Context in the Clinic: How Well Do Cognitive-Behavioral Therapies and Medications Work in Combination?

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Cognitive-behavioral therapy (CBT) and pharmacotherapy demonstrate efficacy across the anxiety disorders, but recognition of their limitations has sparked interest in combining modalities to maximize benefit. This article reviews the empirical literature to examine whether combining treatments influences efficacy of either monotherapy.

We conducted a comprehensive literature search of published randomized trials that compared combined treatment with pharmacologic or CBT monotherapies. Ten studies that met our inclusion criteria were reviewed in detail, and within-subjects effect sizes were calculated to compare treatment conditions within and across studies.

At posttreatment and follow-up, effect size and percentage responder data failed to clearly demonstrate an advantage or disadvantage of combined treatment over CBT alone for obsessive-compulsive disorder, social phobia, and generalized anxiety disorder. Some advantage of combined treatment over pharmacotherapy alone emerged from the few studies that allowed for such a direct comparison. In contrast, combined treatment for panic disorder seems to provide an advantage over CBT alone at posttreatment, but is associated with greater relapse after treatment discontinuation.

The advantage of combined treatment may vary across the anxiety disorders. The potential differences in usefulness of combined treatment are discussed, directions for future research are suggested, and implications for clinical practice are considered. Biol Psychiatry 2002;52: 987–997

Key Words: Anxiety disorders, CBT, pharmacotherapy, combined treatment, emotional processing, randomized controlled trials

Introduction

The purpose of this article is to review the advantages and disadvantages of adding medication to cognitive–behavioral therapy (CBT) and pharmacotherapy for anxiety disorders. Because other articles in this special issue address neural pathways and pharmacotherapy, we focus primarily on examining how CBT fares when delivered with and without medication and how information-processing theory of pathologic anxiety can account for the empirical picture. We first discuss the theory and practice of CBT for anxiety disorders and the mechanisms thought to underlie its efficacy. We then review some theoretical considerations for and against adding medication to CBT, and we summarize empirical studies that compare the benefit of combined treatment over monotherapies. Finally, we consider the empirical findings within an information-processing perspective and outline questions for future research.

Early behavioral models for the treatment of anxiety have been based on two suppositions: First, fears and phobias are acquired through classical conditioning, that is, through the formation of association between a neutral stimulus and an aversive stimulus such the former acquires the aversive properties of the latter. The neutral stimulus is then designated as a conditioned stimulus (CS), and the original aversive stimulus is called an unconditioned stimulus (UCS). Second, the acquired fears can be unlearned through extinction, that is, through presentation of the CS in the absence of the UCS. This conceptualization gave rise to exposure therapy (EX), in which patients systematically confront their feared situations, objects, responses (e.g., tachycardia), or memories, under safe circumstances with the goal of extinguishing their phobic fear. Although there have been debates about the mechanisms through which exposure therapy reduces anxiety symptoms, the benefit of this therapy has been demonstrated by a large body of research (cf. Barlow 2002).

Discontent with nonmediational (automatic) accounts for acquisition and extinction of pathologic anxiety led to the development of theories that posited a pivotal role for cognitive factors in anxiety (e.g., Beck et al 1985). The assumption here is that it is not the events themselves but rather their threat meaning that is responsible for the evocation of anxiety. Meaning in these theories is often assumed to be represented in language. Accordingly, cognitive therapy (CT) for anxiety disorders uses verbal discourse to challenge the patient's threat interpretations of events and to help replace them with more realistic ones.

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The focus on the meaning of events as accounting for pathologic anxiety paralleled the reconceptualization of conditioning in learning theories. For example, Rescorla noted that "conditioning depends not on the contiguity between the CS and US but rather in the information that the CS provides about the US," (Rescorla 1988, p. 153) and that the "organism is better seen as an information seeker using logical and perceptual relations among events along with its own preconception to form a sophisticated representation of its world" (Rescorla 1988, p. 154). In the same vein, when discussing the phenomenon of extinction, Bouton (1994, 2000) stated that "in the Pavlovian conditioning situation, the signal winds up with two available 'meanings' " (Bouton 2000, p. 58). Obviously, for rats the meaning of events cannot be represented in verbal language; rather, it is represented as associations between stimuli, responses, and outcomes.

Advances in information-processing theories of conditioning and of pathologic anxiety (e.g., Lang 1977) influenced conceptualizations of treatment for the anxiety disorders. One such conceptualization, emotional processing theory, was proposed by Foa and Kozak (1986). In this theory, fear is viewed as a cognitive structure in memory that serves as a blueprint for escaping or avoiding danger that contains information about the feared stimuli, fear responses, and the meaning of these stimuli and responses. When people are faced with a realistically threatening situation (e.g., a car accelerating toward them), the fear structure supports adaptive behavior (e.g., swerving away); however, a fear structure becomes pathologic when the associations among stimulus, response, and meaning representations do not accurately reflect reality in that harmless stimuli or responses assume threat meaning. In emotional processing theory, meaning is thought to be embedded in associations among stimuli, responses, and consequences (as in Rescorla 1988), as well as in language in the form of thoughts, beliefs, and evaluations (as in Beck 1976).

