significant (63% vs. 70%, respectively; p=.28).

A key difference between these studies that may explain the discrepant outcomes is the form of antidepressant medication used. In the second study, the pharmacotherapy was more reflective of real-world practice, allowing switching and augmentation strategies, whereas the earlier study applied only one medication: nefazodone. After six weeks of treatment, the symptom-reducing effects of nefazodone approached a plateau—an effect that has been observed in another trial using nefazodone in combination with interpersonal therapy (35) and in a study of nefazodone for posttraumatic stress disorder (36).

The strongly positive effect of combination treatment with CBASP on remission was not replicated in two subsequent studies of chronic forms of major depressive disorder (37, 38), both of which permitted flexible antidepressant medication treatment using multiple antidepressants. Although CBASP was developed specifically to target chronic

depression, CBASP has not been directly compared as a single intervention against an active control psychotherapy among patients not receiving antidepressant medication (although see the discussion of the Research Evaluating the Value of Augmenting Medication With Psychotherapy [REVAMP] study below). This open question will be informed by forthcoming results from a recently concluded trial in Germany that compared CBASP and a supportive psychotherapy among adults with early-onset chronic depression (39).

Interpersonal Therapy With Antidepressant Medication

Combining interpersonal therapy with antidepressant medication from the beginning of treatment has been examined more frequently than CBT combinations. A meta-analysis of ten studies of interpersonal therapy alone versus interpersonal therapy with medication found a small, nonsignificant effect in favor of combination treatment on acute outcomes of depressive symptoms among patients with major depressive disorder, dysthymia, or double depression (40). The original combination trial of interpersonal therapy and amitriptyline versus either component alone or placebo suggested superior antidepressant effects of the combination among outpatients (41), but few subsequent trials have demonstrated significant acute phase benefits of interpersonal therapy in combination with medication. One large trial conducted in the Netherlands found that 12–16 weeks of interpersonal therapy combined with nefazodone significantly increased remission rates over nefazodone alone (remission odds ratio=3.22, 95% confidence interval=1.02–10.12, p=.045), but not interpersonal therapy alone (35). In studies of dysthymia, interpersonal therapy in addition to medication has not proven to be of benefit (42).

Several trials have examined interpersonal therapy combination treatments, specifically among patients experiencing interpersonal challenges. In a small randomized trial, patients with major depressive disorder and borderline personality disorder did not achieve greater remission rates after six months of combined treatment with interpersonal therapy and fluoxetine versus fluoxetine alone (75% vs. 63%, respectively; p=.45), although mean depressive symptoms were lower and interpersonal functioning was higher after combined treatment among patients who completed the study (43). Among patients 50 years of age or older who had suffered a recent bereavement-related major depressive episode, combining interpersonal therapy with nortriptyline produced numerically higher remission rates after 16 weeks of treatment compared with nortriptyline with CM, interpersonal therapy with placebo, or placebo with CM (69%, 56%, 29%, and 45%, respectively); however, the advantage of combination over nortriptyline with CM did not reach statistical significance (44).

Interpersonal therapy was also examined in a large trial of patients with coronary artery disease and major depressive disorder; these patients often experience life challenges in the wake of their medical illness that may map well onto interpersonal therapy interventions. However, combination treatment of interpersonal therapy with citalopram was not superior to citalopram with CM, and interpersonal therapy with placebo was not superior to placebo with CM (45). The authors suggested that patients with coronary artery disease and low levels of social support or poor functioning may become overwhelmed by the challenge of addressing both cardiac care needs and interpersonal issues and that less burdensome supportive therapy may be a better option for such patients (45).

In contrast to the outpatient studies showing little or no benefit from combination treatment, substantial short-term benefits of combining medication with interpersonal therapy versus medication with CM were observed among hospitalized German patients with major depressive disorder (46). Using a version of interpersonal therapy modified for inpatient settings (15 individual and eight group sessions over five weeks), significantly higher response rates with combined treatment (70% vs. 51%, respectively; p=.043) and nonsignificantly higher remission rates (49% vs. 34%, respectively; p=.105) were observed. Unfortunately, these impressive results have limited generalizability to health care systems in which lengths of inpatient hospitalization are much shorter.

Psychodynamic Psychotherapy With Antidepressant Medication

Brief psychodynamic psychotherapy treatments have demonstrated inconsistent results when combined with medication, in part because of differences in trial designs and differing emphases in the therapeutic approach. Short psychodynamic supportive psychotherapy, which may be considered a psychodynamically informed supportive therapy, emphasizes supportive components without challenging psychological defenses or interpreting transference. Two large trials of this therapy (provided as 16 sessions over 24 weeks), enrolling primarily patients with nonchronic major depressive disorder, found that combination treatment was significantly superior to an antidepressant alone (remission rates: 37% vs. 16%, respectively; $p<.01$) (47), but combination treatment was not significantly superior to short psychodynamic supportive psychotherapy alone (remission rates: 42% vs. 32%, respectively; p=.14) (48). The patients in these studies appeared to strongly prefer psychotherapy because 32% of the patients refused assignment to medication alone in the first trial, and 16% of the patients refused assignment to the medication plus psychotherapy arm in the second trial. In contrast to the findings from these studies, 15–30 sessions of brief dynamic therapy, which emphasizes interpretation and clarification of transference relationships, did not improve remission rates when combined with a selective serotonin reuptake inhibitor (SSRI) compared with an SSRI alone (64% vs. 61%, respectively) among adults with nonrecurrent major depressive disorder treated for six months (49).

