

Combined Psychotherapy and Pharmacotherapy for the Treatment of Major Depressive Disorder

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Studies comparing the efficacy of combined psychotherapy and pharmacotherapy to single treatment (i.e., either psychotherapy or pharmacotherapy alone) for major depression have not found consistent differences in outcome, resulting in a range of conclusions regarding the efficacy of combined treatment. In order to clarify the efficacy of combined treatment for depression, the authors conducted both a meta-analytic and qualitative review. Our findings suggest that combined treatment is associated with a small improvement in efficacy, and that this finding appears consistent across studies. Trends in the literature suggest that adding psychotherapy to antidepressant medication may be particularly efficacious among chronic or severely depressed patients. Further, adding cognitive-behavioral therapy to medication may be particularly efficacious in preventing relapse, particularly among individuals discontinuing medication use. The authors propose an illness-cognition model for better understanding outcomes in combined treatment.

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Major depression represents one of the most serious mental health problems in the country with substantial consequences of human suffering, loss of life, and lost productivity (Klerman, 1989; Klerman & Weissman, 1992). Patients who have had a major depressive episode are at risk for future episodes, and the number of such events significantly increases the risk for relapse (Mueller et al., 1999; Solomon et al., 1997). Individuals with major depressive disorder and depressive symptoms have substantial and long-lasting impairment in multiple areas of functioning and well-being that equal or exceed those of patients with chronic physical illness (Hays, Wells, Sherbourne, Rogers, & Spritzer, 1995; Hirschfeld et al., 2000).

Currently, numerous treatments for depression have been developed, including both pharmacological and psychosocial interventions. There has been an extensive research literature investigating the use of single treatments (i.e., either pharmacotherapy or psychotherapy alone) in the management of major depression. For

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example, cognitive, behavioral, and interpersonal psychotherapies have established efficacy in treating depression (for a review, see DeRubeis & Crits-Cristoph, 1998), as do a range of tricyclic and serotonin reuptake inhibitor antidepressants (for a review, see Thase & Kupfer, 1996). However, despite the extensive work developing and investigating the efficacy of both pharmacotherapy and psychotherapy, a substantial number of depressed patients either do not respond fully to initial treatment or relapse within a year (Khan, Warner, & Brown, 2000; Westen & Morrison, 2001).

One method that has been proposed to improve efficacy is to combine treatment (i.e., deliver both psychotherapy and pharmacotherapy together) in the management of depression. There was initial reluctance in the field to utilize this approach, as it was thought that each alternative therapy would undermine the effects of initial treatment. For example, there was concern that combining medication with psychotherapy would lead to a reduction in symptoms that would undermine motivation to engage in psychotherapy (Rounsaville, Klerman, & Weissman, 1981). Further, in the context of taking medication, patients may attribute treatment gains to medication rather than skill development, thus undermining sustained recovery. Conversely, the expression of negative emotion that may arise from psychotherapy may undermine the symptom remission associated with pharmacotherapy (Rounsaville et al., 1981).

In contrast to the skepticism regarding the efficacy of combined treatment, several possible ways combined treatment might be beneficial have been elucidated (Karasu, 1990; Miller & Keitner, 1996; Paykel, 1995). For example, additive models suggest simply that more treatment is better. Complementary models propose that psychotherapy and pharmacotherapy target different symptoms of depression (e.g., hopelessness vs. reduced appetite), and thus a combined approach would address a wider range of symptoms. Finally, synergistic models suggest that one treatment may actually enhance the efficacy of another. For example, medication may result in enough symptom reduction to allow a patient to engage in psychotherapy more effectively. Similarly, engaging in psychotherapy may provide more interaction with a treatment provider, thus improving overall treatment compliance.

Perhaps in recognition of the often poor response of depressed individuals to single treatment, the use of combined treatment appears to be rising, making it a common form of treatment for depression (Olfson et al., 2002). Yet, despite its widespread use, in contrast to the concerted effort to understand the efficacy of single treatment, much less is known about the efficacy of combined treatment for major depression. Perhaps in part because of the limited number of studies and the mixed findings from those studies, there has been considerable debate as to the utility of combined treatment for major depression. Specifically, previous reviews of the combined-treatment literature have suggested a range of conclusions, with some suggesting that combined treatment offers either little or no benefit over single treatment (Conte, Plutchik, Wild, & Karasu, 1986; Hollon, Shelton, & Loosen, 1991; Karp & Frank, 1995; Robinson, Berman, & Neimeyer, 1990; Wexler & Cicchetti, 1992), others that combined treatment has a clear advantage (American Psychiatric Association, 1993; Miller & Keitner, 1996; Weissman, 1979), and others that combined treatment is particularly beneficial in specific cases (Depression Guideline Panel, 1993; Hollon, Thase, & Markowitz, 2002; Persons, Thase, & Crits-Cristoph, 1996; Segal, Kennedy, & Cohen, 2001).

When considering the extensive use and substantial added cost of combined-treatment approaches, clarifying the efficacy of combined treatment is critical for improving care for depressed individuals. In order to understand this literature better, we first present the results of both a meta-analytic and a qualitative review of the existing literature. We then examine trends in the literature that may provide insight into who may benefit most from combined treatment and how combined treatment may be delivered most effectively. Finally, we examine issues that may improve the efficacy of combined treatment.

METHOD

Studies Cited

The authors examined the effect size of particular studies that met several criteria. First, each study needed to be a randomized treatment control study of major depression that compared a combined treatment condition to at least one active single treatment (i.e., either pharmacotherapy or psychotherapy). Next, the single

active treatment needed to be one of the treatments used in the combined-treatment condition (e.g., combined cognitive therapy and imipramine as compared to imipramine alone). Further, the sample needed to suffer from major depression, as opposed to other psychiatric disorders or other mood disorders (e.g., bipolar disorder). Studies utilizing a cutoff on a depression severity measure were not included. Finally, the data needed to be presented in a form that allowed for the calculation of at least one effect size of a relevant dependent variable.

A total of 20 articles based on 17 independent studies met these criteria. The papers that were included based on the above criteria are described in Table 1. As can be seen in Table 1, few studies utilized similar methods. For example, there was a range of psychotherapies (e.g., cognitive therapy, interpersonal therapy), medications (e.g., imipramine, fluoxetine), and different measures (e.g., Beck Depression Inventory, Hamilton Rating Scale for Depression) across studies. Because of the limited overlap in the methods of these studies, a full meta-analysis was not possible. However, we utilize meta-analytic techniques in order to quantify the results presented in the studies. We present our methods for these meta-analytic techniques below.

This study is based on a review of 20 articles describing 17 independent studies that examined the efficacy of combined psychotherapy and pharmacotherapy for adults with depression. The search procedure began with a search of computerized databases (PsycINFO, Medline) by entering the key words *psychotherapy and depression*, and *pharmacotherapy and depression*. When the computerized search produced relevant articles, those articles were obtained and their bibliographies were scanned for related articles. The studies compiled were published between 1967 and 2002 and did not include studies written in languages other than English. Dissertation abstracts were not included, and we did not make an effort to locate unpublished studies or to contact authors regarding data that were not presented in the articles themselves. Also, if preliminary reports of a later study were presented, only the latest report was utilized in the analyses.

Calculation of Effect Sizes

Signs were affixed to effect sizes to reflect the comparative efficacy of each treatment. A positive sign

in this case indicated lower levels of depression in the combined-treatment group at the given period of assessment, thus suggesting greater efficacy for combined treatment. A negative sign was an indication that, at a given assessment period, the depression score of the single-treatment group was lower than that of the combined-treatment group. For the purposes of this review, we interpreted effect sizes as being small, medium, or large based on the standards for Cohen's *d* described in Cohen (1992). Thus, effect sizes of 0.0–0.49 were interpreted as representing small effects, 0.5–0.79 were interpreted as medium or moderate effects, and 0.8 and above were interpreted as representing large effects (Cohen, 1992).

In order to determine the overall effects of combined treatment, our meta-analysis relied primarily on the average of effect sizes across studies. Effect sizes were calculated utilizing Cohen's *d* (Cohen, 1977). This was accomplished by taking the absolute value of the difference of the mean score of the depression measure from the combined-treatment group and the single-treatment group, and dividing this difference by the pooled within-group standard deviation of the sample. In the case of data that was presented as a categorical measure (e.g., relapse vs. sustained recovery), chi-square analyses were conducted to determine effect. Chi-squares were then converted into *d* scores based on procedures described in Rosenthal (1991; 1984).

