Efficacy of Combined Pharmacological and Cognitive-Behavioral Treatments For Anxiety Disorders

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KEY WORDS

anxiety, anxiety disorders, combined treatment, cognitive-behavioral treatment, pharmacological treatment, panic disorder

ABSTRACT

Cognitive-behavioral therapy (CBT) and pharmacotherapy have both demonstrated success in treating the anxiety disorders. Recent controversy and much clinical debate have arisen over the potential benefits of using both treatments in combination. Although the possible advantages of simultaneous combining of CBT and medication treatments for anxiety could have significant impact on patient care, it has been generally difficult to demonstrate benefits of combined versus single modality treatments because of the relative efficacy of single modality treatments for anxiety and mood disorders. This article reviews the empirical literature on the relative efficacy of combined treatments for anxiety disorders as compared to single modality treatments. Findings are summarized from treatment-outcome studies examining the unique and combined efficacy of CBT and medication approaches. The advantages and disadvantages of combined approaches are highlighted with respect to the anxiety disorders. Collectively, research on combination therapies showed considerable variability in usefulness of these approaches across the anxiety disorders, and considerations for combining medication and psychotherapy treatments in practice are reviewed. Mental Fitness. *2003;2(4):37-44*

INTRODUCTION

Anxiety disorders are one of the most frequent and challenging disorders seen by primary care physicians. Fortunately, they are also among the most treatable psychiatric complaints. The outlook for patients with anxiety disorders has greatly improved over the past 2 decades with the refinement of empirically supported psychotherapies and the advances of new medications targeting these disorders. Although there is an increasing selection of possible treatments, this requires clinicians to choose among options without obvious advantages or disadvantages for a particular patient. This is further complicated by the fact that many patients see multiple caregivers for the same problem[1,2] or may request both psychotherapy and medication treatments simultaneously.[3,4] Very little is known about how different treatments interact and, as Gray[2] observed, the interactions may not always be favorable. This article discusses the state of the field with regard to combined treatments for anxiety disorders, reviews several clinical trials examining the combined treatment studies, and discusses the advantages and/or disadvantages of combining somatic and empirically supported psychotherapies.

Anxiety disorders are prevalent,[5] and patients with anxiety disorders commonly present in primary care settings for treatment. In fact, the majority of patients with anxiety disorders are seen in general medical rather than specialty mental health settings.[6] Considerable evidence in community, psychiatric, and primary care settings documents the disabling effects of anxiety.[7-11] While much information is known about the efficacy of psychotherapies and psychotropic medications alone, comparatively little is known about combining these therapeutic approaches. This lack of research is regrettable given the prevalent use and acceptance of combined treatments in real world clinical practice. Though combined treatment research

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Dr. Bruce receives grant and research support from Pfizer and Wyeth and honoraria from Pharmacia. This paper discusses unlabeled or unapproved uses of some drugs.

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is relevant to both psychologists and psychiatrists, primary care physicians may need to be updated on this literature for a number of reasons. First, many patients with anxiety disorders seek medical attention for somatic complaints prior to being diagnosed with an anxiety disorder. Secondly, primary care physicians are increasingly serving as gatekeepers to mental health services, providing both pharmacotherapy as well as referrals to mental health experts. The commonplace of combined treatments in clinical practice makes the interaction between the psychotropic provider and the treating psychotherapist vital to ensure proper treatment. Primary care providers should also be cognizant of findings from combined treatment studies because the results from these studies can assist in determining which medications, when added to psychotherapy, may enhance or possibly be deleterious to overall treatment outcome.

COMBINED PHARMACOLOGICAL AND PSYCHOSOCIAL TREATMENTS IN MENTAL HEALTH

Combined treatment approaches are common in everyday practice for the treatment of anxiety disorders. A significant percentage of patients receiving psychotherapy are also concomitantly receiving psychotropic medications.[12-14] Other results suggest that a majority of patients with anxiety disorders have received both medication and psychotherapy.[15] However, very little research has examined the additive or synergistic benefits of combining proven pharmacologic treatments with empirically supported psychotherapies for anxiety disorders. The need for high quality and innovative research on combined treatments has become increasingly apparent within the last several years. In the area of psychosocial treatment research, there have been critical advances in the ability to define and assess the adherence to as well as quality of treatment interventions.