Benefits of Acute-Phase Combination Treatment

Speed of response. A theorized benefit of combination treatment is that patients will recover more quickly than with a single treatment intervention, which may be particularly important for patients with strong suicidal ideation or severe role dysfunction. An early mega-analysis of studies that compared combining interpersonal therapy with medication versus psychotherapy alone (either interpersonal therapy or CBT) concluded that for patients with mild depression, time to sustained remission recovery did not differ; however, among patients with more severe depression, psychotherapy alone was significantly slower to generate a response compared with combination treatment (50). More recent studies have produced inconsistent results, with some studies finding that combination treatment reduced depressive symptoms significantly more quickly than medication alone or psychotherapy alone (47, 51), whereas other studies have not found such results (34, 35, 48). In a trial in which patients could choose psychotherapy alone or in combination with an antidepressant, more rapid improvement occurred among patients receiving cognitive therapy alone than those receiving treatment combining cognitive therapy with medication (52). Presumably, this paradoxical result arose from patient-level factors (e.g., severity, functioning, locus of control, comorbid conditions) that informed their treatment choices.

Sustained benefits after initiation of combination treatment. Two kinds of follow-up studies have examined the enduring effects of combination treatment provided from the initiation of treatment: (a) naturalistic studies in which patients are free to pursue additional treatments of their choosing, with evaluation of psychiatric status at set intervals, and (b) experimental studies evaluating a continuation or maintenance phase of an active treatment compared with observation-only or placebo maintenance.

Naturalistic follow-up studies have found sustained benefits among patients randomly assigned to receive combination treatment compared with medication alone, whether the psychotherapy was CBT (27, 53) or psychodynamic (49). Long-term follow-up of inpatients who received five weeks of modified interpersonal therapy with medication found significantly lower relapse rates during the three months after hospital discharge in the combination treatment group (3% vs. 25%, respectively; p=.008) (46). At 12 months postdischarge, the relapse rate was still lower, nonsignificantly, in the combination treatment group (13% vs. 29%, respectively; p=.21); however, among people in remission receiving acute phase treatment, the protection of combination treatment against recurrence rate was significant (7% vs. 32%, respectively; p=.049) (46). After five years of naturalistic follow-up, the proportion of patients free of recurrence remained higher among the patients receiving combination treatment (28% vs. 11%, respectively; p=.032) (54).

The influential study combining nefazodone with CBASP included two parallel maintenance phase comparisons. Among patients who responded to acute and continuation phase treatment with psychotherapy plus nefazodone or with nefazodone alone, assignment to continued nefazodone or switch to placebo during a one-year maintenance phase demonstrated the importance of maintaining the medication to prevent recurrence (recurrence rates: placebo=48%, nefazodone=30%; p=.043) (31). Having received CBASP during the acute treatment phase did not provide additional protection against recurrence in either the nefazodone or placebo treatment arms. Among patients who responded to acute and continuation phase CBASP alone (either as an initial monotherapy or after not responding to nefazodone with subsequent switch to CBASP), patients randomly assigned to receive up to 13 therapy booster sessions during the one-year maintenance had lower rates of recurrence than those randomly assigned to observation only (recurrence rates: maintenance psychotherapy=11%, observation=32%; $p<.05$) (32). However, because this study did not randomize the patients who responded to combined treatment in the acute phase to maintenance treatment with either nefazodone or psychotherapy, the relative importance of these two active components in preventing recurrence could not be determined.

Three large, well-conducted trials have evaluated the relative contribution of continuation treatments in preventing recurrence among patients who achieved recovery after acute and continuation phase treatment with the combination of interpersonal therapy and medication. These trials demonstrated that maintenance phase antidepressant medication was as effective overall in preventing recurrence as combining maintenance medication with monthly interpersonal therapy sessions over two to three years of follow-up. These results held true in a general adult population (with imipramine as the antidepressant) (55) and in trials of adults >60 years (nortriptyline) (44) and ≥70 years of age (paroxetine) (56). In contrast, maintenance interpersonal therapy, either alone or with placebo, was inferior in preventing recurrence compared with maintenance medication. Recurrence rates among patients randomly assigned to placebo with CM ranged from 58% to 90%, indicating poor preventive effects of acute combination treatment in the absence of an active maintenance treatment. The benefits of medication in these trials in the elderly populations are particularly remarkable because these antidepressants would generally be considered third-line or later treatment options in practice today because of their adverse cardiac, anticholinergic, and abrupt discontinuation effects.

Summary of Combination Treatment From Initiation of Therapy

Despite the size and importance of the study combining nefazodone with CBASP (29), the overall picture suggests that an absolute improvement in acute phase remission rates of about 10% occurs with combination treatment over single-modality treatment. Other than the trials evaluating short supportive dynamic psychotherapy (47,48), which may have

had significant selection bias, the trials that showed the greatest benefit for combination treatment both used nefazodone as the antidepressant, which is not representative of the flexible medication management of clinical practice. The maintenance phase data after acute and continuation phase combination treatment strongly indicate the need to continue to provide at least one of the two components during maintenance, with some suggestion that maintenance medication provides greater protection against relapse than maintenance phase interpersonal therapy alone.

An important caveat for trials evaluating long-term outcomes between patients who received differing acute phase treatments is the *differential sieve* effect (57). This effect emerges if, by the end of the acute or continuation treatment phase, one treatment arm has been able to push into remission a greater proportion of patients who are harder to treat and if those same patients carry a greater vulnerability to depressive recurrence. In this case, recurrence may be more frequent in the treatment arm that was most effective in the acute phase because that arm contains a greater proportion of patients who are sicker. This differential sieve has the effect of diminishing the apparent durability of the more efficacious acute phase treatment (58).