We calculated separate effect sizes for each "independent sample" in a study. Independent samples existed when data was reported separately for groups that underwent different treatments. For example, in some studies, combined treatment was compared to both a psychotherapy group and a pharmacotherapy group. For the purpose of this meta-analysis, the difference between the effects of the combined and each individual treatment represented separate effect sizes. Further, each effect size was affixed with a weight based on sample size. In order to assess the mean effect size of a group of studies, the weight assigned to a given study was calculated based on the number of subjects in the study using the formula $(2N)/8 + d^2$, *N* being the number of subjects in the sample, and *d* being the effect size (Wolf, 1986; Rosenthal, 1991). The mean effect size of a group of studies was calculated based on the sum of the weight multiplied by the effect size of each study,

Table 1. Characteristics of studies reviewed

Study	Combined Treatment	Psychotherapy	Pharmacotherapy	Primary Phase of Treatment Delivery	Outcome Measure
Blackburn et al. (1981)	Cognitive Therapy + Amitriptyline or Clomipramine (30)	Cognitive Therapy (30)	Amitriptyline or Clomipramine (28)	Acute	HRSD and BDI
Blackburn et al. (1986)	Cognitive Therapy + Amitriptyline or Clomipramine (16)	Cognitive Therapy (15)	Amitriptyline or Clomipramine (10)	Acute	HRSD and BDI
Bowers (1990)	Cognitive Therapy + Nortriptyline (10)		Nortriptyline (10)	Acute	HRSD and BDI
Covi & Lipman (1987)	Cognitive-Behavioral Therapy + Imipramine (34)	Cognitive-Behavioral Therapy (32)		Acute	BDI
de Jonghe et al. (2001)	Short Psychodynamic Supportive Therapy + Fluoxetine, Amitriptyline, and Moclobemide (83)		Fluoxetine, Amitriptyline, and Moclobemide (84)	Acute	HRSD
DiMascio et al. (1979)	Interpersonal Psychotherapy + Amitriptyline (24)	Interpersonal Psychotherapy (25)	Amitriptyline (24)	Acute	HRSD
Evans et al. (1992)	Cognitive Therapy + Imipramine (13)	Cognitive Therapy (10)	Imipramine (10)	Acute	HRSD and BDI
Fava et al. (1998)	Cognitive-Behavioral Therapy + Amitriptyline (20)		Amitriptyline (20)	Maintenance/Sequential	RDC episode of major depression
Frank et al. (1990)	Interpersonal Therapy + Imipramine (25)	Interpersonal Therapy (26)	Imipramine (28)	Maintenance	HRSD
Hersen et al. (1984)	Social Skills Training + Amitriptyline (30)		Amitriptyline (26)	Acute	HRSD and BDI
Hollon et al. (1992)	Cognitive Therapy + Imipramine (25)	Cognitive Therapy (25)	Imipramine (57)	Acute	HRSD and BDI
Keller et al. (2000)	Cognitive-Behavioral Analysis System + Nefazodone (227)	Cognitive-Behavioral Analysis System (228)	Nefazodone (226)	Acute	HRSD
Miller et al. (1989)	Cognitive Therapy + Amitriptyline or Desipramine (28)		Amitriptyline or Desipramine (17)	Acute	HRSD and BDI
Murphy et al. (1984)	Cognitive Therapy + Nortriptyline (22)	Cognitive Therapy (24)	Nortriptyline (24)	Acute	HRSD and BDI
Mynors-Wallis et al. (2000)	Problem Solving + Fluvoxamine or Paroxetine (35)	Problem Solving (41)	Fluvoxamine or Paroxetine (36)	Acute	HRSD and BDI
Paykel et al. (1999)	Cognitive Therapy + Amitriptyline or Fluoxetine (80)		Amitriptyline or Fluoxetine (78)	Maintenance	HRSD and BDI
Perlis et al. (2002)	Cognitive Therapy + Fluoxetine (66)		Fluoxetine (66)	Maintenance	HRSD and BDI
Reynolds et al. (1999)	Interpersonal Therapy + Nortriptyline (22)		Nortriptyline (24)	Maintenance	HRSD and BDI
Roth et al. (1982)	Self Control Therapy + Desipramine (16)	Self Control Therapy (16)		Acute	HRSD and BDI
Simons et al. (1986)	Cognitive Therapy + Nortriptyline (14)	Cognitive Therapy (10)	Nortriptyline (9)	Acute	HRSD

Note. The studies by Bowers (1990) and Miller et al. (1989) were conducted in inpatient treatment settings; all others were in outpatient treatment settings.

divided by the sum of the weights of each study (Wolf, 1986; Rosenthal, 1991). Further, we conducted chi-square analyses among the effect sizes in order to determine consistency of effects across studies (Rosen-

thal, 1991). Significant chi-square results suggested that the effect size was not consistent across studies, while nonsignificant chi-squares suggested consistency of effect across studies.

Categorization of Treatment

Treatments that consisted of both active psychotherapy and active pharmacotherapy were considered to represent “combined” treatments. In general, psychotherapy was delivered at least once a week for a period of 50 minutes or more. Since “clinical management” (i.e., assessing the side effects of medication, determining appropriate dosage) is considered an important aspect of pharmacotherapy, the use of clinical management in combination with pharmacotherapy was not considered a “combined” treatment for the purposes of this review, but rather a single pharmacotherapy trial. A similar distinction is made in Persons et al.’s (1996) discussion of the combined-treatment literature.

Further, because of statistical and methodological complications arising from combining psychotherapy with pharmacotherapy placebos, this condition was not considered a pure “psychotherapy” condition for the purposes of this review (Hollon & DeRubeis, 1981). As Hollon and DeRubeis point out, the comparison of combined treatment to psychotherapy plus placebo controls is useful for determining mechanism of treatment, but not as effective in determining differences in outcome. In addition, because combined psychotherapy and pharmacotherapy placebo is not a typical standard of care, we felt that examining the efficacy of this treatment condition would not ultimately be as informative to later research. Therefore, while the use of placebo groups is sometimes discussed when describing the design of a particular study, the aspects of studies that examine psychotherapy in combination with placebo were not included in this review.

Dependent Measures

In order to provide consistency across effect sizes, we restricted our analyses of mean differences and recovery to studies that utilized either the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), the Modified Hamilton Rating Scale for Depression (MHRSD; Miller, Bishop, Norman, & Maddover, 1985), or the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). For studies that examined relapse, there was little consistency in criteria across studies in measure of relapse. Thus, any measure of relapse utilized was acceptable in these analyses, and all analyses are pooled.

RESULTS

Efficacy of Combined Treatment as Compared to Medication Alone

Evidence suggests that there is a small and consistent benefit of combined treatment as compared to medication alone in acute symptom reduction (see Table 2). Specifically, with regard to mean differences between treatment conditions, there is a small benefit of combined treatment among treatment completers on depressive symptoms (BDI: $d = 0.34$, $\chi^2 = 6.42$; HRSD: $d = 0.18$, $\chi^2 = 4.26$). Endpoint analyses (i.e., analyses including patients who did not complete treatment) reveal similar results (BDI: $d = 0.41$, $\chi^2 = 0.50$; HRSD: $d = 0.42$, $\chi^2 = 0.13$). With regard to more discrete analyses of recovery, there is a moderate and consistent effect of combined treatment on recovery rates for treatment completers as measured by the HRSD ($d = 0.65$, $\chi^2 = 5.35$), and a moderate but inconsistent effect as measured by the BDI ($d = 0.61$, $\chi^2 = 19.24$, $p < .001$). However, endpoint analyses of studies utilizing the HRSD to measure recovery suggested a smaller effect ($d = 0.32$, $\chi^2 = 5.76$). Only one study examined endpoint recovery using the BDI ($d = 0.14$). Further, there was only a slight benefit of attrition ($d = 0.26$, $\chi^2 = 15.53$). Thus combined treatment appears to have a small benefit over medication alone and may have a moderate benefit on some measures of recovery.