Clinical research of psychosocial as well as pharmacological treatments has become increasingly sophisticated. In many of the mental disorders, clinical trials have demonstrated not only efficacy, but also the limitations of single treatment modality approaches. Particularly within the area of mood disorders, controlled studies have shown that despite significant improvements, many, if not most, patients remain partially symptomatic and/or relapse following treatment.[16] High rates of chronicity and recurrence have also been shown in many of the anxiety disorders.[17-20] There is a need for treatment research to test innovative strategies of combining and sequencing treatment modalities that will lead to better treatment compliance and symptom recovery, and to optimal functional capacity. The increasing demand for efficient and cost-effective treatments for mental disorders also highlights the need to demonstrate whether and which combinations of pharmacological and psychological treatments work most rapidly, most durably, and for which kinds of patients.

Combined treatment studies for anxiety disorders have lagged behind combination studies for other mental health disorders. In other psychiatric disorders, including depression, insomnia, headaches, and bulimia nervosa, combined treatments have demonstrated significant advantages over monotherapy.[21-25] For mood disorders, combined treatment approaches for major depression have generally had better outcome than singular treatment approaches. Keller and colleagues[21] found that the combination of cognitive-behavioral treatment (CBT) with nefazodone was significantly better than medication or psychotherapy alone. Similarly, Miller et al[21] also found increased efficacy for combined CBT and pharmacotherapy for the treatment of depression.

COMBINED TREATMENT STUDIES OF ANXIETY DISORDERS

Below are brief summaries of combined treatment studies that have been conducted in the past 15 years. Additionally, the forward Table is a reprint of a table by Foa and colleagues[26] on the overall effect sizes from studies the authors selected that met adequate methodological design criteria.

Panic Disorder

Although panic attacks can occur as part of all anxiety disorders, panic disorder is distinguished by the occurrence of unexpected, seemingly "out of the blue" panic attacks. Panic disorder can occur with and without the presence of agoraphobia (ie, avoidance or endurance of situations that might be difficult to escape from or in which help may be unavailable in the event of a panic attack or panic-like symptoms). Lifetime prevalence of panic disorder with agoraphobia is estimated to be between 1.5% and 3.5%, with 1-year prevalence rates estimated between 1% and 2%.[21] Panic disorder rarely occurs in isolation: majority (60%) of patients also experience concurrent comorbid psychological disorders,[27] including other anxiety disorders,[28] mood disorders,[29] substance use disorders,[30] and personality disorders.[31] The clinical picture for many patients with panic disorder is also often complicated by the fact

EFFECT SIZES FOR INCLUDED STUDIES

TABLE

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

*This study only reported percent responders.

From Foa, Franklin, & Moser (2002).[26] Reprinted with permission from the Society of Biological Psychiatry.

that many other medical disorders, including endocrine disorders, cardiovascular disorders, respiratory disorders, neurological disorders, and substance-related anxiety states, can mimic panic-like symptoms. As a result, nearly 85% of patients with panic disorder initially seek medical attention from a general medical provider for their panic symptoms.[32]

Monotherapy with CBT or pharmacological agents individually has been shown to be successful in the treatment of panic disorder. The hallmark components

of CBT for panic include psychoeducation (physiology of the anxiety system, the fight-or-flight response), cognitive restructuring (identifying and challenging anxious thoughts and beliefs), interoceptive exposure (activities that mimic physiological symptoms of a panic attack; eg, breathing through a thin straw, spinning in a chair), and in vivo exposure (experiencing situations that often bring on a panic attack; eg, elevators, crowded places). The efficacy of CBT for panic disorder has been demonstrated in more than 25 independently conducted clinical trials.[33,34] Several classes of medication have also been shown to be effective for the treatment of panic disorder, including benzodiazepines,[35] tricyclic antidepressants (TCAs),[36] selective serotonin reuptake inhibitors (SSRIs),[37,38] as well as others (ie, venlafaxine;[39] nefazodone[40]). It is valuable for patients to know that they have a choice of effective monotherapies for their panic disorder.