SEQUENTIAL COMBINATION TREATMENTS IN THE ACUTE PHASE

Sequencing treatments requires initially selecting a single-modality treatment. Given that acute treatment with CBT or antidepressant medication is equally likely to be effective for most patients (22, 59), the choice of treatment may be driven by patient preference and other practical factors. The specific form of any added second treatment will depend on the patient status at the end of monotherapy. Specifically, the second treatment can be designed to address a lack of response to the initial treatment (i.e., patient still in a full major depressive episode), residual symptoms after improvement with initial treatment, or prevention of relapse and recurrence.

Despite the large number of studies examining sequential treatment of depression, the variety of designs used limits clear interpretation of the results. Some trials have compared an active second intervention, typically psychotherapy, with treatment as usual, in which patients may or may not adjust their mental health treatments on the basis of their preferences and clinician's recommendations. Treatment-as-usual designs are relatively easy to implement, but treatment as usual is a weak comparator arm for sequential treatment combination studies because a significant percentage of patients may not be receiving an active treatment of any kind (38, 60). Moreover, treatment-as-usual comparisons carry a significant bias in favor of finding efficacy of the added treatment because of placebo responses. Specifically, because blinding of patients in such designs is not possible, patients randomly assigned to treatment as usual may experience demoralization effects of not getting the desired treatment, whereas those in the active condition have greater interaction with mental health professionals, with consequent mobilization of known placebo effects. In medication-augmentation trials, improvement after open-label addition of a second medication is not considered adequate evidence for a specific beneficial effect of the medication because improvement may derive from nonspecific benefits of attention, support, and mobilization of hope (61). However, it is also possible for treatment-as-usual designs to bias results toward finding no benefit from an additional treatment because in both groups other treatments are not controlled, modifications of which may have greater effects on outcomes than the active intervention. Stronger sequential treatment designs involve randomization to two intervention arms in which patients can have reasonably similar expectations of gaining benefits.

Another important caveat for results of sequential treatment studies is their risk for bias arising from participant selection factors. Specifically, when all trial participants receive a specific initial treatment modality (whether medication or psychotherapy), the trial may experience selection bias, enrolling patients who are specifically seeking the initial treatment modality (or, alternatively, who strongly dislike an alternative). Another limitation of sequential treatment strategies is that patients may refuse to enter the second (sequential) phase of treatment. In a study of 141 patients with mild to moderate major depressive disorder who were initially randomly assigned to short-term supportive psychodynamic therapy or antidepressant treatment, those with <30% improvement (by the Hamilton Depression Rating Scale) by the eighth week of treatment were offered the alternative treatment (62). Of the 63.6% of the patients who showed inadequate improvement, nearly 40% of the patients refused the additional treatment (62). Similarly, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, 71% of patients not in remission with citalopram monotherapy were not willing to be considered for possible randomization to CBT (63). Reasons for patients being unwilling to receive additional treatment are unknown but may include time burdens, demoralization from lack of improvement with initial treatment, or sufficient satisfaction with partial improvement that reduces motivation to pursue additional treatment to achieve full remission.

Sequential Combination After Nonresponse to Monotherapy

Most studies evaluating sequential combination treatment among patients failing to respond to a monotherapy have tested the addition of psychotherapy after antidepressant medication. It is surprising that so few studies have examined addition of an antidepressant after poor response to psychotherapy, given that most patients prefer psychotherapy to antidepressant medication (64). Furthermore, many patients in clinical care initally receive psychotherapy, albeit often of limited duration or supportive rather than evidence-based

(65, 66). The potential value of sequential addition of an antidepressant for poor responders to psychotherapy is suggested from a study of women with recurrent major depressive disorder treated for up to 24 weeks with interpersonal therapy. Among 86 women who received interpersonal therapy alone and who either failed to respond by week 12 or failed to remit by week 24, addition of an open-label SSRI to ongoing interpersonal therapy produced remission in 67% of the women (67). Unfortunately, no large randomized trials have compared addition of an antidepressant versus placebo among psychotherapy nonresponders, which would be necessary to quantify the specific benefit of antidepressants in this form of sequential combination treatment.

The largest randomized trial to examine the value of sequential treatments was REVAMP, in which 808 patients with chronic forms of major depression all received an initial 12-week course in phase 1 of algorithm-guided medication management. Patients not in remission by week 12 (N=491) were randomly assigned in phase 2 to another 12 weeks of treatment in one of three arms: antidepressant medication with further algorithm-guided adjustments, continued phase 1 medication plus 16 sessions of CBASP, or continued phase 1 medication plus 16 sessions of brief supportive psychotherapy (37). The three treatments did not significantly differ in efficacy, achieving similar remission rates (medication only, 40%; CBASP, 39%; brief supportive therapy, 31%). The degree of improvement from phase 1 medication (partial response vs. nonresponse) did not moderate the degree of benefit derived from each of the three treatments (37). A similar lack of difference between adding cognitive therapy versus augmenting with a second medication was found in the STAR*D trial, in which people not in remission who completed 12–14 weeks of citalopram in step 1 were randomly assigned to second-step treatments. Patients in step 2 who received cognitive therapy added to citalopram had nonsignificantly lower remission rates than the patients who received buspirone or bupropion augmentation of citalopram (23% vs. 33%, respectively; p=.19) (68).