Within emotional processing theory the anxiety disorders are thought to reflect the operation of specific pathologic fear structures (cf. Foa and Kozak 1985). For example, the fear structure of individuals with panic disorder is characterized by erroneous interpretations of physiologic responses associated with their panic symptoms (e.g., tachycardia) as dangerous (e.g., leading to heart attack). As a result of this misinterpretation, individuals with panic disorder avoid locations they anticipate will give rise to panic attacks or similar bodily sensations, such as physical exertion. The fear structure of individuals with obsessive–compulsive disorder (OCD) most often involves the erroneous interpretation of safe stimuli (e.g., brown spots) as dangerous (e.g., AIDS-contaminated blood). Accordingly, the core pathology in panic disorder lies in the erroneous meaning of physiologic responses, whereas the core pathology of OCD lies in the erroneous meaning of external events. The supposition that inaccurate negative cognitions underlie the anxiety disorders has also been at the heart of theories posed by cognitive therapists (e.g., Clark 1986; Rapee and Heimberg 1997; Salkovskis 1985).

If fear and avoidance reflect the activation of an underlying cognitive fear structure, then changes in the fear structure should result in corresponding changes in emotions and behavior. Indeed, Foa and Kozak (1986) proposed that psychologic interventions known to reduce fear, such as EX, achieve their effects through modifying the fear structure. According to emotional processing theory, two conditions are necessary for therapeutic fear-reduction to occur: first, the fear structure must be activated; second, information that is incompatible with the pathologic aspects of the fear structure must be available and incorporated into the existing structure. Thus, within this framework, exposure therapy is thought to correct the erroneous cognitions that underlie the specific disorder (e.g., tachycardia = heart attack). This is also the explicit mechanism by which CT is thought to reduce fear. In this way the mechanisms that are thought to operate during exposure greatly overlap with those of CT. Moreover, some cognitive therapists (e.g., D.M. Clark, personal communication 2002) explicitly posit that fear activation is necessary to refute the patient's false interpretations, and CT programs routinely include an exposure component in the form of "behavioral experiments."

The essence of both exposure and behavioral experiments is to engineer fear-arousing situations in which the patient is expecting unrealistically that something bad will happen, but where the bad consequences do not occur. Accordingly, exposure and behavioral experiments do not substantially differ from one another, but the way they are conducted can be somewhat different. It is interesting to note that this view of exposure therapy is consistent with contemporary conditioning theories that "emphasize the importance of a discrepancy between the actual state of the world and the organism's representation of that state. They [learning theorists] see learning as a process by which the two are brought into line" (Rescorla 1988, pp. 153).

The cognitive–behavioral treatments derived from the theoretical approaches discussed above have generally proven quite efficacious for the anxiety disorders (cf. Nathan and Gorman 2002). Medication, including serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and benzodiazepines, has also been found efficacious with these disorders (e.g., Abramowitz 1997; Gould et al 1997; van Etten and Taylor 1998); however, among treatment completers, neither CBT nor pharmacotherapy helps all individuals, and those who are helped remain, on the whole, somewhat symp-

tomatic. The limitations of these therapies are compounded by refusal and dropouts.

In the quest to improve on the available interventions, experts (e.g., Greist 1992) have advocated combining CBT with pharmacotherapy. One way by which medication is thought to enhance CBT outcome is through the reduction of the patient's anxiety and thereby promotion of his or her ability to tolerate longer exposures to feared situations. Indeed, long exposure has been found more effective than short duration (Chaplin and Levine 1981; Rabavilas et al 1976; Stern and Marks 1973). Furthermore, moderate anxiety during exposure is thought to enhance processing of the corrective information embedded in the exposure situation and thereby promote amelioration of pathologic fear.

In contrast to these arguments, other theoretical considerations suggest that the addition of medication to CBT may impede its outcome. Specifically, the reduction of anxiety by medication may block fear activation that, as noted earlier, is a necessary condition for the cognitive changes that mediate treatment success. Blocking of fear during CBT may be particularly detrimental for panic disorder, for which the erroneous cognitions involve a catastrophic belief about anxiety-related bodily responses and treatment aims at disconfirming this belief. For example, a panic patient whose panic attacks stopped or were largely attenuated after the administration of alprazolam is likely to attribute the nonoccurrence of heart attack during exposure therapy to the medication. Under this circumstance, the perception that panic sensations are dangerous cannot be disconfirmed. Because the core erroneous cognition had not been eradicated, after treatment discontinuation the panic and associated threat meaning will return.

We now turn to review empirical studies that examine the relative efficacy of combined treatment versus that of monotherapies.

Method for Inclusion/Exclusion of Studies for the Literature Review

In preparing this article, we first located all randomized controlled trials (RCTs) involving combined treatments for anxiety disorders via PsycINFO and MEDLINE electronic database searches and via reference lists in the extant anxiety disorder literature. Next, we selected studies for the review by using the following four criteria: 1) study patients had an established diagnosis; studies using samples with mixed diagnoses were excluded; 2) the study included at least two treatment groups, one of which received pharmacotherapy or CBT monotherapy (CBT with or without pill placebo) and the other received treatment combining CBT and medication; 3) the study design had to permit unequivocal test of combined versus monotherapy; studies using crossover designs were excluded; 4) the study had to employ adequate methodology including a) random assignment, sufficiently large sample sizes for statistical power, use of manualized psychotherapies, and adequate treatment quality, dosage, and duration to allow for symptom reduction; b) blind independent evaluation conducted by a trained assessor; and c) presentation of essential statistics for calculating within-group effect sizes.