Although monotherapies have demonstrated great success in the treatment of panic disorder, in practice, many studies have shown that more often than not patients seek both medication and psychotherapy contiguously. Unfortunately, there are very few controlled studies that establish the clinical indications or added therapeutic benefit of such treatment. And it is far from clear whether the addition of psychotherapy to a drug regimen, or vice versa, will result in enhanced efficacy. For this reason, it is important to consider the medication classes separately in combination treatment studies.

First, with regard to the benzodiazepines, the combination of CBT with benzodiazepines has been shown to be quite controversial. Much of the data indicate that combination treatments involving the benzodiazepines are no better than CBT alone,[41] and there is some evidence suggesting that concurrent benzodiazepine therapy may undermine the long-term outcome of exposure therapy[42] or CBT.[43,44] For example, it has been hypothesized that patients need to experience anxious arousal during the initiation of exposure therapy. Concomitant benzodiazepine use could significantly reduce this anxious arousal, making exposure therapy less effective.[41] Additionally, benzodiazepines have been found to interfere with both acquisition and retention of new information, which could disrupt the learning process in exposure therapy.[45] Moreover, administration of medication may play an important role: Westra and Stewart[46] concluded that PRN (as needed) use of benzodiazepines may inhibit CBT outcome to a greater extent than regularly scheduled use. In sum, these findings indicate that the cognitive effects of benzodiazepines may hamper psychotherapy or that learning under the influence of a benzodiazepine may not carry over to the drug-free state (state-dependent learning). In contrast, a few small studies have shown that administration of CBT to patients withdrawing from benzodiazepines may facilitate successful drug discontinuance and reduce relapse at long-term follow-ups.[47,48]

Second, with regard to the TCAs, studies have shown some fairly modest short-term benefit to the addition of a TCA to CBT. In the largest combined treatment study to date, the combination of CBT (ie, Panic Control Treatment) was compared with the unique and combined treatment of imipramine, a pill placebo, and CBT plus a pill placebo in over 300 patients with mild to moderate agoraphobia.[49] This study demonstrated that the combination of imipramine and CBT conferred some advantage in the acute treatment with a continued advantage by the end of maintenance treatment in comparison with CBT alone (see Figure). However, at the 6-month follow-up, patients in the combination condition reported comparatively high rates of relapse. As a result, the authors concluded that the addition of imipramine to CBT may reduce the long-term durability of CBT.[49]

Third, the SSRIs have also shown considerable efficacy in the treatment of panic disorder. In fact, the first nonbenzodiazepine to receive the Food and Drug Administration (FDA) approval for the treatment of panic disorder was paroxetine. The efficacy of paroxetine has been demonstrated in several multi-center clinical trials.[37,38,50] Similar findings have been shown for other SSRIs including sertraline[51] and fluvoxamine.[52] Although few studies have investigated the long-term treatment of panic disorder with SSRIs, the treatment response rate appears to be slightly longer than that of the TCAs. Relapse rates and optimal duration of treatments have not been reported. Though no studies of combination treatment of panic disorder with SSRIs have been published, some have argued that such treatment may be beneficial with refractory patients, particularly those with comorbid mood disorders.[53]

Social Phobia/Social Anxiety Disorder

Social phobia, also known as social anxiety disorder, is a very common and often disabling disorder; lifetime prevalence rates are estimated to be 13%.[5] Many experts have labeled social phobia as the "neglected anxiety disorder." It typically onsets at an early age and is often accompanied by other comorbid mood or anxiety disorders.[28] Individuals with social phobia report significantly more impairment in all functional domains than primary care patients without mental

disorders.[54] Despite this high prevalence and disability, many sufferers either do not seek treatment or are not recognized as suffering from social anxiety disorder when seeking medical advice for other conditions. For individuals who do seek treatment for social phobia, several different pharmacologic agents have shown some efficacy in its treatment, including the SSRIs,[55,56] MAOIs,[57,58] benzodiazepines,[59] and buspirone (at higher doses[60]). Similarly, CBT, with its primary components of exposure therapy, social skills training, and cognitive restructuring, has also been found to significantly improve social phobia's clinical course.[61]