In contrast, studies evaluating psychotherapy added to treatment as usual have generally found benefits for combination treatment. The CoBalT study enrolled 469 routine clinical care patients who continued to meet full major depressive episode criteria despite having received an adequate course of antidepressant medication treatment (69). Assignment to 12 sessions of CBT in addition to treatment as usual provided better short-term and long-term outcomes compared with treatment as usual alone. Patients receiving CBT had a response rate (on the basis of a 50% score reduction on the self-rated Beck Depression Inventory–II [BDI-II]; 70) more than double that of the treatment as usual group after six months (46% vs. 22%, respectively; $p<.001$). Self-reported remission rates (BDI-II<10) were also superior in the CBT group (28% vs. 15%, respectively; $p<.001$). At one-year posttreatment follow-up, remission rates continued to improve in the CBT group but did so only minimally in the treatment-as-usual group (40% vs. 18%, respectively; $p<.001$) (69). In a smaller trial of 106 patients with chronic depression, addition of eight 2.5-hour sessions of group-based CBASP to treatment as usual produced superior remission rates to treatment as usual alone (26% vs. 6%, respectively; p=.02) (70). Another trial found that MBCT combined with treatment as usual was not statistically superior to treatment as usual for remission (17% vs. 6%, respectively; p=.15), and was inferior to combining CBASP with treatment as usual on overall depressive symptoms (71). Finally, a randomized trial of individually delivered CBASP (provided as 24 sessions over one year) added sequentially to treatment as usual found only small benefits over treatment as usual alone among 139 clinical care adults with chronic forms of major depressive disorder (38). Although the reduction in depressive symptoms at week 52 was significantly greater in the CBASP group, remission rates were low and not statistically superior to the treatment-as-usual group (19% vs. 10%, respectively; p=.11) (38).

A sequential treatment strategy that is not truly a form of combination treatment is switching to, instead of adding, a second form of treatment. A patient's ability to respond specifically to psychotherapy or medication may depend on his or her pretreatment brain activity state (23, 24), which implies that failure to benefit from one treatment modality should lead to strong consideration for initiating the alternative form of treatment. In this approach, learning obtained from initial psychotherapy may persist and continue to be applied by patients during subsequent treatment, but medication effects are not believed to be sustained. In the study combining nefazodone with CBASP described above (29), 140 nonresponders to an initial 12-week monotherapy treatment with nefazodone or CBASP were switched to receive the alternative treatment. Remission rates after 12 weeks with the second treatment were numerically, but not statistically, superior among patients switched from nefazodone to CBASP than vice versa (36% vs. 27%, respectively; p=.11), demonstrating that maintenance of the initial treatment is not always necessary after nonresponse, and therefore switching, as opposed to combining, can be a rational strategy (33). In step 2 of STAR*D, patients not in remission after 12–14 weeks of citalopram who were switched to CBT achieved a 31% remission rate; this outcome did not significantly differ from the 27% rate achieved among those who switched to another antidepressant (68).

Sequential Combination to Address Residual Symptoms After Monotherapy

The importance of residual symptoms after acute treatment as a potent predictor of eventual return of full-syndrome major depressive episode is one of the most robust findings in depression research (72–74). Patients who improve after acute treatment but who have persisting subthreshold symptoms of major depressive disorder carry a significant risk of relapse and recurrence, whether the initial treatment was medication (31, 75) or CBT (32, 76, 77). These data have led to great interest in applying combination treatments to achieve full remission (1). The long-term protective effect of

combination treatments has proven to be greatest among those patients with the highest risk of recurrence, with the two most important risk factors being the level of residual symptoms after acute or continuation phase treatment and the number of prior major depressive episodes.

Most trials targeting residual symptoms have added psychotherapy to patients previously treated with an antidepressant medication. An early randomized study found that among 40 patients who improved but had residual symptoms after three to five months of medication, the addition of ten sessions of CBT administered over 20 weeks reduced residual symptoms significantly more than a similar number of sessions of CM (75). After the ten sessions, all patients were tapered off their antidepressant. During subsequent follow-up, patients who had received CBT had lower rates of recurrence, although by six years, 50% of the CBT group and 75% of the CM group had experienced recurrence (78, 79). These results were supported by subsequent larger trials. Sixteen sessions of cognitive therapy combined with five monthly sessions of CM delivered over 20 weeks was superior to CM alone among patients with residual symptoms despite at least eight weeks of antidepressant medication (80). Though relatively few patients in this trial achieved remission after 20 weeks (cognitive therapy and CM, 24%; CM alone, 11%; p=.03), the cognitive therapy combined with CM group experienced a significantly lower rate of relapse-recurrence than the CM group during the one-year follow-up (29% vs. 47%, respectively; p=.02), despite all patients being maintained on an antidepressant through this phase (80). In contrast to these results, phase 1 partial responders to 12 weeks of antidepressant medication in the large REVAMP trial showed no meaningful benefits in phase 2 from the addition of CBASP or brief supportive therapy to continued medication compared with 12 weeks of algorithm-guided medication alone (37). The REVAMP trial differed from other sequential trials in that enrollment was limited to patients with chronic forms of major depressive disorder, and it included an active psychotherapy as a comparator.

Two large trials have also found that combining MBCT with treatment as usual for patients with residual symptoms of major depressive disorder reduced levels of depressive symptoms compared with treatment as usual alone (81, 82) and that these gains were still present after 12-month follow-up (82). However, in both trials, half or fewer of the patients were taking an antidepressant medication, limiting interpretation of the value of MBCT as a combination treatment for residual depressive symptoms.