Several studies comparing the relative effects of combined treatment and pharmacotherapy alone found no significant differences in posttreatment efficacy among depressed outpatients. One possible reason may be that, in some of these studies, psychotherapies that are not established as “empirically supported” were utilized in treating depression (DeRubeis & Crits-Cristoph, 1998). For example, Hersen, Bellack, Himmelhoch, and Thase (1984) compared 30 outpatients receiving combined social-skills training plus amitriptyline to 26 patients receiving amitriptyline alone. This study found no additional benefit of combining social-skills training with amitriptyline compared to amitriptyline alone among treatment completers after 12 weeks of treatment, as measured by the BDI ($d = 0.05$), and combined treatment demonstrated poorer outcome than medication alone as measured by the HRSD ($d = -0.33$). Further, when measuring recovery based on both BDI

Table 2. Combined Therapy vs. Medication Alone

Study	Cohen's <i>d</i>	Weight
Post-Treatment Completers—BDI		
Bowers (1990)	1.37	4.05
Hersen et al. (1984)	0.05	8.75
Hollon et al. (1992)	0.39	11.78
Miller et al. (1989)	0.39	8.10
Murphy et al. (1984)	0.02	8.50
Average <i>d</i> = 0.34		
$\chi^2 = 6.42$		
Post-Treatment Endpoint—BDI		
Miller et al. (1989)	0.56	10.82
Murphy et al. (1984)	0.26	11.41
Average <i>d</i> = 0.41		
$\chi^2 = 0.50$		
Post-Treatment Completers—HRSD		
Bowers (1990)	0.42	4.89
de Jonghe et al. (2001)	0.42	22.50
Hersen et al. (1984)	-0.33	8.63
Miller et al. (1989)	0.06	8.25
Murphy et al. (1984)	0.05	8.50
Average <i>d</i> = 0.18		
$\chi^2 = 4.26$		
Post-Treatment Endpoint—HRSD		
de Jonghe et al. (2001)	0.45	40.71
Miller et al. (1989)	0.41	11.02
Murphy et al. (1984)	0.35	11.33
Average <i>d</i> = 0.42		
$\chi^2 = 0.13$		
Post-Treatment Recovered BDI		
Bowers (1990)	2.67	2.65
Hollon et al. (1992)	0.24	11.91
Murphy et al. (1984)	0.47	8.27
Average <i>d</i> = 0.61		
$\chi^2 = 19.24$		
Post-Treatment Recovered—HRSD		
Bowers (1990)	1.50	3.90
de Jonghe et al. (2001)	0.47	22.38
Hollon et al. (1992)	0.43	11.73
Keller et al. (2000)	0.69	81.62
Murphy et al. (1984)	0.61	8.12
Average <i>d</i> = 0.65		
$\chi^2 = 5.35$		
Post-Treatment Recovered—Both		
Hersen et al. (1984)	0.00	8.75
Miller et al. (1989)	0.64	7.85
Average <i>d</i> = 0.30		
$\chi^2 = 1.70$		
Recovery Endpoint—HRSD		
de Jonge et al. (2001)	0.51	40.42
Hollon et al. (1992)	0.36	20.18
Mynor-Wallis et al. (2000)	-0.14	17.71
Average <i>d</i> = 0.32		
$\chi^2 = 5.76$		
Relapse—Naturalistic		
Blackburn et al. (1986)	1.33	4.70
Evans et al. (1992)	0.80	5.32
Miller et al. (1989)	0.60	6.22
Simons et al. (1986)	0.10	5.74
Average <i>d</i> = 0.68		
$\chi^2 = 4.06$		

Table 2. Continued

Study	Cohen's <i>d</i>	Weight
Relapse—Continued Completers		
Frank et al. (1990) Cont.	0.07	10.00
Paykel et al. (1999)	0.31	31.37
Perlis et al. (2002)	0.09	21.23
Reynolds et al. (1999)	0.59	11.02
Average <i>d</i> = 0.26		
$\chi^2 = 2.26$		
Relapse—Continued Endpoint		
Paykel et al. (1999)	0.39	38.75
Perlis et al. (2002)	0.06	32.99
Reynolds (1999)	0.50	12.84
Average <i>d</i> = 0.28		
$\chi^2 = 2.81$		
Attrition		
Blackburn et al. (1981)	0.04	14.50
Bowers (1990) ₂	0.00	5.50
de Jonghe et al. (2001)	0.68	39.50
DiMascio (1979)	0.71	11.29
Hersen et al. (1984)	0.44	14.90
Hollon et al. (1992)	0.15	20.44
Keller et al. (2000)	0.12	113.06
Miller et al. (1989)	0.53	10.87
Murphy et al. (1984)	0.35	11.33
Mynor-Wallis et al. (2000)	0.01	17.75
Average <i>d</i> = 0.26		
$\chi^2 = 15.53$		

and HRSD scores, there was no effect of combined treatment ($d = 0.00$). Similarly, Mynors-Wallis, Gath, Day, and Baker (2000) compared 36 individuals receiving either fluvoxamine or paroxetine alone to 35 patients receiving medication plus brief (six sessions) problem-solving therapy delivered over the course of 12 weeks. The use of endpoint analyses revealed that combined treatment actually resulted in a slightly lower rate of recovery as measured by the HRSD ($d = -0.14$). In contrast, de Jonghe, Kool, van Aalst, Dekker, and Peen (2001) examined the relative benefit of adding Short Psychodynamic Supportive Psychotherapy to pharmacotherapy alone among 167 depressed patients over a 24-week period. The results, while still being small, demonstrated a somewhat stronger effect, with combined treatment resulting in improved symptom severity scores ($d = 0.42$) as well as recovery rates ($d = 0.47$) for treatment completers as measured by the HRSD. Further, there was a moderate benefit of combined treatment on level of attrition ($d = 0.68$).

Yet studies examining the efficacy of adding cognitive therapy, an empirically supported treatment for depression, to pharmacotherapy among depressed

outpatients found similar results. Murphy, Simons, Wetzel, and Lustman (1984) compared 24 outpatients who received 12 weeks of pharmacotherapy alone and 24 patients receiving cognitive therapy alone to 22 outpatients assigned 12 weeks of pharmacotherapy plus cognitive therapy, and they found no significant differences between combined treatment and medication alone in efficacy among completers as measured by the BDI ($d = 0.02$) or HRSD ($d = 0.05$). Small effects were also found using endpoint analyses as measured by the BDI ($d = 0.26$), and HRSD ($d = 0.35$). However, while the results were not significant, combined treatment resulted in a moderate effect in improving the percentage of patients recovered as measured by the HRSD ($d = 0.61$), and a near moderate effect as measured by the BDI ($d = 0.47$). Hollon et al. (1992) found similar results to Murphy et al. (1984) when comparing the differential posttreatment efficacy of combined cognitive therapy plus imipramine ($n = 25$) to that of imipramine alone ($n = 57$) and cognitive therapy alone ($n = 25$) for 12 weeks of active treatment based on both the BDI and HRSD. This study found that cognitive therapy combined with imipramine was no more efficacious in level of recovery than medication alone immediately following treatment as measured by the BDI among completers ($d = 0.39$). Further, there was not a significant difference when examining recovery status among completers based upon either the BDI ($d = 0.24$) or HRSD ($d = 0.43$). Similar results were found using endpoint analyses using the BDI ($d = 0.14$) and HRSD ($d = 0.36$).

While the results of these studies point to a small to moderate benefit of combined treatment, there are methodological issues that make it difficult to draw definitive conclusions from these results. Perhaps the most glaring methodological weakness was the unusually small sample sizes found across studies. Specifically, few studies had posttreatment data on more than 40 patients in a treatment group (see Table 1). Although these studies may have been representative of the size of treatment studies conducted at that point in time, these studies did not appear to have adequate power to detect the small to moderate treatment effects of combined treatment on recovery status. Further, because of the relatively small samples, there was little opportunity to determine whether treatment effects varied across any

variables within the depressed sample. In addition, the majority of these studies were conducted 10–20 years ago. As a result, while more recent studies of treatment outcome require stringent ratings of adherence and competency to treatment protocols, with some exceptions (Hollon et al., 1992; Murphy et al., 1984) the studies reviewed generally did not meet these standards. Thus, there is little overall evidence that these treatments were delivered in a consistent, standardized manner. Finally, there are a number of empirically supported psychotherapies (e.g., behavior therapy) that have not been examined in combination with medication. Thus, it is unclear whether the lack of findings will be consistent across all treatments. Thus, while these results provide an initial impression, there is serious question as to whether these studies have adequately tested the improved benefit of adding psychotherapy to pharmacotherapy for the treatment of major depression.