Although a variety of treatment outcome studies of social anxiety disorder have contrasted the effects of pharmacotherapy and psychosocial therapy, only a handful of studies have examined the effectiveness of these treatments in combination. In a randomized, double-blind study of 387 patients with social anxiety disorder, Blomhoff and colleagues[62] examined the efficacy of sertraline (50-150 mg) or exposure therapy, administered alone or in combination in a primary care setting. Results indicated that combined sertraline and exposure therapy and sertraline alone were significantly superior to placebo (see Table). Though not statistically significant, the authors suggest that combined treatment with sertraline and exposure therapy may enhance the treatment efficacy in primary care settings. Preliminary analyses from an ongoing study by Heimberg and Liebowitz,[63] in which group CBT is combined with phenelzine, have showed some symptom improvement that is greater than either of the monotherapies when compared to placebo; however, these reported findings are based on only partial samples of the entire study group and should be taken with due caution. Thus, conclusions about combined treatments for social phobia are hopeful, though still incomplete until more conclusive evidence exists of superiority over singular treatments.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD), characterized by intrusive, obsessive thoughts which are usually alleviated by compulsive actions and checking behaviors, is a prevalent and often chronic disorder that is currently treated with pharmacological and psychological approaches. Both CBT, using exposure and ritual prevention (EX/RP), as well as the SSRIs are recommended for OCD. Though treatments using the SSRIs and CBT have been found to be efficacious, oftentimes patients remain symptomatic or have residual symptoms of OCD.

Several studies on the relative efficacy of combined treatments have been conducted over the past decade for OCD (see Table). For example, Hohagen and colleagues[64] investigated whether the combination of behavior therapy with fluvoxamine was significantly better then behavior therapy with placebo in 58 patients with OCD. Results from this study indicate that while both groups showed significant symptom reduction after treatment, the combined treatment group showed a significantly higher response rate than patients receiving behavior therapy and a placebo (see Table). Another study also found some advantage (though not statistically significant) of combined treatment over monotherapy.[65] Still others, however, found no differences between combined pharmacotherapy and CBT when compared to CBT alone.[66] Thus, results from combined treatment clinical trials for OCD are mixed. These studies do suggest, however, that CBT is not hindered by concomitant medication, and there may be some benefit for certain patients with the addition of medications to CBT.

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is a highly prevalent, disabling, and chronic anxiety disorder associated with substantial vocational, social, and academic impairment.[17,67,68] It has been found to be the most common anxiety disorder in primary care patients.[69,70] A recent primary care study indicated that patients with GAD make twice as many visits to primary care doctors as other patients.[71] While efficacious treatments (both pharmacological and psychological) with moderate to large effect sizes have been developed for GAD,[72-74] only 1 study has examined the effects of a combined treatment approach for GAD.[75] This study, conducted over a decade ago, randomly assigned 113 patients to 1 of 5 treatment conditions, including CBT, diazepam, and their combination (see Table). At post-treatment, combined treatment was found to be superior to diazepam alone but not to CBT alone. Given the significant modifications in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, (*DSM-IV*) criteria for GAD since this study was conducted, and the fact that newer medications have been developed and approved for the treatment of GAD, a significant research gap exists.

PTSD

Posttraumatic stress disorder (PTSD) is a relatively common disorder, especially among women, with lifetime prevalence rates of 10% for women and 5% for

men.[76] Additionally, there is accumulating evidence to suggest that PTSD is a persistent disorder. Though there now exist FDA-approved medications (sertraline, paroxetine) for the treatment of PTSD as well as empirically supported CBTs, combined treatment studies of PTSD are in its infancy. Preliminary findings from an ongoing study examining augmenting sertraline with CBT (prolonged exposure) indicate that CBT may enhance the effects of sertraline, particularly in subjects who had only a partial response to medication.[77] Though promising, much more research is needed on combined treatment research in PTSD to help fill the significant gap in our knowledge.