Although adding antidepressant medication to address residual symptoms after psychotherapy may appear to be a poorly supported treatment on the basis of analyses finding minimal antidepressant efficacy over placebo among patients who were mildly ill in clinical trials (83, 84), other analyses have suggested that antidepressants are effective for mild depressive symptoms (85, 86). Unfortunately, the efficacy of sequential addition of medication after nonremission to psychotherapy has received little empirical evaluation, but limited data suggest this form of combination treatment may have value. In a unique trial design, patients who achieved an unstable remission and who were considered to carry a significantly higher risk for relapse after 16–20 sessions of cognitive therapy were randomly assigned to (a) eight months of continuation cognitive therapy (ten 1-hour cognitive therapy sessions targeting relapse prevention over eight months), (b) initiation of fluoxetine 40 mg/day, or (c) placebo (87). Remission rates at the end of this continuation phase were nearly identical in the continuation cognitive therapy and fluoxetine groups, and both were higher than placebo (72%, 71%, and 58%, respectively; p=.13) (87). In another large trial, a similarly high remission rate of 67% was observed among women who did not remit with up to 24 weeks of interpersonal therapy who subsequently then received addition of an SSRI to ongoing interpersonal therapy sessions. Among those who remitted after 17 weeks of continuation treatment with interpersonal therapy plus SSRI, the SSRI was discontinued with a taper, and patients were followed for two years while receiving maintenance interpersonal therapy sessions (67). Recurrence rates among these patients were significantly higher during follow-up than among those who were in remission with interpersonal therapy alone (SSRI plus interpersonal therapy with subsequent SSRI tapering: 50%; interpersonal therapy alone: 26%) (67). These data again point to the need to sustain maintenance treatments among patients at high risk of recurrence.

Symptom-Targeted Combination Treatments

Among patients who respond to initial treatment but who have specific residual symptoms, an added treatment that targets the specific symptoms may prove to be an efficacious combination treatment.

Insomnia. Sleep disturbance, particularly insomnia, is a depressive symptom that frequently persists even after improvements in the core depressive symptoms of mood, interest, and energy (88, 89). Persistence of insomnia after depression improvement may increase the risk for relapse (90, 91), and cotreatment with a sedative-hypnotic and an antidepressant increases remission rates compared with an antidepressant plus placebo (92). Data from small trials indicate that CBT for insomnia combined with antidepressant medication improves remission rates among patients with major depressive disorder and prominent insomnia, both when the CBT is started at the beginning of medication treatment (93) and as a sequential treatment added to medication for residual insomnia (94, 95). Large ongoing trials (ACTRN12611000121965; NCT00620789) will soon provide greater clarity about the value of CBT for insomnia when CBT is used as a component of combination treatment for major depressive disorder.

Anxiety. Greater intensity or number of anxiety symptoms during major depressive episodes is strongly associated with persistence of depressive symptoms (96). Among patients

with chronic depression and high levels of depressive symptoms, high levels of anxiety reduce treatment efficacy, with no meaningful improvement in remission rates from combination treatment of nefazodone with CBASP over monotherapy treatment (51). However, among patients with major depressive disorder and a diagnosed comorbid anxiety disorder, combination treatment may provide greater symptom reduction compared with CBASP alone (97). Given the high prevalence of anxiety disorders among patients with major depressive disorder, there may be value in combination treatment strategies that specifically target the anxiety disorder after acute treatment of the depressive episode. An example of such a combination could be addition of an exposure-based psychotherapy for fear disorders (e.g., posttraumatic stress disorder, panic disorder, social anxiety disorder) after initial medication treatment for depression. Alternatively, patients successfully treated with an evidence-based treatment for major depressive disorder who have ongoing anxiety that is not responsive to psychotherapeutic interventions may benefit from addition of an anxiolytic medication (98). Unfortunately, controlled data that would inform the value of these common clinical problems are lacking.

COMBINATION TREATMENTS TO PREVENT RELAPSE AND RECURRENCE

Maintenance antidepressant medication has well-established superiority over placebo for preventing future depressive episodes among patients with recurrent major depressive disorder who have responded to acute and continuation phase medication, with reduction in absolute risk of recurrence by about 20% over 12–24 months (99–101). Other data support the prophylactic value of ongoing psychotherapy among acute phase responders to interpersonal therapy or CBT (77, 102, 103). Patients in remission who complete acute phase CBT alone demonstrate greater protection against recurrence than patients in remission who took acute phase antidepressant medication if the medication discontinued during follow-up (104). In contrast, acute phase CBT is not significantly better in preventing recurrence if the acute phase antidepressant is continued during recovery (105). Despite the enduring effect of psychotherapy, relapse-recurrence rates of 40%−50% within two years of achieving remission occur among responders to acute CBT or medication if maintenance treatments are not instituted (77, 99, 100, 102). Thus, continuation and maintenance treatments are indicated for patients with major depressive disorder at risk of recurrence, regardless of the form of beneficial acute treatment.

Sequential addition of psychotherapy to prevent depressive relapse-recurrence after response to antidepressant medication has been the focus of many studies, all of which have evaluated CBT or its related variants. A meta-analysis of 13 studies that added CBT or a related psychotherapy to patients who responded to acute phase antidepressant medication concluded that addition of psychotherapy produced an absolute reduction of relapse-recurrence risk by 22% (106). Additional psychotherapy was most effective in trials in which the medication was discontinued during follow-up (33% absolute risk reduction), but it also provided protection when patients were maintained on medication (19% absolute risk reduction) (106).

The protective value against relapse-recurrence of adding MBCT for patients in remission receiving treatment as usual has emerged primarily among patients with recurrent (≥3 episodes) major depressive disorder. Compared with treatment as usual, MBCT reduced relapse rates by 5%−42% over 12–24 months of follow-up, along with consistently longer times to relapse, compared with treatment as usual (82, 107–111). Similarly, eight sessions of group CBT added to treatment as usual (112, 113) or 16 sessions of individual CBT (114) significantly reduced relapse-recurrence rates among patients highly likely to experience recurrence (≥5 lifetime episodes) during long-term follow-up, with no benefits for patients having fewer than five lifetime episodes. Only one of these trials demonstrated specific prophylactic effects of CBT versus an active control condition (psychoeducation) among patients with highly recurrent major depressive disorder (114). As part of treatment as usual, patients in these trials could continue or discontinue their antidepressant medication under the guidance of their prescribing clinician, typically with 30%−60% of patients in these trials not taking or discontinuing an antidepressant.