Twenty-six RCTs evaluating combined treatments were identified through the literature searches. Nine studies met the inclusion criteria and are discussed here. Of the 17 studies that were excluded, 5 did not allow for a clear test of combined versus monotherapy, 9 failed to use adequate methodology, 4 failed to include blind independent evaluation, and 10 failed to present essential statistics for calculating within-group effect sizes. Table 1 presents the studies that were excluded from the review and the reasons for their exclusion.

Three departures from the criteria should be noted. Because of the paucity of treatment outcome studies in social phobia (SP) that compared combined treatment and monotherapy, we included the Blomhoff et al (2001) study, despite the absence of independent assessment and essential statistics for calculating within-group effect sizes; we included here percent responders data from that study. Second, to illustrate issues emerging from the discussion, two studies that did not meet the above criteria were included: the Otto et al (1993) panic disorder study and the Connor et al (2002) posttraumatic stress disorder (PTSD) study. It should also be noted that for the van Balkom et al (1998) study, we collapsed the EX and CT conditions because the study design allowed for the introduction of behavioral experiments (exposure) into the CT and discussion of expectations of disastrous consequences (cognitive procedures) into the EX after the midtreatment assessment.

Method for Calculating Effect Sizes

When available, we present the completer data only because we are interested in comparing combined treatment to monotherapies when the treatments are delivered at adequate doses and for sufficient periods of time; use of intent-to-treat data would allow for the inclusion of patients who did not receive optimized treatment, and thus their inclusion here could obscure effects of interest. For each of the studies presented, we selected the main independent evaluator measure of the primary symptoms (e.g., Yale–Brown Obsessive Compulsive Scale [Y-BOCS]for OCD) for calculation of within-subject effect sizes using Cohen's (Cohen 1977) *d*. The formula for Cohen's *d* is as follows:

$$d = M_{pre} - M_{post}/SD_{pooled},$$

Table 1. Reasons for Exclusions of Studies

Study	Diagnosis (es)	Failed unambiguous test	Inadequate methods	No blind assessment measures	No essential stats
Sharp et al 1996	PD				X
Lader and Bond 1998	GAD				X
Marks et al 1980	OCD	X	X		
Falloon et al 1981	SP		X		X
Mavissakalian and Michelson 1986	PD				X
Mavissakalian et al 1983	PD		X; N = 18		
Marks et al 1983	PD	X	X		
Hussain 1971	Mixed PD, SP	X	X; Mixed group		X
Johnston et al 1995	PD			X	X
Marks et al 1988	OCD	X			X
Whitehead et al 1978	Phobics		X; N = 12	X	X
Marks et al 1972	Phobics	X	X; N = 18		X
Foa et al 1992	OCD	X			
Clark and Agras 1991	SP		X	X	
Zitrin et al 1980	PD		X		
Telch et al 1985	PD			X	
de Beurs et al 1995	PD				X

PD, panic disorder; GAD, generalized anxiety disorder; SP, social phobia; OCD, obsessive-compulsive disorder

where M_{pre} and M_{post} denote the pretreatment and posttreatment means for each treatment group on the selected outcome measure and SD_{pooled} represents the pooled SD. When follow-up data were provided, we calculated the effect sizes by replacing the posttreatment means with follow-up means and pooling the pretreatment and follow-up standard deviations. To ease the reader's task, all of the within-subjects effect sizes are presented in Table 2.

Combined versus Monotherapy Treatment Outcome

Obsessive-Compulsive Disorder

Four studies met our inclusion criteria. Cottraux et al (1990) randomized 60 patients to one of three conditions: exposure and ritual prevention (EX/RP) + fluvoxamine (FLV), EX/RP + placebo (PBO), and FLV. Treatment was discontinued after 24 weeks, with a 4-week medication taper. The EX/RP treatment was conducted weekly and involved eight sessions of imaginal exposure in sessions and in vivo exposure as homework followed by 16 sessions of therapist-guided in vivo exposure and ritual prevention. Follow-up assessment was conducted 6 months posttreatment. It is important to note that 55% of those who received FLV only were on medication during follow-up in contrast to 21% in the combined group and 25% in the EX/RP + PBO group. Assessment included blind assessors' ratings of daily duration of rituals. At posttreatment (week 24, $n = 44$) there was a trend for EX/RP + FLV to be superior to EX/RP + PBO on this measure, which disappeared at follow-up. Percent responders, defined as reduction in daily rituals of greater than or equal to 30%, were as follows: 69% for EX/RP + FLV, 40% for EX/RP + PBO, and 54% for FLV at posttreatment; 64% for EX/RP + FLV, 50% for EX/RP + PBO, and 45% for FLV at follow-up. Chi-square analyses failed to detect group differences at either posttreatment or follow-up.