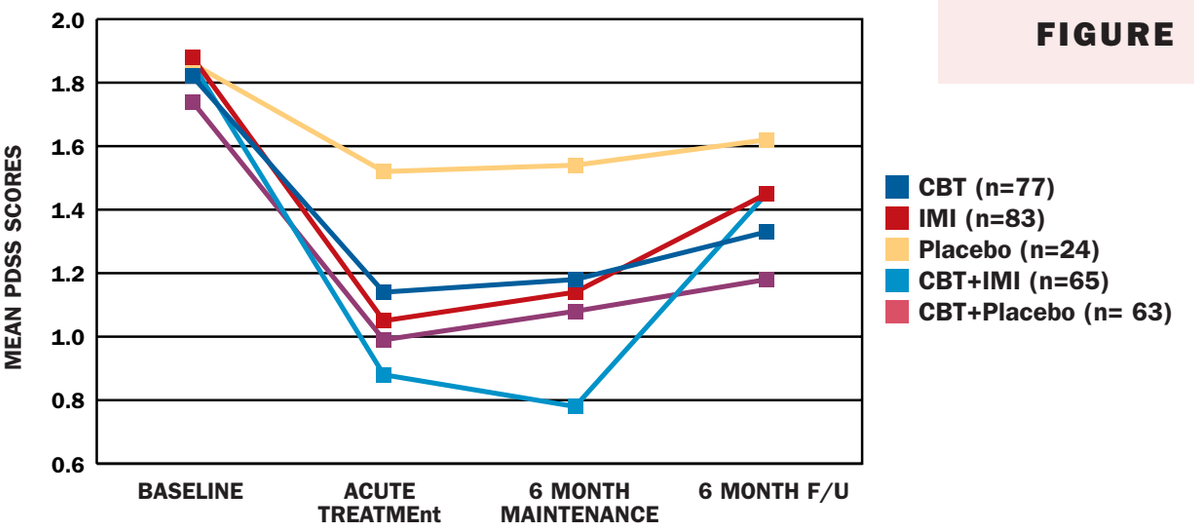
CONCLUSION

On the whole, this review demonstrates that research on the efficacy of combined medication and cognitive-behavioral treatments is far from clear or ideal. As can been seen in the studies cited above, it is apparent that effective pharmacotherapeutic and psychotherapeutic options for the treatment of anxiety disorders exist; however, the challenge of evaluating combination treatments has not been easy. This difficulty is due in part to the particularly effective single modalities, leaving a more restricted range of improvement. Another barrier to demonstrating the benefits of combined treatment has been the small sample size of most of this research, raising the possibility of type II error (ie, not finding a difference where one may truly exist). Overall, the combined treatment outcome is often not worse than the monotherapies; however, it is undoubtedly more costly and taxing on patients. The foremost challenge for clinical researchers appears to be identifying those patients or subgroups of patients with a given anxiety disorder who will do best with monotherapy with one type of treatments, or combination treatments.

In practice, there appears to be a marked disparity between research settings and the real-world appli-

INTENT-TO-TREAT ANALYSES FOR MEAN SCORES ON THE PANIC DISORDER SEVERITY SCALE AT BASELINE, END OF TREATMENT, 6-MONTH MAINTENANCE TREATMENT, AND 6-MONTH FOLLOW-UP[49]

FIGURE



CBT= cognitive-behavioral treatment, IMI= imipramine, PDSS= Panic Disorder Severity Scale.

Pairwise comparisons. After acute treatment, IMI was superior to placebo (.009), CBT was superior to placebo (.02), CBT+IMI was superior to CBT (.02). After 6-month maintenance, IMI was superior to placebo (.04), CBT was superior to placebo (.05), CBT+IMI was superior to CBT (.004), CBT+Placebo (.04) and IMI (.01). At 6-month f/u, CBT was superior to placebo (.05).

Data presented are from Barlow, Gorman, Shear & Woods (2000)[49]

cation of combination treatments. Conclusions from past studies examining the unique and combined efficacy of treatments may help guide practitioners who assist the anxious patient. With the exception of panic disorder, combined treatments do not appear to hamper progress in treatment outcome. Moreover, as reviewed above, specific combinations of medication and behavioral therapy may be particularly compatible.

This review makes evident the need for future research on the relative efficacy of combined treatment approaches beyond that of monotherapies. In addition to treatment outcome, exciting areas for future examination include the potential value of sequencing treatments (ie, concurrent, consecutive), the possibility that psychotherapy may facilitate medication compliance and adherence (eg, whether combination treatments impact patient dropout rates, perhaps due to medication side effects), and the identification of which patients or subgroups of patients may benefit most from which monotherapy or combination therapy (ie, treatment-refractory subgroups). If any of these advantages can be found with combined treatment studies, such combinations may also assist in reducing overall health care utilization and long-term costs. MF

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