Efficacy of Combined Pharmacotherapy and Psychotherapy Versus Monotherapy in the Treatment of Anxiety Disorders

Donald W. Black, MD


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Faculty Affiliations and Disclosures

Dr. Black is professor of psychiatry at the University of Iowa Roy J. and Lucille A. Carver College of Medicine in Iowa City.

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Please direct all correspondence to: Donald W. Black, MD, University of Iowa Carver College of Medicine, 2-126-B Medical Education Building, Iowa City, Iowa 52242-1000; Tel: 319-353-4431; Fax: 319-353-3003; E-mail: donald-black@uiowa.edu.

Focus Points

• Anxiety disorders are prevalent, disabling, and costly.
• There exist numerous pharmacologic options and psychological treatments for anxiety disorders which exhibit varying degrees of effectiveness.
• Despite insufficient evidence, many experts have recommended combined treatment, generally consisting of medication and cognitive-behavioral therapy (CBT), to treat anxiety disorders.
• Results from a literature review did not show an advantage or disadvantage of combined treatment over CBT alone and indicated...
that efficacy of combined treatment may vary across anxiety
disorders.
• Combined treatment is commonly recommended; empirical support
is limited.

Abstract

Anxiety disorders in the United States are prevalent, widespread, and disabling. These illnesses may account for
almost one third of the $148 billion total mental health bill each year. Pharmacologic options include tricyclic
antidepressants, monoamine oxidase inhibitors, serotonin norepinephrine reuptake inhibitors, selective serotonin
reuptake inhibitors, and anxiolytics. Psychological treatments include cognitive-behavioral therapy (CBT), cognitive
therapy, exposure, and ritual prevention therapies. Despite insufficient evidence, many experts recommend combined
treatment, generally medication with CBT. A literature review was conducted to examine studies with random
assignment, adequate methods and sample sizes, blind assessments, sufficient dosages and durations of treatment, and
satisfactory reporting of data, to determine whether combined treatment was superior to monotherapy. Twenty-six
randomized clinical trials were identified; nine met review criteria. A review of relevant studies could not confirm the
superiority of combined treatment over monotherapy. In one of four studies of obsessive-compulsive disorder,
combined treatment produced better results than monotherapy. There was no evidence of superiority for combined
therapy over monotherapy for the treatment of social phobia or generalized anxiety disorder. There were no studies
that met review criteria for either specific phobia or posttraumatic stress disorder (PTSD). With panic disorder, there
was evidence that combined treatment might actually lead to worse outcome. Combined treatment is commonly
recommended, but empirical support is limited. More research is needed. There are few well-designed studies, and
little data regarding PTSD and specific phobias.

Introduction

In any treatment area involving mental health, organized knowledge about the efficacy of psychological or
pharmacologic interventions too often yields a confusing mix of results that ranges from the unequivocally positive, to
the mildly suggestive, to the thoroughly inconclusive. Investigators comb through these studies on the basis of design,
methods, patients, treatments, and comparisons, to uncover situations from which valid conclusions can be drawn.

The purpose of this article is to review published results of randomized controlled trials (RCTs) that meet rigorous a
priori criteria in order to summarize and critique the evidence supportive of combined pharmacotherapy and
psychotherapy versus monotherapy, and to draw conclusions that may aid practitioners.

Background

Anxiety disorders are prevalent, widespread, and disabling. These conditions are estimated to account for about one
third of the entire economic cost of all psychiatric disorders combined.1 They are associated with increased healthcare
utilization, including primary or emergency services, and mental health services. The prevalence of anxiety disorders
varies with the population studied. In a primary care setting the prevalence of anxiety disorders in the United States was
estimated to be 19% (generalized anxiety disorder [GAD], 10.3%).2

Kessler and colleagues have estimated that ~18.1% of American adults ≥18 years of age (or 40 million people) have
anxiety disorders.3 Another study by Kessler and colleagues4 found that most people who experience one episode of
anxiety, do so by the age of 21.5 years, and three quarters of them will experience another episode during their lifetimes.
In comparison, the overall lifetime prevalence of anxiety disorders in Iceland was estimated to be more than 44%. The most common anxiety disorders, GAD, was 22%, and was almost three times more common in women than in men.