Hohagen et al (1998) randomized 58 patients to either EX/RP + FLV or EX/RP + PBO. In this study, CBT comprised a 3-week assessment followed by a 4-week treatment that included six 3-hour involving therapist-aided EX/RP sessions that included cognitive restructuring and daily homework exposure assignments. Medication began 1 week into the assessment and was gradually increased over 5 weeks. Assessment was conducted weekly, with posttreatment conducted at week 9. The main outcome measure was assessor's ratings on total score of the Y-BOCS (Goodman et al 1989a, 1989b). Analyses were conducted on a subset of patients ($n = 49$), with nine outliers dropped to equate the two groups on baseline Y-BOCS severity. Both groups improved significantly from pre- to posttreatment on Y-BOCS total scores, with no significant group differences. Percent responders, defined as greater than or equal to 35% reduction on the total Y-BOCS, were as follows: 87.5% for EX/RP + FLV and 60% for EX/RP + PBO. Chi-square analyses revealed an advantage for combined treatment.

In a third study, van Balkom et al (1998) randomized 117 patients into 1) CT; 2) EX/RP; 3) FLV + CT; 4) FLV + EX/RP; and 5) wait-list. In this study, CBT was conducted over 16 45-min sessions (6 in the first 8 weeks, 10 during the remaining weeks). In the two combined treatments, FLV was administered alone for 8 weeks, after which medication was stabilized and a 10-session CBT

Table 2. Effect Sizes for Included Studies

Study	Diagnosis	Outcome Measure	Tx Conditions	Post-Tx	Post-Maintenance	Follow-Up
Cottraux et al (1990)	OCD	Ratings of daily	EX/RP + FLV	1.89	N/A	1.55
$n = 60$		duration of	EX/RP + PBO	1.00	N/A	1.37
		rituals	FLV	1.37	N/A	1.35
Hohagen et al (1998)	OCD	Y-BOCS	EX/RP + FLV	2.97	N/A	N/A
$n = 58$			EX/RP + PBO	2.02	N/A	N/A
van Balkom et al (1998)	OCD	Y-BOCS	CBT + FLV	1.85	N/A	N/A
$n = 117$			CBT	1.20	N/A	N/A
			Wait-list	.10	N/A	N/A
Foa et al (in preparation)	OCD	Y-BOCS	EX/RP + CMI	2.14	N/A	2.49
$n = 122$			EX/RP	2.01	N/A	2.57
			CMI	1.28	N/A	1.37
			PBO	.64	N/A	-
Marks et al (1993)	PD	Assessor-rated	EX + ALP	4.31	N/A	2.72
$n = 154$		phobic avoidance	EX + PBO	3.45	N/A	3.54
			RLX + ALP	1.91	N/A	1.43
			RLX + PBO	.99	N/A	1.58
Cottraux et al (1995)	PD	WP2	CBT + BUS	.44	N/A	.76
$n = 77$			CBT + PBO	.57	N/A	.66
Barlow et al (2000)	PD	PDSS	CBT + IMP	2.33	2.68	.91
$n = 312$			CBT + PBO	1.98	1.98	1.98
			CBT	1.44	1.58	1.97
			IMP	1.86	2.10	1.43
			PBO	.99	1.17	-
Blomhoff et al (2001)[a]	SP	CGI	EX + SRT	45%	N/A	N/A
$n = 387$			EX + PBO	33%	N/A	N/A
			SRT	40%	N/A	N/A
			PBO	24%	N/A	N/A
Power et al (1990)	GAD	HAM-A	CBT + DZ	3.19	N/A	N/A
$n = 113$			CBT + PBO	2.57	N/A	N/A
			CBT	3.29	N/A	N/A
			DZ	1.46	N/A	N/A
			PBO	1.04	N/A	N/A

TX, treatment; OCD, obsessive-compulsive disorder; PD, panic disorder; SP, social phobia; GAD, generalized anxiety disorder; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; WP2, Anxious Inhibition Widlocher-Pull; PDSS, Panic Disorder Severity Scale; CGI, Clinical Global Improvement; HAM-A, Hamilton Anxiety Scale; EX/RP, exposure and response prevention; FLV, fluvoxamine; PBO, placebo; CBT, cognitive-behavioral therapy; CMI, clomipramine; ALP, alprazolam; EX, exposure; RLX, relaxation; BUS, buspirone; IMP, imipramine; SRT, sertraline; DZ, diazepam.

[a] This study only reported percent responders

was added for an additional 8 weeks. The wait-list condition was conducted over 8 weeks. Assessment was conducted at pre, mid, and posttreatment. The main outcome measure was the independent assessor's ratings of the Y-BOCS. Results indicated that at midtreatment ($n = 100$), all four active treatments were superior to waitlist, with no significant differences among active treatments. At posttreatment ($n = 86$), the four active treatments did not differ from one another. Because we focus here on the relative efficacy of monotherapies versus CBT + medication, and because of the considerable procedural overlap between cognitive therapy and EX/RP after the 8-week midpoint assessment, we collapsed the pre- and posttreatment data for the four active treatments into two groups: 1) CBT + FLV; 2) CBT alone. Percent responders data are not reported by the authors.