In one trial that required maintenance antidepressant medication for all participants, MBCT added to medication did not reduce relapse-recurrence risk over 15 months of follow-up versus maintenance medication alone (115). Other randomized trials have found MBCT with antidepressant tapering to be equivalent to maintenance medication without psychotherapy in protection against depressive recurrence (116, 117). MBCT with antidepressant tapering was superior to placebo substitution for medication among patients with unstable remission, but it was not superior among those patients with fully asymptomatic remission (116). An important limitation of all these trials is that they did not include a comparative psychotherapy arm, so the specificity of the MBCT components in protecting against recurrence could not be distinguished from the nonspecific effects resulting from being in psychotherapy. Importantly, recent randomized trials that compared patients who were fully or partially in remission and who were randomly assigned to MBCT or to a credible active psychotherapy control condition have not found a specific prophylactic effect against relapse-recurrence that can be attributed to MBCT (118–120).

The previously described trial that evaluated continuation phase treatment with continuation cognitive therapy, fluoxetine, or placebo among people in unstable remission after acute phase cognitive therapy also evaluated relapse-recurrence rates with these treatments (77). Not surprising, dropout in the fluoxetine and placebo arms was much higher

during the first month of continuation treatment compared with the continuation cognitive therapy arm. Nevertheless, during the eight-month continuation phase, both continuation cognitive therapy and fluoxetine reduced estimated relapse rates compared with placebo (18% for fluoxetine or continuation cognitive therapy vs. 33% for placebo; p=.01). All treatments were then discontinued for a 24-month follow-up period. Across the entire 32 months following completion of acute phase cognitive therapy, relapse recurrence rates were not significantly different across the treatment arms (continuation cognitive therapy=45%, fluoxetine=41%, placebo=56%) (77). Although in routine clinical practice it is unlikely that many patients who have improved with cognitive therapy will want to start an antidepressant medication, the high recurrence rates over the follow-up period demonstrate again the need for maintenance treatments among patients with recurrent depression. Importantly, the protective effects against relapse-recurrence of maintenance antidepressant medication have been suggested to stem from being studied only in an "enriched sample" of medication responders (101). This unique trial of continuation cognitive therapy versus fluoxetine suggests that, at least during continuation treatment, antidepressant medication provides relapse protection even among patients not selected on the basis of acute phase response to medication.

FUTURE DIRECTIONS

Non–Office-Based Delivery Methods for Combination Treatment

A potentially more affordable means of providing combination treatment is provision of psychotherapy via telephone or Internet. A large trial comparing telephone-administered CBT versus in-person CBT among primary care patients with major depressive disorder (only one third of whom were taking an antidepressant) found similar levels of short-term efficacy, but inferior benefits at six months posttreatment, among the patients who were treated with telephone-administered CBT (121). In contrast, a 12-week trial of patients with major depressive disorder started on open-label escitalopram (10–20 mg/day) who were randomly assigned from the beginning of treatment to receive either eight telephone-delivered CBT sessions or eight medication adherence reminder calls found no symptomatic benefit of the added CBT (122). Similarly, patients starting treatment with agomelatine who were randomly assigned to receive eight weeks of telephone delivery of either CM or social rhythm therapy showed no difference in outcomes between treatment arms (123). Thus, combination treatment of antidepressant medication with telephone-administered psychotherapy has yet to demonstrate efficacy over medication treatment alone.

Many trials are currently underway evaluating the efficacy of Internet-delivered psychotherapies for major depressive disorder. In the largest randomized trial to date, provision of ten sessions of Internet-delivered CBT added to treatment as usual was superior to treatment as usual alone among 210 primary care patients with major depressive disorder who provided outcome data at four months post-randomization (recovery rates [defined as BDI-II score <10]: 38% vs. 24%, respectively; p=.011) (124). However, only half the participants were on an antidepressant in this trial, and the benefit of added CBT was found only among patients with more severe symptoms (BDI-II score >28) (124). A smaller trial evaluated ten weeks of Internet-based CBT versus an active control condition (as-needed therapist nonspecific support delivered via e-mail) with 84 patients in partial remission for depression after treatment with either psychotherapy or antidepressant medication (125). At the six-month follow-up time point, more patients in the Internet-CBT group than the control group were in remission on the basis of a self-report scale (41% vs. 24%, respectively; p=.10), and significantly fewer patients had relapsed (11% vs. 38%, respectively; p=.006) (125). These benefits on remission and relapse-recurrence persisted after two years of naturalistic follow-up (126). For patients with major depressive disorder and prominent insomnia, the development of the "Sleep Healthy Using the Internet" therapy program (127) may offer a broadly accessible means of combining CBT for insomnia with medication (128).

Family Therapy

An understudied approach to combination treatment is the value of adding family or couples therapy for patients treated with antidepressants. A majority of hospitalized patients with major depressive disorder experience problematic family functioning (129). Most psychotherapy interventions in combination treatments have focused on the individual with the illness, whether via a one-on-one or group psychotherapy format, despite the clear contribution of family systems to the maintenance of depressive symptoms (130). In a large randomized study of patients on antidepressant medication and recently hospitalized for major depressive disorder, postdischarge receipt of family therapy resulted in significantly lower depressive symptoms and a trend to higher remission rates at six months compared with patients who did not receive family therapy (23% vs. 9%, respectively; p<.10) (131). Marital distress increases the risk for depressive relapse (132), and behavioral marital therapy improves relationship quality (133, 134), suggesting that combination treatment that includes couples therapy may have a prophylactic benefit among patients with depression experiencing relationship discord, although this has not been empirically tested.