Young and colleagues found that during a 1-year period 83% of adults with a probable depressive or anxiety disorders saw a healthcare provider (95% confidence interval [CI], 81% to 85%) and 30% received some form of treatment (95% CI, 28% to 33%), mostly from primary care providers. Primary care practitioners provided appropriate care to 19% (95% CI, 16% to 23%), and mental health specialists provided care for 90% (95% CI, 85% to 94%) of patients. Among those who were less likely to receive appropriate care were men, African Americans, persons with lower levels of education, and persons <30 years of age or >59 years of age.

According to The Economic Burden of Anxiety Disorders in the 1990s study commissioned by the Anxiety Disorder Association of America (ADAA) and based on data gathered by the ADAA, anxiety disorders cost the United States more than $42 billion/year, almost one third of the $148 billion total mental health bill for the nation ($79 billion in indirect costs and $69 billion in direct costs). Interestingly, the total cost estimate for anxiety disorders ($42 billion) is similar to those previously reported for depression ($44 billion). Approximately $23 billion of the more than $42 billion/year spent on anxiety disorders is associated with the frequent use of health care services, as those with anxiety disorders seek help for symptoms that mimic physical illnesses.

Gould and colleagues estimated the costs for cognitive-behavioral therapy (CBT) services at $90 per session for an individual session, $40 for a group session, and $60 per session for individual follow-up sessions. In comparison, pharmacologic treatment was estimated at $60 per session. The same team of researchers estimated that a course of individual CBT treatment cost $1,650 over 2 years. In contrast, treatment with alprazolam ranged from $1,800 to $3,312, varying with treatment dose in the United States.

**Treatment Options**

Pharmacologic options include tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), serotonin norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), and benzodiazepine tranquilizers. The medications have proven remarkably effective for a range of anxiety disorders, and the newer generation of medications is generally well tolerated. Salient pluses are their efficacy, convenience, and safety in the event of an overdose. Negatives are dependency (for the benzodiazepines), compliance, cost, and potential adverse side effects.

Psychological treatments for anxiety disorders include CBT, cognitive therapy, exposure, and response-prevention therapies. As with medication, psychological treatment is often effective, and can bring about important emotional, attitudinal, or behavioral changes. Negatives can include duration of therapy and cost, while poor compliance can frustrate treatment objectives. A frequent but often unacknowledged drawback is lack of access to therapy, either due to limitations imposed by inadequate insurance coverage, or to a shortage of therapists trained to administer these treatments.

Combined therapy is a complementary approach frequently recommended and often employed. The accepted rationale is that medication corrects any underlying biological abnormality and the psychological treatment corrects cognitive or behavioral alterations. Combined therapy is viewed by some as necessary because neither medication nor psychotherapy (generally CBT in the context of anxiety disorders) helps everyone. Even with successful treatment, symptoms may persist; for this reason, clinicians seek to find whatever treatment, or combination of treatments, will help reduce the symptoms that remain.

Despite the lack of empirical evidence supporting its efficacy, many experts continue to recommend combination treatment. For example, the Expert Consensus Guidelines for posttraumatic stress disorder (PTSD), the American Psychiatric Association (APA) Practice Guideline for PTSD, the Expert Consensus Guideline for obsessive-
compulsive disorder (OCD),\textsuperscript{15} and the APA Practice Guidelines for panic disorder\textsuperscript{16} all recommend the combined approach.

Many experts who support combined treatment hold that medication enhances CBT outcomes by decreasing anxiety. This allows the patient to tolerate longer exposures to feared situations, which is essential in overcoming dreaded fears. Adding medication may also allow individuals to endure CBT, which increases anxiety; this appears to be particularly true in patients with OCD.