In a recently completed multicenter study conducted at the University of Pennsylvania and Columbia University (E.B. Foa and M.R. Liebowitz, principal investigators), 122 patients were randomized to four conditions: EX/RP + clomipramine (CMI), EX/RP alone, CMI alone, and PBO. EX/RP included a two-session assessment period followed by 15 sessions of two hours each, conducted over 3 weeks and 8 weekly maintenance sessions. Medication was administered for 12 weeks, after which it was tapered over 3 weeks. Assessment was conducted at pretreatment, posttreatment (12 weeks), and at follow-up 12 weeks later (week 24). The main outcome measure was assessor's ratings on the Y-BOCS. At posttreatment ($n = 87$), all active treatments were superior to PBO; EX/RP + CMI and EX/RP alone were both superior to CMI but did not differ from one another (Franklin et al 2002b). At follow-up ($n = 46$), again the groups that received EX/RP were superior to CMI alone but did not differ from one another. Percent responders, defined as a Clinical Global Improvement (CGI) rating of 1 or 2, at posttreatment were as follows: 79% for EX/RP + CMI, 86% for EX/RP, 48% for CMI, and 10% for PBO. At the week 24 follow-up, percent responders were 80%

for EX/RP + CMI, 89% for EX/RP, and 55% for CMI. As with the Y-BOCS data, at posttreatment and at follow-up, the groups that received EX/RP were superior to CMI but did not differ from one another.

Taken together, the studies of combined treatment in OCD suggest that CBT is not impeded by medication, nor does the addition of medication enhance the efficacy of CBT. The Franklin et al (2002b) study also found that both conditions that involved CBT were superior to SRI monotherapy, whereas Cottraux et al (1990) failed to detect such a difference.

Panic Disorder

Three studies on panic disorder (PD) met our inclusion criteria. In a multicenter study, Marks et al (1993) randomized 154 patients into four conditions: Exposure (EX) + alprazolam (ALP), EX + PBO, relaxation (RLX) + ALP, and RLX + PBO. The EX and RLX were conducted over 8 weeks; ALP and PBO were administered simultaneously with EX or RLX for 8 weeks and were tapered over the following 8 weeks. In this study, RLX was conceived of as a psychologic placebo; EX comprised six 2-hour sessions conducted over 8 weeks, which included therapist-aided exposure during sessions and self-directed homework exposure 1 to 2 hours per day. In RLX, patients underwent therapist-aided relaxation training during 6 1-hour sessions conducted over 8 weeks. Homework consisted of practicing relaxation 1-hour daily with the aid of an audio tape. Measures included assessor's ratings on the phobic avoidance scale (Gelder and Marks 1966). At posttreatment (n = 129), both EX + ALP and EX + PBO produced greater improvement in phobic avoidance than did ALP and PBO. At a medication-free follow-up (n = 76) conducted 5 months posttreatment, EX + PBO was superior to all other groups; the combined treatment lost its superiority over ALP. Percent responders, defined as a CGI 1 or 2, at posttreatment were as follows: 71% for EX + ALP, 71% for EX + PBO, 51% for RLX + ALP, and 25% of RLX + PBO. Percent responders at follow-up were as follows: 36% for EX + ALP, 62% for EX + PBO, 29% for RLX + ALP, and 18% for RLX + PBO. Chi-square analysis again indicated that, at posttreatment, the groups that received EX were superior to those who did not. At follow-up, the EX + PBO group was superior to all other groups.

In contrast to the findings of Marks et al (1993), in a randomized study (n = 77), Cottraux et al (1995) failed to detect differences between CBT + buspirone (BUS) and CBT + PBO. In this study, CBT consisted of 16 1-hour weekly sessions of panic control treatment (PCT; Barlow and Cerny 1988), which included cognitive restructuring, imaginal and in vivo exposure, and exposure to anxiety-related physical sensations. Patients were instructed to conduct self-exposure between sessions. The BUS was administered simultaneously with PCT for 16 weeks and tapered over 1 week following posttreatment assessment. During the follow-up period, no patients in the CBT + BUS condition and five patients in the CBT + PBO condition required further CBT treatment for their agoraphobia. Moreover, four patients in the CBT + BUS condition and one patient in the CBT + PBO condition required the prescription of additional medication during the follow-up period. Measures included assessor's ratings on the Anxious Inhibition Widlocher–Pull (WP2). In contrast with the modest effect sizes found for the WP2 measure (see Table 2), percent responder rates, defined as at least 50% reduction on the first agoraphobic target behavior, were quite sizable: 67% for CBT + BUS and 74% for CBT + PBO at posttreatment; 44% of the CBT + BUS and 68% of CBT + PBO at follow-up. No treatment differences were detected here as well.