Beyond Symptomatic Improvement

Beyond improvements in depressive symptoms and prevention of relapse-recurrence, combined treatments may have effects on quality of life and functioning that are of great value to patients (135). Although functioning and quality of life typically improve along with reduction in symptom burdens, treatments may have independent effects on these measures. A recent meta-analysis concluded that

quality of life at end of treatment is modestly higher among patients with chronic depression receiving combination treatment than patients receiving medication only, despite a relatively small effect size on depressive symptoms (42). Combining interpersonal therapy with antidepressant medication for five weeks during inpatient hospitalization produced higher levels of social adjustment one year after hospital discharge compared with medication treatment alone (46). Treatment combining CBASP with nefazodone significantly improved social and work functioning to a greater degree than either component individually; furthermore, only in the combined treatment arm did psychosocial function improve beyond what could be attributed to the decline in depressive symptoms (136). Several other trials have also found benefits to social functioning and quality of life with combination treatment versus medication alone or treatment as usual, although end-point social functioning often remains below that of the general population (71, 137, 138).

QUESTIONS AND CONTROVERSY

The major question around combination treatment strategies is in regard to the issue of moderators—that is, the characteristics that can be used to identify which patients with depression are likely to benefit from combination treatment. Despite extensive exploration of trial data, remarkably few patient characteristics have been identified consistently that could inform this important decision. Several expert reviews have recommended sequential use as the preferred form of application of combination treatment (as opposed to combination from treatment initiation) for most patients with depression (103, 106, 139, 140) because it avoids unnecessary costs and burdens for patients capable of remission with monotherapy. Complicating matters, it is likely that the variables that predict remission from the acute major depressive episode differ from those that place patients at risk for relapse-recurrence (141).

Chronicity

A key question is whether combination therapy is specifically indicated from the beginning of treatment for patients with forms of chronic depression (persistent depressive disorder). The large effect of combination treatment in the study combining nefazodone with CBASP (29) has been a key driver in supporting this recommendation, although it should be noted that there was no psychotherapy comparator arm; therefore, the specificity of CBASP, as opposed to other psychotherapies, was not proven in this study. Countering the results of this trial are several other sources of evidence. First, several studies have shown minimal added value of combination treatment over antidepressant medication alone in the treatment of dysthymia (*DSM-5*: persistent depressive disorder with pure dysthymic syndrome) (11, 142, 143), although these trials have been limited by the relatively brief duration of psychotherapy and frequent use of non-evidence-based psychotherapies. Additionally, the generally lower depression severity scores of patients with dysthymia may create a "floor effect" so that benefits of combination treatment are hard to detect on symptom scales. Second, in the sequential-treatment REVAMP trial there was an absence of benefit from combination treatment. Third, a trial from the Netherlands combining CBASP with medication found mostly negative results (38). Finally, a large study recently found no benefit of combination treatment over medication alone, even after one year of treatment (34). In that trial, patients with a chronic depressive episode actually had a nonsignificantly higher recovery rate with medication alone than with treatment combining cognitive therapy with medication (70% vs. 63%, respectively; p=.28) (34).

Severity

In contrast to chronicity, more consistent data support the combination of psychotherapy with antidepressant medication for patients with severe depression. Among patients with more severe depression, combined treatment shows greater benefits and cost-effectiveness compared with patients with moderate depression (144). An early mega-analysis of studies that compared combining interpersonal therapy with medication versus psychotherapy (interpersonal therapy or CBT) alone found that duration of episode did not predict the benefit of combination treatment, but severity did: remission rates among patients with mild to moderate depression were nonsignificantly higher for combination treatment versus psychotherapy alone (48% vs. 37%, respectively; p=.10); however, among patients with more severe depression, combination treatment was statistically superior (43% vs. 25%, respectively; p=.001) (50). The benefits of combination treatment among hospitalized patients also speak to its value among patients who are more severely ill (46), with benefits enduring beyond the acute treatment phase (54). Furthermore, a large trial demonstrated that patients with severe, nonchronic depression demonstrated substantially better long-term (three-year) recovery rates with the combination of cognitive therapy with antidepressant medication versus medication alone (81% vs. 52%, respectively); in contrast, among patients with severe, chronic depression the recovery rates did not differ (roughly 60% in both groups) (34).

Patient Preference

Most randomized trials have not found patient preference for medication or psychotherapy treatment to strongly affect treatment outcomes (145). However, a meta-analysis that examined the effects of preference across all studies (not limited to randomized trials) found slightly larger benefits among patients who received their preferred treatment and greater rates of dropout among patients who did not receive their preferred treatment (146). In the large study combining nefazodone with CBASP (29), receipt of one's preferred treatment strongly predicted remission, particularly among patients preferring psychotherapy, who had a notably lower remission rate with nefazodone alone compared with CBASP

alone (8% vs. 50%, respectively) (147). Among the small number of patients in this trial who preferred treatment with nefazodone only, remission rates were twice as high with nefazodone than with the psychotherapy (46% vs. 22%, respectively) (147). In contrast to these strong effects, in the REVAMP trial outcomes from the sequential addition of medication or psychotherapy after acute phase nonremission with medication was not predicted by treatment preferences assessed at treatment initiation. In this trial, however, all patients knew that they would initially receive an antidepressant medication, which may have biased the participant sample (148). In a naturalistic trial in which patients with major depressive disorder could choose treatment with either an interpersonal therapy or CBT alone or either in combination with medication, remission rates after 26 weeks of treatment did not significantly differ across the four treatment arms (range=29%−37%) (52). These variable findings highlight the impact of trial design features on the willingness of patients to participate in a trial and the preference effects detected among the participants.