Efficacy of Combined Treatment as Compared to Psychotherapy Alone

Overall, there were few studies examining the acute effects of combined treatment as compared to psychotherapy alone on symptom reduction (see Table 3). These studies suggest almost no benefit of combined treatment as compared to psychotherapy alone on depressive symptoms among treatment completers as measured by the BDI ($d = 0.10$, $\chi^2 = 0.01$). Only one study examined the effects of combined treatment compared to psychotherapy alone among completers using the HRSD ($d = -0.05$). Further, only one study utilized endpoint analyses to examine symptom reduction using the BDI ($d = 0.08$) and HRSD ($d = -0.07$). However, there was a moderate effect of combined treatment on recovery status as measured by the HRSD among treatment completers ($d = 0.69$, $\chi^2 = 6.88$), although this effect was not similar to the effect found in studies using endpoint analyses ($d = 0.24$, $\chi^2 = 0.61$). Further, studies utilizing the BDI to examine recovery status found a small benefit of combined treatment ($d = 0.31$, $\chi^2 = 0.89$), and the one study utilizing endpoint analyses found little benefit of combined treatment on recovery as measured by the BDI ($d = 0.08$). Finally, there was almost no benefit of combined treatment on level of attrition ($d = 0.04$, $\chi^2 = 4.85$).

Table 3. Combined Therapy vs. Psychotherapy Alone

Study	Cohen's <i>d</i>	Weight
Post-Treatment Completers—BDI		
Hollon et al. (1992)	0.12	7.99
Murphy et al. (1984)	0.08	9.24
Average <i>d</i> = 0.10 $\chi^2 = 0.01$		
Post-Treatment Recovered—BDI		
Covi et al. (1987)	0.18	12.45
Hollon et al. (1992)	0.36	7.38
Murphy et al. (1984)	0.55	8.92
Roth et al. (1982)	0.16	6.48
Average <i>d</i> = 0.31 $\chi^2 = 0.89$		
Post-Treatment Recovered—HRSD		
Hollon et al. (1992)	0.53	7.72
Keller et al. (2000)	0.76	82.09
Murphy et al. (1984)	0.18	9.22
Average <i>d</i> = 0.69 $\chi^2 = 6.88$		
Recovery Endpoint—HRSD		
Hollon et al. (1992)	0.41	12.24
Mynor-Wallis et al. (2000)	0.13	18.96
Average <i>d</i> = 0.24 $\chi^2 = 0.61$		
Relapse—Naturalistic		
Blackburn et al. (1986)	0.04	6.75
Evans et al. (1992)	0.12	5.74
Simons et al. (1986)	-0.53	5.80
Average <i>d</i> = -0.12 $\chi^2 = 1.48$		
Attrition		
Blackburn et al. (1981)	0.00	15.00
Covi et al. (1987)	-0.40	16.18
DiMascio et al. (1979)	0.38	12.03
Hollon et al. (1992)	0.00	12.50
Keller et al. (2000)	0.07	113.68
Murphy et al. (1984)	0.07	11.49
Mynor-Wallis et al. (2000)	0.12	18.97
Roth et al. (1982)	0.00	8.00
Average <i>d</i> = 0.04 $\chi^2 = 4.85$		

Similar to studies comparing combined treatment to pharmacotherapy, studies that have examined the differential efficacy of adding pharmacotherapy to psychotherapy for the treatment of major depression have generally reported few significant differences in outcome. Further, this finding has been consistent across studies of different treatment modalities. For example, Roth, Bielski, Jones, Parker, and Osborn (1982) compared 16 patients receiving self-control therapy to 16 patients receiving combined self-control therapy plus desipramine. There was no significant difference in the percentage of patients recovered at posttreatment (*d* =

0.16). Similarly, Mynors-Wallis et al. (2000), comparing problem-solving treatment alone to combined problem-solving treatment and either fluvoxamine or paroxetine, found no differences in recovery status as measured by the HRSD using endpoint analyses (*d* = 0.13).

Several studies of combined treatment as compared with cognitive therapy alone have also found no differences in outcome. For example, Murphy et al. (1984) found no differences between combined treatment and cognitive therapy alone among treatment completers as measured by the BDI (*d* = 0.08) or HRSD (*d* = -0.05). Similar results were found using endpoint analyses (BDI, *d* = 0.08; HRSD, *d* = -0.07). There were also no significant differences in recovery, although there was a moderate effect on percentage recovered as measured by the BDI (*d* = 0.55) as compared with the HRSD (*d* = 0.18). Further, Blackburn, Eunson, and Bishop (1986) compared 30 patients receiving combined treatment to 30 patients receiving cognitive therapy alone and 28 patients receiving medication. Blackburn et al. (1986) found no significant differences in the percentage of patients recovered as measured by threshold scores on either the BDI or HRSD (*d* = 0.24). Similar results were found in Hollon et al. (1992) when looking at BDI scores of posttreatment completers (*d* = 0.12). There was, however, evidence of a moderate effect of combined treatment as compared to CBT alone on recovery status based on HRSD score (*d* = 0.53), although this effect was somewhat less when using the BDI (*d* = 0.36). Finally, in a study comparing the efficacy of treatment completers on group CBT (*n* = 32) as compared with CBT alone (*n* = 32), Covi and Lipman (1987) found no differences in the percentage of patients recovered as measured by the BDI (*d* = 0.18).

In addition to the previously described issue of small sample sizes and delivery of psychotherapy, the most important methodological issue in these studies, perhaps, is the questionable consistency with which pharmacotherapy was delivered and monitored across studies (Meterissian & Bradwejn, 1989). First, in most studies, little information was provided about the experience or training of the pharmacotherapist. In addition, what was considered "clinical management" across studies could have represented very different interactions between pharmacotherapists and patients, ranging from the assessment of side effects of medication to more

supportive psychotherapy (Persons et al., 1996). Further, there was little information provided in these studies regarding the monitoring of the patient's reaction to medication. Perhaps most striking is that compliance with medication regimens was not routinely assessed in a standardized manner in most studies. Thus, while patients were receiving pharmacotherapy, the nature of their actual treatment was unclear. In addition, in many cases, neither actual doses of medication utilized nor blood serum levels were reported to describe the level of medication given to patients. It is therefore questionable whether consistent or optimal pharmacotherapy was delivered both within, and across, studies.

Overall, the evidence of studies examining acute, posttreatment effects among depressed patients suggests a small benefit of combined treatment as compared to either psychotherapy or pharmacotherapy alone on overall symptom reduction and attrition, with the effects of combined treatment as compared to medication alone being somewhat stronger. There does, however, appear to be some evidence that combined treatment may result in moderately improved rates of recovery among treatment completers as measured by the HRSD, although this effect was not consistent when using the BDI. We believe that several competing conclusions may be drawn from existing research. First, if one were to accept that the existing research is methodologically sound and conceptually complete, then one would accept the general proposition that combined treatment is only slightly, or maybe moderately, more efficacious than single treatment. We reject this approach, however, because there are significant limitations in portions of the existing research, both in methods and in scope. Second, one could dismiss the existing literature entirely and propose that the issue has not been studied in sufficient detail to warrant specific conclusions. We believe this stance is similarly unjustified, because much is known about certain treatment-relevant variables.

EXAMINING TRENDS: WHICH PATIENT AND TREATMENT FACTORS PREDICT OUTCOME?

A third approach is to determine whether combined treatment may be useful for some individuals, but perhaps not others, and which methods of combined treatment delivery may be more efficacious than others. There is now increasing evidence that depression is

heterogeneous, representing a broad phenotypic category that encompasses many different illnesses and clinical profiles (Coryell et al., 1994), with differential responses to treatment (Persons et al., 1996; Robinson et al., 1990; Thase & Kupfer, 1996). Further, there may be ways in which the overall delivery of combined treatment can be improved in order to bolster efficacy.

Patient Factors: Severity or Chronicity of Depression

There is evidence that a significant percentage of individual depressive episodes tend to be more severe, requiring hospitalization, or have a more chronic course, lasting for several years each (Keller et al., 1992). Individuals suffering from severe or chronic depression may be less likely to respond to single treatment, whether it is pharmacotherapy (Dunner, 2001; Howland, 1991) or psychotherapy (Markowitz, 1994; Thase & Friedman, 1999). There are clear theoretical reasons that combined treatment may be more efficacious for severely or chronically depressed patients. For example, individuals with more severe or chronic depression may be more likely to demonstrate significant social difficulties following pharmacological treatments (Agosti, Stewart, Quitkin, & Ocepek-Welikson, 1993; Keller et al., 1992; Miller & Keitner, 1996; Thase & Kupfer, 1996). If these areas of functioning are not modified through psychotherapy, they may remain problematic following recovery and lead to relapse (Butzlaff & Hooley, 1998; Segal, Gemar, & Williams, 1999). Similarly, higher severity or chronicity of depression may be associated with increased biological dysfunction, including the increased presence of somatic symptoms such as loss of energy and disturbance of sleep and appetite, that may be particularly responsive to pharmacological interventions (Thase & Kupfer, 1996). Treating more severe or chronic depression with combined treatment may lead to change across a wider range of functioning, thus resulting in better outcome.