On the other hand, some experts believe that combined treatment may be detrimental because medication could interfere with CBT by blocking the fear reaction necessary for cognitive changes. This is thought to be particularly problematic for patients with panic disorder because erroneous cognitions typically involve catastrophic beliefs about anxiety-related bodily responses. Thus, CBT attempts to disconfirm these beliefs by showing the patient that panic symptoms (eg, chest pain) are not dangerous. If medication has blocked the somatic symptoms, the patient is unable to disconfirm these erroneous cognitions.

Evidence

Foa and colleagues\textsuperscript{17} assessed all RCTs involving a clear test of combined treatment and reported their results. Using rigorous criteria, they chose to review only those studies which employed random assignment, adequate methods and sample sizes, blind assessments, sufficient dosages and durations of treatment, and provided satisfactory reporting of data, in an effort to determine whether combined treatment was better than pharmacologic treatment alone. They identified a total of 26 RCTs; nine met their a priori criteria. The results of these nine trials are detailed here.

Obsessive-Compulsive Disorder

Cottraux and colleagues\textsuperscript{18} enrolled 60 subjects with OCD; 44 completed treatment. Treatment conditions were exposure/response-prevention therapy and fluvoxamine, exposure/response prevention and placebo, or fluvoxamine alone. Responses at 24 weeks posttreatment were as follows: 69\% for exposure/response prevention + fluvoxamine; 40\% for exposure/response prevention + placebo; and 54\% for fluvoxamine. Responses at the 6-month follow-up were as follows: 64\% for exposure/response prevention + fluvoxamine; 50\% for exposure/response prevention + placebo; and 45\% for fluvoxamine. There were no group differences at the 24-week posttreatment assessment or at the 6-month follow-up. Fluvoxamine reduced both rituals and depression in the short term but its effects disappeared in the long term.

Hohagen and colleagues\textsuperscript{19} reported a 10-week OCD trial with 58 subjects. Treatment conditions were behavioral therapy (exposure/response prevention) + pharmacotherapy versus exposure/response prevention + placebo. At 9 weeks posttreatment there was a response rate of 88\% for exposure/response prevention + fluvoxamine and 60\% for exposure/response prevention + placebo, suggesting an advantage for combined treatment when obsessions dominate and when secondary depression is present.

Van Balkom and colleagues\textsuperscript{20} reported a 16-week trial in which 117 subjects were randomly assigned to cognitive therapy, exposure/response prevention, fluvoxamine + cognitive therapy, fluvoxamine + exposure/response prevention, or a wait-list control condition. Assessments were conducted before treatment, after 8 weeks, and at 16 weeks. The main conclusion was that there was no significant difference in effectiveness among active treatments. The sequential combination of fluvoxamine with cognitive therapy or exposure/response prevention was not superior to either cognitive therapy or exposure alone.

Foa and colleagues\textsuperscript{21} randomized 122 patients with OCD to exposure/response prevention + clomipramine, exposure/response prevention, clomipramine, and placebo. At 12 weeks posttreatment, there was a complete response rate of 79\% for exposure/response prevention + clomipramine, 86\% for exposure/response prevention 48\% for
clomipramine, and 10% for placebo. At the 24-week follow-up, there was a response rate of 80% for exposure/response prevention + clomipramine, 89% for exposure/response prevention, 55% for clomipramine, and no results for placebo.\textsuperscript{21} The results indicated that exposure/response prevention + clomipramine, exposure/response prevention, and clomipramine are effective treatments for OCD. Intensive exposure/response prevention + clomipramine were more effective than clomipramine alone on all measures. However, exposure/response prevention + clomipramine did not show superiority over exposure/response prevention alone. Thus, intensive exposure/response prevention alone may be better than clomipramine alone.

The combined OCD results from Cottraux and colleagues,\textsuperscript{18} Hohagen and colleagues,\textsuperscript{19} Van Balkom and colleagues,\textsuperscript{20} and Foa and colleagues\textsuperscript{21} indicate that there is limited evidence that combined treatment is better than monotherapy in the treatment of patients with OCD.