Socioeconomic Deprivation

The studies discussed to this point have been conducted primarily in academic medical centers using participant samples with the wherewithal to attend psychotherapy visits and adhere to medication. Largely unrepresented in these studies are patients who are severely socioeconomically disadvantaged, so the study results reviewed here may not generalize to this highly vulnerable subset of patients with depression. Adverse socioeconomic circumstances are associated with greater chronicity of depression (149) and predict poorer treatment adherence and poorer response to treatments for major depressive disorder (150–153). In STAR*D, adverse socioeconomic circumstances (low education, poverty, unemployment) were stronger than any clinical characteristic in predicting outcome in response to citalopram (154). The Threshold for Antidepressant Response study, which randomly assigned primary care patients with mild to moderate depression to treatment with either supportive care alone or supportive care plus an SSRI, found that rates of remission among those experiencing marked social adversity were less than half the rates of patients without social adversity (18% vs. 46%, respectively; $p<.001$) (155). Some data suggest that the poorer outcomes associated with chronic major depressive disorder stem more from the highly associated poor socioeconomic status among those with chronic major depressive disorder than the duration of the depressive episode itself (156, 157).

For individuals with severe socioeconomic disadvantages, collaborative care models that apply case management appear to provide the greatest benefit. Patients with low-income often need case management to address barriers to care, including transportation and child care, to prevent treatment dropout, especially among racial-ethnic minority populations (158). Substantial efforts to repeatedly reach out to patients experiencing impoverishment to encourage them to enter care, followed by efforts to reduce barriers to continue in care, can improve treatment engagement (150, 151). The practical barriers to attending clinic visits are particularly problematic for effective application of psychotherapy treatments in this population, with only a minority of patients who were socioeconomically disadvantaged attending an adequate number of sessions in controlled studies (151, 159). For these individuals, combination treatment may be better formulated as a monotherapy combined with intensive case management, rather than psychotherapy combined with medication. Some data suggest that medication with case management may be superior to psychotherapy with case management in this population (150). Going beyond case management, there is growing evidence that programs directly targeting contextual problems contributing to depression (e.g., housing insecurity, chronic unemployment) have antidepressant effects that warrant greater consideration (160).

Personality Characteristics

Comorbid personality disorders are generally predictive of major depressive disorder persistence and shorter time to relapse-recurrence after remission, with borderline personality disorder a particularly strong predictor of poor naturalistic outcomes (161, 162). However, in the study combining nefazodone with CBASP (29), in which 50% of patients had a personality disorder, outcomes among patients with and without a personality disorder did not meaningfully differ; furthermore, the presence of a personality disorder was not associated with differential outcomes across the three treatment arms (163). In contrast, when short psychodynamic supportive psychotherapy was added to medication, remission rates among those with a personality disorder were substantially higher with combination treatment compared with medication alone (47% vs. 19%, respectively) (164). In addition, behavioral passivity and lower positive emotions at the end of acute phase treatment with cognitive therapy or behavioral activation are replicated predictors for depressive recurrence, even after application of a continuation phase treatment of psychotherapy or antidepressant medication (141, 165, 166).

Childhood Trauma

Higher levels of childhood trauma have been found to predict better acute phase outcomes with combination treatment compared with nefazodone alone (167). Remitted patients with recurrent major depressive disorder who had higher levels of childhood trauma were better protected against recurrence if they received MBCT compared with maintenance medication (117) or treatment as usual (119). Interpersonal therapy provided in combination with antidepressant medication during psychiatric hospitalization for major depressive disorder also improved long-term depressive symptom scores among patients with moderate-to-severe childhood trauma, with no additional benefit of interpersonal therapy among patients without childhood trauma (54).

RECOMMENDATIONS

The evidence for combining psychotherapy with medication at treatment initiation is strongest for patients with severe forms of depression (high levels of symptoms; inpatients). It is difficult to justify routine application of combination treatments for patients from the initiation of care for nonsevere depression, especially when flexible application of antidepressant medication is available. Despite extensive efforts to improve outcomes among patients with chronic forms of major depressive disorder, combination treatments have proven to have only small effects in this population, with benefits of combination treatment demonstrated primarily in trials that either used no active comparison treatment to an added psychotherapy or used limited pharmacotherapy that is not reflective of clinical practice. CBASP, despite being developed specifically to target chronic forms of major depressive disorder, has not proven to be superior to other forms of psychotherapy. Given the associations between chronic depression and adverse socioeconomic status, efficacy of antidepressant medication in this population may be enhanced by targeting relevant social interventions, rather than by treatments combining medication with psychotherapy.

Patients in remission with combination treatment typically require maintenance antidepressant medication to remain well over the long term, particularly if they have a history of recurrent episodes. For nonresponders to a single-modality treatment, switching to another modality is a reasonable treatment option. Much of the evidence supporting sequential addition of a psychotherapy after medication treatment is based on the comparison against treatment as usual; these designs are susceptible to significant placebo effects and cannot determine the specificity of the added psychotherapy over any other form of added treatment. For patients with residual symptoms after antidepressant treatment alone, addition of an evidence-based psychotherapy can improve acute phase outcomes but not necessarily more than continued medication optimization. There are insufficient controlled data to make an evidence-based recommendation for sequential addition of medication after psychotherapy improvement with residual symptoms. Sequential treatment with the addition of a relapse prevention–focused psychotherapy is beneficial for patients with highly recurrent depression, and it may allow for tapering off antidepressant medication among patients achieving full recovery.

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