In contrast to the findings among studies of depressed outpatients, two studies of depressed inpatients have reported improved efficacy for adding cognitive and behavioral treatments to pharmacotherapy both at posttreatment and long-term follow-up. Miller, Norman, and Keitner (1989) studied 45 depressed inpatients randomly assigned either to pharmacotherapy with hospital milieu support, or to pharmacotherapy and

milieu plus either cognitive therapy or social skills training. This treatment was initially delivered while the patient was hospitalized, and treatment continued for approximately four months following hospitalization. Both the BDI and HRSD were utilized as outcome measures in this study. Significant differences were found for the combined treatment group at the end of outpatient treatment on the BDI both when examining completers ($d = 0.39$) and when using endpoint analyses ($d = 0.56$). No significant effects were found for HRSD scores when examining completers ($d = 0.06$) or using endpoint analyses ($d = 0.41$). However, when using a stringent definition of recovery that took into account both HRSD and BDI scores, the combined treatment group had increased recovery rates among treatment completers ($d = 0.64$) and when using endpoint analyses ($d = 0.76$). Similar results were found in a study that examined the efficacy of combined treatment while patients were still hospitalized (Bowers, 1990). In a sample of 20 patients, this study found that, among completers, those who were treated with cognitive therapy had significant improvement on the BDI ($d = 1.37$) but not for HRSD scores ($d = 0.42$). Further, patients were more likely to recover as measured by the HRSD ($d = 1.5$) as well as the BDI ($d = 2.67$). Thus, there is initial evidence suggesting that combined treatment may be more beneficial, particularly on rates of recovery, among depressed inpatients as compared to outpatients.

Further, evidence suggests that combined treatment may be more efficacious than single treatment for chronic depression. In a recent large-scale study, 681 adult patients with either chronic, recurrent, or “double depression” (i.e., co-morbid major depression and dysthymia) were assigned to 12 weeks of treatment with either nefazadone, cognitive-behavioral analysis system of psychotherapy (CBASP), or the combination of both treatments (Keller et al., 2000). Patients in the combined treatment condition were more likely to recover than patients receiving medication ($d = 0.69$) or psychotherapy ($d = 0.76$) alone. These results provide initial evidence that the effects of combined treatment may be somewhat improved among individuals with chronic depression. Future studies need to be conducted to compare the differential response to combined treatment and single treatment of chronic as compared with nonchronic depression.

No study has ever directly compared the differential efficacy of combined versus single treatment among more severely or chronically depressed individuals as compared to nonchronic or less severely depressed individuals. However, Thase et al. (1997) conducted a “mega-analysis” or meta-analysis of original data of 595 patients with major depressive disorder previously enrolled in six different standardized treatment protocols. In these original studies, all patients were treated for 16 weeks with either cognitive-behavioral therapy (CBT) or interpersonal psychotherapy alone (IPT), or with both interpersonal psychotherapy and antidepressant pharmacotherapy. This study found that whereas combined treatment was not significantly more efficacious than psychotherapy alone among individuals with less severe depression, individuals with higher severity or chronicity of depression had a markedly improved outcome for combined treatment as compared to psychotherapy alone. The authors acknowledge that there are important limitations of this research. For example, the combined treatment examined in this study included only IPT as a form of psychotherapy, whereas the single treatment condition included patients who received both IPT and CBT. Further, this study only examined the relative benefit of combined treatment versus psychotherapy alone, but did not evaluate the relative efficacy of combined treatment as opposed to pharmacotherapy. Finally, Thase et al. (1997) examined posttreatment differences in efficacy but did not report other aspects of outcome, such as treatment retention or long-term follow-up.

Overall, these studies provide some evidence suggesting that combined treatment may be somewhat more efficacious in treating more severely or chronically depressed patients. Thus, these studies represent an important first step in understanding the role of severity and chronicity of depression as a predictor of combined-treatment outcome. However, future work needs to be conducted to replicate these results and more directly test the hypothesis that there is a differential benefit to combined treatment among severely or chronically depressed patients.

Treatment Factors: Adding Psychotherapy to Medication to Prevent Relapse

There has been increasing recognition of the need not only to help depressed patients initially recover from

depression, but also to maintain these gains and prevent future relapse (Depression Guideline Panel, 1993; Paykel, 2001). Some studies have examined the long-term effects of combined treatment delivered during the acute phase of treatment. These studies utilized a naturalistic follow-up, such that patients were free to seek additional treatment, but were not required to continue standardized treatment based on study protocol. Overall, these studies demonstrated a moderate effect of combined treatment resulting in reduced relapse rates as compared to medication alone ($d = 0.68$, $\chi^2 = 4.06$). In contrast, the effect of combined treatment on relapse rates as compared to psychotherapy alone is small ($d = -0.12$, $\chi^2 = 1.48$).

For example, Blackburn et al. (1986) examined the efficacy of either cognitive therapy ($n = 15$) or pharmacotherapy alone ($n = 10$), or the combination of the two ($n = 16$) among individuals who had initially responded to that acute treatment condition (e.g., patients recovering from medication alone). These patients initially received maintenance treatment for one year; patients who received pharmacotherapy during the acute phase of treatment received medication at a lower dosage rate during maintenance treatment, whereas patients receiving cognitive therapy received maintenance phase “booster” cognitive therapy sessions every six weeks, as opposed to every week. Following this initial maintenance treatment, patients were followed naturalistically for an additional year, and treatment during this period was not reported in the study. Patients in the combined-treatment group reported significantly lower rates of relapse as compared with patients receiving medication alone ($d = 1.33$), but not when compared with CBT alone ($d = 0.04$). Similarly, in a follow-up of the Hollon et al. (1992) study, Evans et al. (1992) examined relapse after initial recovery among patients receiving acute-phase combined CBT and medication ($n = 13$), cognitive therapy alone ($n = 10$), and initial drug treatment ($n = 10$). Neither patients’ CBT nor medication was continued during follow-up. Patients were followed naturalistically, and only 15% sought out additional treatment. Patients initially receiving combined treatment were less likely to relapse than patients receiving medication alone ($d = 0.80$), but not cognitive therapy alone ($d = 0.12$). Further, in a naturalistic follow-up of the Murphy et al.

(1984) study in which follow-up treatment was not reported, Simons, Murphy, Levine, and Wetzel (1986) found that combined treatment did not result in a reduced relapse rate as compared to medication alone ($d = 0.10$). However, in contrast to cognitive therapy alone, combined treatment was less efficacious in preventing relapse ($d = -0.53$). Finally, in a one-year naturalistic follow-up of depressed inpatients, Miller et al. (1989) examined rates of relapse among initial responders to treatment. This study reported approximately 75% of patients continuing treatment, although the nature of the treatment was unspecified. They found that acute-phase combined treatment was associated with lower rate of relapse as compared to the treatment as usual condition ($d = 0.60$).

While this work examined the long-term effects of acute-phase combined treatment, initial work has been conducted to determine whether using combined treatment as maintenance treatment following initial recovery as compared with either maintenance pharmacotherapy (i.e., medication dosage is maintained after initial response) or psychotherapy alone improves relapse rates. Comparisons of combined treatment as compared to medication alone produced small effects ($d = 0.26$, $\chi^2 = 2.26$). Studies using interpersonal psychotherapy in combination with continued medication use have produced somewhat mixed results. Frank et al. (1990) examined the three-year outcomes of combined and single treatments as maintenance therapies for patients who responded to acute-phase pharmacotherapy and IPT. This study utilized a five-cell design to examine, among other treatment conditions, the effects of imipramine alone ($n = 28$), IPT alone ($n = 26$), and the combination of IPT and imipramine ($n = 25$) as maintenance treatments. This study found no significant benefit of adding IPT to imipramine with clinical management alone in preventing relapse ($d = 0.07$). However, there was a benefit of combined treatment as compared to IPT alone ($d = 0.82$). In a similar study among older adults, Reynolds et al. (1999) also examined the use of combined psychotherapy and pharmacotherapy as a maintenance treatment following acute-phase combined treatment among 107 patients over the age of 59. Specifically, this study examined the use of maintenance nortriptyline in combination with IPT ($n = 22$) as compared with nortriptyline alone

($n = 24$). In this study, acute treatment consisted of weekly psychotherapy and monthly medication visits to achieve remission of depressive symptoms. During the maintenance condition, IPT was delivered once a month, and medication was maintained at a dosage comparable with the dosage utilized during the acute phase of the trial. The recurrence rate between the two treatments was not significantly different, although the effect size indicating a benefit of combined treatment was moderate ($d = 0.59$).