In the largest study of PD to date, Barlow et al (2000) randomly assigned 312 patients to one of five conditions: CBT + imipramine (IMP), CBT + PBO, CBT alone, IMP alone, and PBO. In this study, CBT consisted of panic control treatment (PCT) conducted over 9 months. During the first 3 months, patients received 11 50-min sessions of PCT and or 11 30-min sessions of medication management. Medication and CBT were conducted simultaneously. Following the acute phase of treatment, responders to treatment received monthly sessions of PCT and or medication management, for an additional 6 months (maintenance). Postdiscontinuation of treatment assessment was conducted 6 months later. The PCT consisted of cognitive restructuring, exposure to interceptive cues, and breathing retraining exercises. Assessment included blind evaluations of panic symptoms, using the Panic Disorder Severity Scale (PDSS; Shear et al 1997).

At both the 3-month (n = 213) and 9-month (n = 170) assessments, CBT + IMP was superior to CBT alone. Six months after treatment discontinuation (n = 116) there was relapse in the combined treatment, so that both groups that received CBT without IMP had a superior outcome to the combined treatment. Percent responders, defined as a 40% reduction on the PDSS, at the end of the 3-month acute phase were as follows: 84% for CBT + IMP, 80% for CBT + PBO, 67% for CBT alone, 75% for IMP, and 39% for PBO. At the end of maintenance, percent responders were as follows: 90% for CBT + IMP, 76% for CBT + PBO, 73% for CBT alone, 80% for IMP, and 38% for PBO. At 6 months postdiscontinuation, 50% for CBT + IMP, 83% for CBT + PBO, 85% for CBT alone, and 60% for IMP. Inconsistent with the picture emerging from the PDSS means, Chi-square analyses failed to detect superiority of the combined treatment over CBT at the end

of acute and maintenance treatment; no differences between combined treatment and IMP were detected on percent responder data at either test point; however, at postdiscontinuation, the two groups that received CBT without IMP were superior to combined treatment.

The overall picture emerging from the three PD studies is more complex than that emerging from the OCD studies: at posttreatment the combined treatment was found advantageous to CBT alone in the Barlow et al (2000) study. After treatment discontinuation, in both Marks et al (1993) and Barlow et al (2000) studies, the groups that received CBT without medication were superior to the combined treatment, suggesting that the addition of pharmacotherapy may have impeded the long-term benefits of CBT.

Social Phobia

No studies of social phobia (SP) met our inclusion criteria, although data from a collaborative study, conducted at the University of Pennsylvania and at Duke University (Bux et al 2002) is currently being analyzed. In that study 309 patients with primary generalized SP were randomized to one of five conditions: CBT + fluoxetine (FLX), CBT + PBO, CBT alone, FLX alone, and PBO. When available, results from that trial will allow for a comparison of combined treatments to both CBT and pharmacotherapy alone.

In light of the paucity of SP studies, we have included here a recent effectiveness study conducted by primary care physicians (Blomhoff et al 2001) despite methodologic limitations that would have precluded its inclusion (e.g., absence of blind assessors). In this study, 387 patients with primary diagnosis of SP were randomized to one of four treatment conditions: EX + sertraline (SRT), EX + PBO, SRT, or PBO. Therapists were 47 physicians who underwent 30 hours of training in assessment and treatment delivery. In this study, EX consisted of nine 20-min sessions conducted over 16 weeks and a final visit at week 24. During these sessions, patients were given assignments for self-exposure homework and feedback for their progress. Medication management consisted of 10 visits, 9 of which were held during the first 16 weeks of treatment and the 10th at week 24. Assessment included clinicians and self-report ratings on degree of improvement on the CGI. At posttreatment (week 24), percent responders were as follows: 45% for EX + SRT, 33% for EX + PBO, 40% for SRT, and 24% for PBO. Both active medication conditions, but not EX + PBO, were superior to PBO; active treatments did not differ from one another, however. Because pre- and posttreatment means and standard deviations were not reported, effect sizes could not be calculated.

Existing data are quite insufficient for arriving at conclusions regarding the benefit of adding medication to CBT or to pharmacotherapy. The available results suggest neither an advantage nor a disadvantage of combined treatment.

Generalized Anxiety Disorder

Only one study of generalized anxiety disorder (GAD) met the inclusion criteria. Power et al (1990) randomly assigned 113 patients to one of five treatment conditions: CBT + diazepam (DZ), CBT + PBO, CBT alone, DZ alone, and PBO. In this study, CBT consisted of a maximum of seven sessions over 9 weeks in which patients received cognitive therapy and progressive muscle relaxation. Homework included exposure to anxiety eliciting thoughts and situations. Medication management was as follows: 1) 1 week of single-blind placebo; 2) 6 weeks of double-blind DZ or PBO; and 3) 3-week drug taper. Follow-up assessment was conducted at 6 months posttreatment. Assessment included assessor's ratings using the Hamilton Rating Scale for Anxiety (HAM-A; Hamilton 1959). At posttreatment (week 10; $n = 83$), combined treatment was superior to DZ alone but not to CBT alone. No HAM-A means were reported for the 6-month follow-up assessment. Percent responders, defined as reduction of ≥ 2 SD from pretreatment at posttreatment were as follows: 90.5% for CBT + DZ, 83% for CBT + PBO, 86% for CBT, 68% for DZ, and 37% for PBO. All active treatments were superior to PBO but did not differ from one another. Percent responders at 6 months follow-up were as follows: 71% for CBT + DZ, 67% for CBT + PBO, 71% for CBT, and 41% for DZ. Chi-square analysis revealed the superiority of treatments that included CBT treatments over DZ alone.