Other studies have examined the effects of adding cognitive therapy to patients who are either continuing maintenance medication, or increasing medication dosage after initial response. Paykel et al. (1999) examined 158 patients who had partially remitted from major depression using antidepressant medication. Patients were then randomized to antidepressant medication plus clinical management alone, or medication in combination with cognitive therapy for 16 sessions during 20 weeks, as well as 2 booster sessions. Antidepressant medication dosage was maintained for all patients. This study found that cognitive therapy reduced rates of relapse, although the effect found was small when both examining treatment completers ($d = 0.31$) and using endpoint analyses ($d = 0.39$). Similarly, Perlis et al. (2002) examined the effect of delivering cognitive therapy to individuals who were increasing medication during the maintenance phase of treatment. In this study, 132 outpatients who recently achieved remission from major depression while taking 20 mg of fluoxetine had their medication increased to 40 mg. Patients were randomized to receive medication alone or cognitive therapy for 12 weeks, and seven biweekly sessions. At a 28-week follow-up, there were no differences between the groups on frequency of relapse either when examining completers or ($d = 0.09$) using endpoint analyses ($d = 0.06$).

Combined treatment has previously been conceptualized as providing both psychotherapy and pharmacotherapy concurrently, with the goal of delivering more intense treatment during the acute phase of illness in order to perpetuate recovery or in the maintenance phase to prevent relapse. However, recent work has suggested that pharmacotherapy and psychotherapy can be combined sequentially, rather than concurrently, for the treatment of major depression among individuals

discontinuing initial medication use (Fava, Grandi, Zielezny, Canestrari, & Morphy, 1996; Fava, Rafanelli, Grandi, Canestrari, & Morphy, 1998). In contrast to acute-phase combined treatment, this treatment approach has the advantage of delivering treatment over a longer period of time. Further, this approach may be more useful than acute-phase combined treatment in helping patients struggle with issues that may arise following medication discontinuation (e.g., concerns about remaining well without medication).

Initial research examining this combined treatment approach was conducted in a study of 40 patients with major depression who had been successfully treated with antidepressant medication. These individuals were then randomly assigned to either cognitive-behavioral treatment of residual symptoms or standard clinical management. In both types of treatment, antidepressant drugs were gradually tapered and discontinued. At a four-year follow-up assessment, cognitive-behavioral treatment resulted in a significantly lower relapse rate than did clinical management ($d = 0.75$). These results dropped to ($d = 0.54$) at a 6-year follow-up, but still represented a moderate effect. Thus, this study provides initial evidence of the efficacy of adding CBT to medication delivered sequentially as compared to pharmacotherapy followed by clinical management.

Generally, combined treatment appears to produce the largest effects of preventing relapse as compared to medication alone in studies of naturalistic follow-ups or among patients discontinuing medication. Further, these studies have generally examined the efficacy of adding cognitive-behavioral therapy to medication alone. In contrast, studies of combined treatment as compared to continued maintenance medication or psychotherapy alone have produced small effects, with the exception of the possible benefit of adding medication to IPT (Frank et al., 1990). While the nature of the ongoing treatment received by patients in the naturalistic follow-up studies was unclear, one way of interpreting the data is to speculate that a significant percentage of patients in the studies using naturalistic follow-up may have discontinued medication (e.g., Evans et al., 1992) or, at the very least, may not have received the same level of structured pharmacological intervention as did patients in medication continuation studies. Thus, taken together, the addition of cognitive-behavioral therapy

improves relapse rates among individuals with discontinued, or less structured, medication use but not among patients receiving continued medication. Further, the effects of CBT seem to continue over long-term follow-up regardless of whether CBT is delivered in the acute or maintenance phase. These findings are consistent with previous research suggesting the long-term benefits of cognitive therapy (DeRubeis & Crits-Cristoph, 1998; Hollon, Thase, & Markowitz, 2002).

GENERAL CONCLUSIONS ABOUT EXISTING RESEARCH

The research conducted thus far points to evidence of a small but consistent benefit to combined treatment as compared to either psychotherapy or pharmacotherapy alone in overall symptom reduction and attrition during acute-phase treatment. There does appear to be evidence that combined treatment results in moderately improved rates of recovery as measured by the Hamilton Rating Scale for Depression, as well as evidence of reduction in relapse rates for individuals receiving cognitive therapy as compared to individuals who are either discontinuing medication or are followed naturalistically. As a point of reference from which to judge the differential effects of combined treatment, meta-analyses of the differential effect size of psychotherapy as compared to no treatment for depression have produced large effects. For example, group treatment ($d = 1.0$; McDermut, Miller & Brown, 2001) and cognitive therapy ($d = 2.15$; Dobson, 1989) have demonstrated large effects in comparison to no treatment controls. The effect sizes found in this review were more comparable to comparisons of cognitive-behavioral as compared to general verbal therapy ($d = 0.37$; Robinson et al., 1990) and group CBT as compared to group psychodynamic treatment ($d = 0.30$; McDermut et al., 2001). Further, these results are slightly lower than, but comparable to, reported differences between antidepressant medication and placebo ($d = 0.50$; Joffe, Sokolov, & Streiner, 1996; Khan et al., 2000).

IMPROVING COMBINED TREATMENT OUTCOME: TOWARD AN ILLNESS COGNITION MODEL OF DEPRESSION

Up until this point, we have discussed the efficacy of combined versus single treatments for depression and have highlighted the need to examine trends in patient and treatment factors in predicting treatment efficacy.

We believe that the observation of a small advantage for combined treatment should not be overlooked. Further, some studies report moderate or large effects, particularly on rates of recovery and relapse, suggesting the potential of combined treatment to improve outcomes. We would now like to ask the following question: What may be limiting the efficacy of combined treatment? We have identified many issues regarding limitations of current studies, including relative paucity of studies, poor monitoring of adherence to either medication or psychotherapy, and small sample sizes.

We would like to conclude this paper by focusing more on the content of combined treatment and the process by which it is delivered. Based on our clinical experience and review of the literature, we are struck by how little attention is given to the role of the patient's subjective model of depression in the theory and practice of combined treatment. Specifically, we argue that the patient's view or personal model of depression (e.g., perception of symptoms, causes, chronicity of depression) may influence adherence to treatment and ultimately treatment outcome. For example, cognitive-behavioral treatments emphasize the importance of the patient's understanding of the cognitive model of depression in facilitating treatment (Beck et al., 1979). The inclusion of two separate therapeutic approaches in one patient (e.g., cognitive therapy and medication) may potentially involve very different models of the etiology, symptoms, course, and treatment of depression. We believe that one of the unique challenges that may arise from delivering two distinct treatments with potentially different models of depression (e.g., depression is caused by biological vs. cognitive factors) is that patients may have difficulty developing coherent models to guide adaptive self-regulation behavior, thus limiting the efficacy of the combined-treatment approach.

Illness cognition models have been utilized to understand the link between somatic symptoms, emotional reactions to those symptoms, and adherence to treatment among individuals with physical disease. Leventhal, Diefenbach, and Leventhal (1992) proposed the common-sense model of illness cognition that suggests that self-regulation is a function of the representation of threats, targets for ongoing coping set by the representation (e.g., symptom reduction, temporal expectancies for change), the procedures used to regulate these targets,

and the appraisal of coping outcomes. There are several dimensions of the illness cognition model: (a) identity, or the label placed on the disease and on the symptoms associated with it; (b) causes, or the ideas about how one gets the disease; (c) consequences, or the expected outcome and sequelae of the disease; (d) timeline, or the expectations about the duration of the disease and its characteristic course; and (e) controllability/cure, or the beliefs about the extent to which the disease is amenable to control or cure. One of the key assumptions of this model is that the coherence, or patient's overall understanding, of the relation of symptoms, coping strategies, and appraisal of the efficacy of these strategies in managing symptoms will determine the maintenance of behavior and ultimate self-management. For example, an individual with heart disease who can feel fatigue, identify fatigue as a symptom of heart disease, and believes that heart disease can be managed at least in part by personal behavior, may experience a coherent model of heart disease management if a coping strategy such as exercise results in reduced fatigue. Further, Leventhal et al. (1992) proposed that in order for effective self-regulation to occur, the illness cognition models of the patient need to be interpersonally coherent or consistent across the primary support system involved in treatment: practitioner(s) and family. For example, if the same patient with heart disease has a family member who thinks that heart disease is "genetic" and can't be managed by personal behavior, that patient may be less likely to engage in exercise as an effective method of self-regulation.

Research exploring common-sense representations of medication has improved our understanding of how people evaluate different treatment modalities (Horne, 1999). There is now compelling evidence from the health psychology literature that the patient's mental representations of illness and treatment predicts treatment retention and adherence, as well as social and physical functioning among individuals with physical disease (for a review, see Hagger & Orbell, 2003). More recently, initial research has attempted to determine the relation of illness cognition to the emotional and behavioral responses to schizophrenia (for a review, see Lobban, Barrowclough, & Jones, 2003).

Currently, there is very little research linking illness representations with outcome in depression. Yet what

work has been done suggests that models of illness may be important to treatment outcome. In an early study of 17 patients receiving cognitive therapy, Fennell and Teasdale (1987) found that individuals who endorsed the cognitive conceptualization of depression were more likely to be rapid responders to treatment and reported a more favorable response to homework within the first 2 weeks of starting treatment. Similarly, in a cross-sectional study of 41 primary care patients with significant depressive symptoms, Brown et al. (2001) found that patients who were currently taking antidepressant medication were more likely to view depression as more chronic. Further, individuals who reported that interpersonal difficulties were the cause of their depression had poorer adherence to medication. Most recently, Manber et al. (2003) examined the relation of medication adherence to illness cognitions among 121 patients receiving an alternative treatment—acupuncture treatment—for depression. This study found that individuals who attributed depression to an unchangeable, personal flaw were more likely to drop out of treatment. Thus, while the data is preliminary, these results suggest that personal models that are consistent and coherent with treatment delivered may enhance treatment adherence.

Why would illness cognition models be particularly important in combined treatment? In either psychotherapy or pharmacotherapy alone, it is possible to imagine very clear, coherent models that a patient could adopt (see Figure 1). For example, in the context of taking medication, a patient may identify primarily biological symptoms (e.g., low energy, poor appetite) and attribute these to a chronic and potentially uncontrollable condition caused by a biological dysregulation for which medication is necessary (Brown et al., 2001). If medication is taken regularly, and symptoms remit, this may create a coherent system for the patient. Similarly, a patient in cognitive therapy could have a very different but equally coherent model. Patients could be encouraged to focus particularly on mood and cognitive symptoms (e.g., sadness, hopelessness) and attribute these to a maladaptive cognitive style that is not chronic and is controllable. If the patient engages in cognitive techniques and sees both immediate and more general change, the patient may have developed a coherent system based on a different collection of

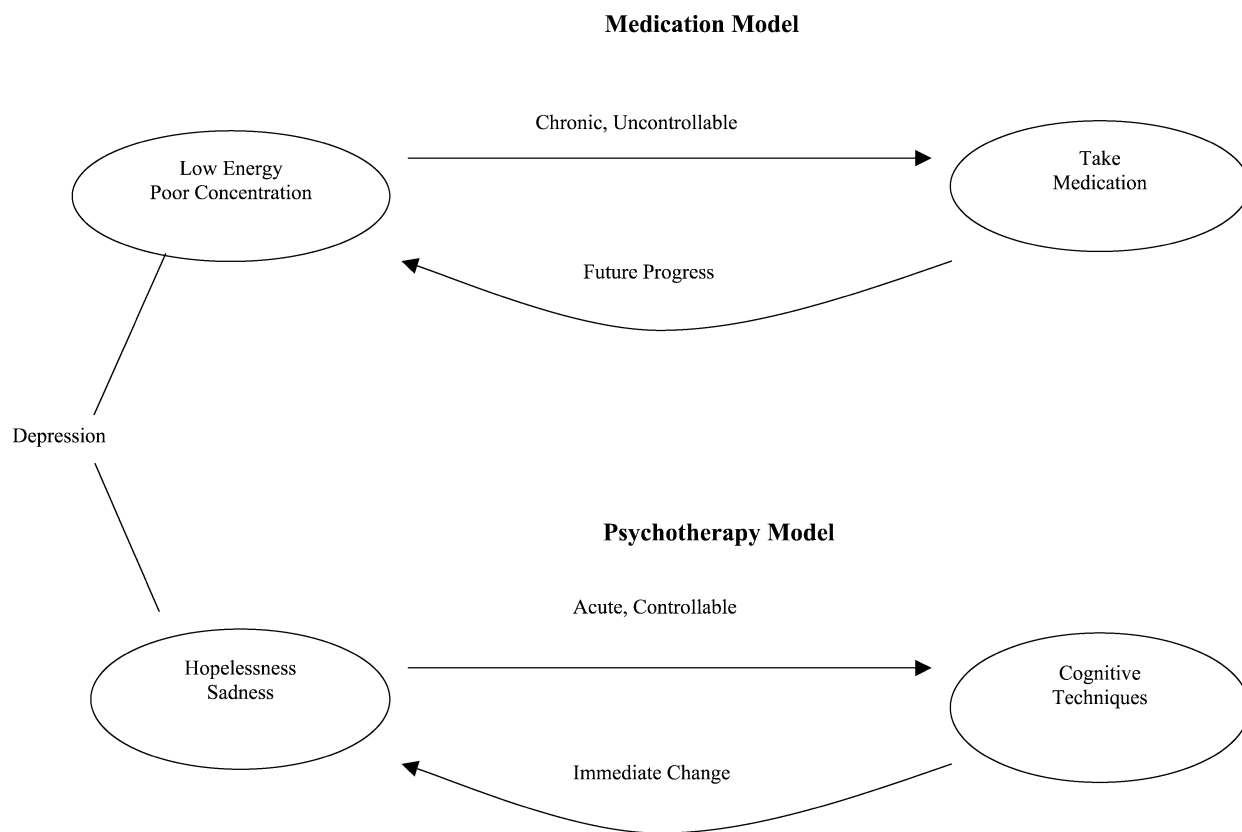


Figure 1. Illness cognition models of depression.

symptoms, representations, and strategies (Fennell & Teasdale, 1987).

We propose that by participating in simultaneous psychotherapy and pharmacotherapy, patients are left to contend with two potentially different models of depression as an illness. Broadly speaking, there are several points at which either (or both) intrapersonal or interpersonal coherence could break down in the context of combined treatment. First, representations of symptoms may be very different across these two treatments. For example, it is possible that pharmacological approaches support the view that depression is attributable to internal, physical dysregulation, which may be more chronic over time, whereas psychotherapy supports the view that depression is attributable to interpersonal, behavioral, and/or cognitive dysregulation, which may tend to be more controllable and episodic over time. If an individual perceives the timeline of her symptoms to be episodic, she may stop taking medication as soon as her symptoms remit. If the

treatment goal is medication maintenance, however, it may be preferable for her to view her symptoms as chronic, such that she will perceive an ongoing need to take medication (Horne & Weinman, 1999). Yet a chronic timeline that is paired with perceived uncontrollability may undermine a patient's efforts in psychotherapy because of a belief that ongoing behavior change may not be feasible (Hagger & Orbell, 2003). When exposed to potentially conflicting explanations of the causes and controllability of depression, patients in the combined treatment condition may choose one explanation (e.g., depression is caused by neurotransmitter imbalance and is controllable through medication) over another (e.g., depression is caused by negative core beliefs and is controllable through cognitive restructuring), and those explanations may influence treatment adherence.

In addition, coping strategies based on these two approaches are very different, and expectations of associated symptom relief may differ as well. Specifically,

consistent with the chronic model often associated with medication use (Brown et al., 2001), medication is to be taken regularly, not necessarily in response to a mood swing, and the effects are not supposed to be immediate, as would be the case with tranquilizers. In contrast, perhaps more consistent with an acute model of depression, psychological techniques like those utilized in cognitive therapy are often designed to be in reaction to increased depressed mood, and the expected effects are rather immediate. Thus, the integration of these models may not be internally coherent to the patient.