Summary

In this article, we present an overview of the advantages and disadvantages of adding medication to cognitive behavioral therapy (CBT) and to pharmacotherapy for four anxiety disorders: OCD, PD, SP, and GAD. We now summarize the findings and discuss them within an information processing framework of pathologic anxiety, which we introduced earlier on.

Obsessive-Compulsive Disorder

Of the four studies reviewed, only Hohagen et al (1998) found an advantage for combined treatment over CBT alone, and only on their categorical analyses of the Y-BOCS. Cottraux et al (1990) observed trends in favor of the combined treatment, which disappeared at follow-up. No value for combined treatment over CBT was found in either Franklin et al (2002b) or van Balkom et al (1998). The failure to find a clear advantage for combined treatment over CBT is consistent with experts' recommenda-

tion that CBT alone should be the first-line treatment for OCD (March et al 1997). Of the two studies that compared combined versus medication treatment, one found benefit for combined and one did not. It should be noted that studies reviewed here conducted combined treatment simultaneously and such programs may not maximize the effects of combined treatment.

A comparison between Franklin et al (2002b) and Cottraux et al (1990), the only two studies that allowed examination of the combined treatment versus the two monotherapies, revealed similar effect sizes for the combined and medication alone treatments, whereas the effect size for EX/RP was much larger in the Foa et al study. Because the two studies were similar in two treatments, the inconsistency with regard to CBT alone outcome is not likely to reflect differences in the two samples. A more plausible explanation lies in the procedural differences in the two EX/RP programs. Indeed, in a meta-analytic review, Abramowitz (1996) noted that procedural variants in EX/RP influence outcome. EX/RP in the Cottraux et al's study involved fewer sessions and thus less therapist-assisted exposure; treatment was delivered once per week as opposed to daily in the Foa et al's study. Given that "diluted" treatment is more likely to be the routine in general clinical practice, the effect sizes in the Cottraux et al's study may point to the potential benefit for combined treatment in settings where EX/RP is not conducted optimally.

Panic Disorder

The picture emerging from the three PD studies discussed here is somewhat different from that of OCD. Just as for OCD, the short-term advantage of combined treatment over monotherapies is unclear. In only one of three studies, albeit the largest one, Barlow et al (2000) found an advantage for combined treatment over CBT whereas Marks et al (1993) found combined treatment superior only to medication. More interesting findings emerged at follow-up, where in two of the three studies combined treatment interfered with long-term maintenance of gains of CBT. No such interference was evident in the two OCD studies with follow-up data. This discrepancy may be due to differences in the fear structures of the two disorders.

Earlier we suggested that the core erroneous belief in PD pertains to threat associated with anxiety-related physical responses such as tachycardia and dizziness. For PD, CBT is designed to elicit such responses and the absence of the anticipated disaster is provides corrective information about their safety. The diminished anxiety responses via medication may hamper the ability of CBT exercises to disconfirm the erroneous beliefs associated with these responses. The absence of disasters attributed to the medication rather than to mistaken beliefs. When medication discontinues and panic sensations return the unshaken beliefs resume their effects in maintaining symptoms. Because the OCD core fear structure involves association between threat and external stimuli, the reduction of anxiety responses by medication does not interfere with disconfirmation of such erroneous beliefs.

Consistent with the view that medication that suppresses panic impedes the necessary cognitive changes for long-term maintenance of gains in PD are findings by Otto et al (1993). In this study, 33 PD patients who were receiving open-label benzodiazepine treatment and wished to discontinue their medication were randomly assigned to CBT for PD or no additional treatment during a 10-week drug taper period. Among the CBT patients, 76% discontinued benzodiazepines successfully, compared with only 25% of patients who did not receive CBT. Presumably, CBT promoted cognitive change that allowed patients to give up their "safety pills." Furthermore, in a secondary analysis from the Marks et al (1993) study, Basoglu (1994) found that patients who at the end of 8 weeks of treatment attributed their gains to medication (either placebo or alprazolam) were more likely to relapse than those patients who attributed their gains to their own efforts.

Social Phobia and Generalized Anxiety Disorder

It is difficult to draw conclusions about combined treatments for SP and GAD given the paucity of well-controlled studies. The two studies discussed above (Blomhoff et al 2001; Power et al 1990) did not demonstrate benefit for combined treatment over CBT, but Power et al found combined treatment superior to diazepam. The limitations of comparing across diagnostic groups should be noted.

Conclusions

As we have seen in this review of the empirical literature, the hope that combined treatment will be a panacea for all patients with anxiety disorder has not been fulfilled. On the other hand, with the exception of PD, the worry that combined treatment will impede CBT also has not been realized. Before concluding from the studies discussed here that combined treatment is irrelevant, several issues warrant considerations.

First, in a review of this kind in which it is necessary to summarize across disorders, different CBT protocols, and different medication classifications, certain information is inevitably lost. For example, because only a small number of studies met our inclusion criteria, it is possible that certain medications may be more compatible with CBT than are others.

Second, all controlled studies to date adopted a simultaneous treatment design, which may not be optimal for

detecting the benefit of combining CBT and medication. For example, in Franklin et al (2002b), intensive CBT was completed before the effects of medication could be expected. To realize the benefit of combined treatment, a sequential design would have been more appropriate. Such a design was indeed adopted in an ongoing study of PTSD (Connor et al 2002) in which all patients are provided open-label SRT, followed by random assignment to either continued SRT alone, or SRT + 10 sessions of CBT delivered over 5 weeks. Preliminary results suggest the advantage of CBT augmentation. Several augmentation studies are now being conducted.

Third, studies in anxiety disorders generally suggested significant relapse upon medication discontinuation (e.g., Ballenger et al 1998; Liebowitz et al 1999; Pato et al 1988). Would the addition of CBT protect against relapse after discontinuation? In OCD (Liebowitz et al 2002) and perhaps also in PD (Barlow et al 2000; Marks et al 1993), this appears to be the case. Future studies should examine this important issue more closely.

Fourth, in all well-controlled studies examining combined versus monotherapy, samples included all patients that met the target diagnosis; however, combined treatment may be more beneficial for certain subsets of patients than for others. Not targeting specific populations may have obscured the benefit of combined treatment. This seems indeed to be the case in the Franklin et al (2002b) PTSD study. Patients who had a modest response to SRT after 10 weeks and received CBT augmentation continue to improve substantially, whereas modest SRT responders that continued on SRT alone did not show any further improvement. The advantage of CBT augmentation over continuing SRT alone was less evident in patients who responded well to SRT.

Another group of patients that may be especially suitable for combined treatment are those with comorbid depression. This hypothesis was supported by post hoc analysis on the Hohagen et al (1998) data. Depressed OCD patients who received combined treatment fared better than those receiving EX/RP alone, whereas no benefit of combined treatment was observed for nondepressed patients. The relationship between patient variables and outcome of treatment programs can greatly enhance our ability to optimize success rates and may also shed light on mechanisms of change.

Several caveats should be kept in mind regarding conclusions that can be drawn from the studies reviewed here. First, we have excluded 17 studies, some of which yielded disparate findings from the selected studies and inconsistencies with one another. For example, whereas four of these more methodologically limited PD studies suggested an advantage for combined treatment over monotherapy (de Beurs et al 1995; Mavissakalian et al 1983; Sharp et al 1996; Telch et al 1985), three found no such advantage (Johnston et al 1995; Marks et al 1983; Mavissakalian and Michelson 1986). As mentioned earlier, the various methodologic limitations of these studies preclude strong conclusions, as does the apparent inconsistency in their outcomes. Second, all the studies we reviewed used multiple measures and raters, the results of which were sometimes inconsistent. In an attempt to present a coherent picture, we focused our review on measures of the primary diagnosis as rated by an independent assessor. A slightly different picture might have emerged in some instances had we selected self-ratings. Third, to allow comparison of outcome across studies of the same disorder and across different disorders, we calculated effect sizes. Because studies vary with respect to placebo response rates, we chose to present within- rather than between-subjects effect sizes, which inevitably inflated our estimates of treatment effects. Fourth, our decision to review in detail only methodologically sound studies that were directly related to the topic at hand limited our discussion to only nine studies, which clearly underscores the provisional nature of our conclusions. Much more work is needed on this critical topic, and we recommend that the following research areas be considered: 1) more randomized controlled trials directly comparing combined treatment to CBT and pharmacotherapy alone for social phobia, PTSD, and GAD; 2) more studies across the anxiety disorders testing combined treatment strategies using designs that better mimic clinical practice, such as an adequate pharmacotherapy trial followed by CBT; 3) examination of long-term outcomes for patients who received combined treatment versus those who received monotherapies, with medication status at follow-up as a key dependent variable; 4) more studies examining augmentation strategies including CBT for pharmacotherapy partial responders; and 5) effectiveness studies that examine patient preferences for CBT, medication, or combined treatment (Zoellner et al, in press).

Implications for Clinical Practice

Information from this review has several implications for treatment providers who offer CBT, pharmacotherapy, or a combination of these therapies in their clinical practice. First and foremost, it is important to recognize that the jury is still out with respect to whether combined treatment is superior to monotherapy because there are few adequate studies from which to draw conclusions. Only in OCD are there more than three studies employing adequate methodology. Second, with the exception of PD, it appears that pharmacotherapy and CBT are compatible in that there is no evidence for interference effects. This conclusion is consistent with results from a recent open study of intensive CBT for OCD in the context of a fee-for-service

clinic, in which patients who received intensive CBT with or without concomitant serotonin reuptake inhibitor pharmacotherapy fared equally well (Franklin et al 2002a). Thus, from the literature on combined treatment it does not appear that concomitant pharmacotherapy is generally necessary for patients to profit from CBT. Third, the few studies that directly compared combined treatment to pharmacotherapy alone did show an advantage for the combined conditions, which may suggest that a course of CBT should be considered for patients receiving pharmacotherapy alone. As highlighted in the preliminary results of Connor et al's (2002) PTSD study, this may be especially important to consider when the patient has evidenced only a partial medication response.

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