Finally, these two models are often not integrated in a coherent way by the patient or by the patient's primary support system (i.e., psychotherapist, pharmacotherapist, and primary caretaker). Patients hold different views about their health than do the health professionals with whom they consult (Eichenberger & Rossler, 2000; Heijmans et al., 2001), or family members (Heijmans, de Ridder, & Bensing, 1999). A psychotherapist's model of depression and the associated roles of medication as compared with psychotherapy, may be very different from that of a pharmacotherapist. This model may be different still from that of the patient, or the patient's support system. Depressed individuals may be more likely to engage in treatment behavior if practitioners and significant others are "on the same page" with the patient regarding the nature of the depression, how to treat it, and how to evaluate treatment. For example, poor practitioner-patient interaction may be associated with poorer treatment adherence in diabetics (Ciechanowski, Katon, Russo, & Walker, 2001). Similarly, Figueiras and Weinman (2003) found that the degree of congruence between a patient's and partner's perception of the nature and consequences of myocardial infarction predicted patient physical and social functioning over a 12-month follow-up period.

Overall, we believe that we currently know very little about patients' personal models of depression or whether these models are intrapersonally or interpersonally coherent. Issues such as patient's beliefs about the combined-treatment approach were generally not addressed in the studies reviewed. Further, there was little discussion of the management of the treatment "team" in integrating care between psychotherapy and pharmacotherapy. Finally, there was almost no discus-

sion of the role of significant family members in facilitating combined treatment. Increased attention to the models of depression of patients, their providers, and their family members may help improve the delivery and efficacy of combined treatment.

IMPROVING OUTCOMES IN COMBINED TREATMENTS

So what can practitioners do to minimize the likelihood that their patients' illness models will interfere with their ability to take advantage of both aspects of a combined treatment? As there is little current evidence that illness cognition models predict outcome in combined treatment, there is accordingly little work on how combined treatments may be improved based on these models. We offer a number of future directions to begin examination of this issue.

Developing Intrapersonal Coherence of Illness and Treatment Cognition Models

First, we recommend that researchers consider including measures of illness cognition models, such as the revised Illness Perception Questionnaire (IPQ-R; Moss-Morris et al., 2002), and of treatment modalities, such as the Beliefs about Medicines Questionnaire (BMQ; Horne, 2000), in future investigations of combined treatment for depression. By including a standardized assessment of patients' (and, perhaps, practitioners') views of their depressive illness and the proposed treatment, we will be able to begin to understand patient's illness cognition models in the context of combined treatment. Further, we will be able to determine whether there is a relation between illness and treatment cognition, patient treatment preferences, adherence, and subsequent clinical outcomes.

Further, we suggest that future research include, and better document, illness cognition models proposed to patients in clinical trials. It is possible that for combined treatment to be most effective, separate descriptions of patient, family, and practitioner models of depression and treatment perceptions and preferences need to be supplemented with a better understanding of how conflicting models can undermine the patient's adherence to both psychological and pharmacological treatments. There is a need for a coherent, biopsychosocial model of depression and treatment that integrates and makes sense of the individual and joint effects of

psychological and pharmacological treatments. This model must be accurate both as to its biology and its social/cognitive features, easy to understand, and available to and shared by all parties directly involved in the treatment: patient, family, and practitioner. One important aspect of such a model would be to provide a framework for the initiation and maintenance of combined treatment by reconciling inconsistencies among pharmacological and psychological treatments by emphasizing the unity of mind and body (i.e., that biology affects experience and behavior and that behavior feeds back and alters biology). Thus, the most effective treatment requires the balanced use of pharmacotherapy and psychotherapy.

One example that is consistent with the evidence of the long-term benefits of adding cognitive therapy to medication would be to explain to patients that depression is a chronically depressed condition of the central nervous system that argues for the use of medication that can over time both raise and help sustain the level of energy. The experience of depression, including mood changes and lack of interest in positive things, may be exacerbated by social challenges (causes) that work against the medication: they deplete the system (consequences) by causing depressed feelings and repetitive, negative thoughts. Psychotherapy helps the individual to identify these negative experiences, the external events that cause them, and provides skills for their management (i.e., control). By controlling these events and their associated moods and thoughts as quickly as possible, psychotherapy prevents the accumulation of negative factors (timeline) that will detract from the energy level of the system and work against medication's benefits. It also provides the skills needed to manage external threats and the negative, internal moods and repetitive, negative thoughts that further deplete energy and work against medication. By identifying and responding effectively to these threats and controlling associated thoughts, such strategies complement and work with medication and allow the central nervous system to restore energy and maintain balance. Psychotherapy provides the moment by moment, ongoing system that allows the medication to work and that sustains its effects. The patient can develop a coherent model that calls for monitoring, treating, and evaluating outcomes over time by

associating the label, "depression," with medication (which sustains the energy needs of the central nervous system) and the more rapid, environmentally induced shifts in symptoms and moods with psychotherapy (which blocks unnecessary strain and further depletion of the system).

Treatments designed to modify illness cognition are associated with improved outcomes in physical disease. In a prospective randomized study, 65 consecutive patients with their first MI were assigned to receive an intervention designed to alter their perception of MI or usual care from rehabilitation nurses (Petric, Cameron, Ellis, Buick, & Weinman, 2002). Patients were assessed before and after the intervention, upon leaving hospital, and at three months. The patients in the intervention group had significantly different attitudes, and returned to work more quickly than did the control group. Further, at three months, they had fewer angina symptoms.

Developing Interpersonal Coherence with Illness Cognition Models

We also think that future work should allow for coordination between the three (or four) major aspects of the patient's interpersonal system: (a) the practitioner responsible for providing psychotherapy, (b) the practitioner responsible for providing pharmacotherapy, (c) the patient, and (d) the primary support system. Specifically, coordination of care would allow the practitioners to compare the models of illness that they each communicate (implicitly and explicitly) to the patient. This would facilitate interpersonal coherence between the patient and his or her two primary support systems.

While work in this area has not been explicitly conducted, Miller, Keitner, Ryan, Solomon and Cardemil (2003) recently examined whether delivering family therapy to depressed patients with poor family functioning would improve outcomes. In this study, 121 hospitalized depressed patients were grouped on the basis of their level of cognitive impairment (high, low) and family dysfunction (high, low), and then were either "matched" or "mismatched" to a treatment designed to directly address this deficit. The four treatment conditions were: (a) *Pharmacotherapy*, which consisted of pharmacotherapy + clinical management, (b) *Combined*

Cognitive Therapy, which consisted of cognitive therapy + pharmacotherapy, (c) *Combined Family Therapy*, which consisted of family therapy + pharmacotherapy, and (d) *Combined Cognitive + Family Therapy*, which consisted of cognitive therapy + family therapy + pharmacotherapy. Randomized treatment began at discharge from the hospital and continued for 24 weeks on an outpatient basis.

Results indicated that while treatment matching only improved short-term outcome for patients who were symptomatic at discharge from the hospital, patients who received additional family therapy had significantly better outcomes than those who did not. Patients receiving family therapy had a significantly faster decrease in depressive symptoms, as evidenced by the random regression results, and had significantly lower levels of symptoms at a Week 12 assessment. These advantages for patients receiving family therapy diminished slightly over time, with fewer significant differences obtained at the Week 24 assessment. However, the overall pattern of results strongly suggests that adding family therapy to pharmacotherapy substantially improves the outcome of severely depressed patients.

CONCLUSIONS

Major depression represents one of the most serious mental health problems in the country. Combined psychotherapy and pharmacotherapy is a commonly utilized, but little understood, approach to the treatment of this disorder. Further understanding the efficacy of this treatment approach could result in important advances in the management of major depression. Previous reviews of the combined-treatment literature have suggested mixed conclusions regarding the efficacy of combined treatment as compared to single treatment (i.e., either psychotherapy or pharmacotherapy alone) for the treatment of major depression. Our review suggests that there are small but consistent benefits of combined treatment on symptom reduction and attrition and more moderate trends suggesting the benefit of combined treatment on level of recovery. There are trends in the literature suggesting that the benefits of combined treatment may be somewhat greater among individuals with severe or chronic depression. Further, adding cognitive-behavioral therapy to medication

alone, either during acute or maintenance phase of treatment, may reduce relapse among individuals not continuing a structured medication protocol.

In the process of completing this review and conceptual analysis of the field, we have found that there are significant gaps in knowledge. The field currently offers incomplete information in almost all areas. Larger samples, longer follow-up, and more comprehensive approaches to outcome are examples. Further, we believe that future research needs to be conducted exploring the potential role that illness cognition models play in patients' experiences with combined treatment. It is possible that there are challenges unique to combined treatment conditions, such as lack of coherence between psychotherapeutic and pharmacological models of depression's causes, timeline, and controllability, that should be addressed in future research. In short, to conclude that combined treatment does not improve efficacy over single treatment is premature and threatens to impede inquiry into an area of potentially enormous importance in the treatment of major depression.

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