**Panic Disorder**

Marks and colleagues\textsuperscript{22} randomized 154 subjects to one of four treatment conditions. These included alprazolam + combined treatment, alprazolam + relaxation, placebo + combined treatment, and placebo + relaxation (double placebo). At 8 weeks posttreatment, there was a response rate of 71% for alprazolam + combined treatment, 51% for alprazolam + relaxation, 71% for placebo + combined treatment, and 25% for placebo + relaxation. At the 43-week follow-up there was a response rate of 36% for alprazolam + combined treatment, 29% for alprazolam + relaxation, 62% for placebo + combined treatment, and 18% for placebo + relaxation. The results suggested that at posttreatment, combined treatment was better than all other treatments, while at follow-up, placebo + combined treatment was better than all other treatments.\textsuperscript{22}

Cottraux and colleagues\textsuperscript{23} treated 77 subjects diagnosed with panic disorder.\textsuperscript{23} Treatment conditions were CBT + buspirone and CBT + placebo. At 16 weeks posttreatment, there was a response rate of 67% for CBT + buspirone and 74% for CBT + placebo. At follow-up, there was a response rate of 44% for CBT + buspirone and 68% for CBT + placebo. The authors concluded that CBT + buspirone was no better than CBT + placebo for panic attacks.\textsuperscript{23}

Barlow and colleagues\textsuperscript{24} assigned 312 subjects with panic disorder to CBT + imipramine, CBT + placebo, CBT, imipramine alone, or to placebo. At the 3-month mark, the response rate was 84% for CBT + imipramine, 80% for CBT + placebo, 67% for CBT, 75% for imipramine, and 39% for placebo. At the 9-month mark, the response rate was 90% for CBT + imipramine, 76% for CBT + placebo, 73% for CBT, 80% for imipramine, and 38% for placebo. At follow-up, the response rate for the five groups was as follows: 50% for CBT + imipramine, 83% for CBT + placebo, 85% for CBT, and 60% for imipramine. The authors concluded that there was no difference among active treatments. At follow-up, the CBT groups showed greater response rates than the combined treatment groups.

The studies by Marks and colleagues,\textsuperscript{22} Cottraux and colleagues,\textsuperscript{23} and Barlow and colleagues\textsuperscript{24} indicated that for patients with panic disorder, CBT alone may be superior to combined treatment, and that medication may adversely impact CBT results.

**Generalized Anxiety Disorder**

A team of researchers led by Power and colleagues\textsuperscript{25} treated 113 subjects with GAD. Treatment conditions were as follows: CBT + diazepam, CBT + placebo, CBT, diazepam, and placebo. At 9 weeks posttreatment, the response rate was 91% for CBT + diazepam, 83% for CBT + placebo, 86% for CBT, 68% for diazepam, and 37% for placebo. At the 6-month follow-up the response rate was 71% for CBT + diazepam, 67% for CBT + placebo, 71% for CBT, and 41% for diazepam. The conclusion was that at posttreatment, all active treatments were better than placebo. At follow-up, CBT treatments were superior to diazepam alone. These results suggest that there is little evidence to support the combination of diazepam and CBT for GAD.
Social Anxiety Disorder

Blomhoff and colleagues\textsuperscript{26} assigned 387 subjects with social anxiety disorder (SAD) to combined treatment + sertraline, combined treatment + placebo, sertraline, or placebo. At the 24-week follow-up assessment, the response rate was 46\% for combined treatment + sertraline, 33\% for combined treatment + placebo, 40\% for sertraline, and 24\% for placebo. The researchers concluded that the combination of combined treatment + sertraline was effective; however, there was little evidence that combined treatment was superior to monotherapy in patients with SAD.

Posttraumatic Stress Disorder, Specific Phobia

In both PTSD and specific phobia there are no studies that meet the criteria outlined by Foa and colleagues,\textsuperscript{17} so no conclusion as to the relative efficacy of combined treatment versus monotherapy can be drawn.

Discussion

The studies reviewed above, with the possible exception of OCD, do not support the widespread enthusiasm for combined treatment. While disappointing, treatment recommendations should derive from empirical research. Foa and colleagues selected rigorously designed RCTs in which there was a clear test of combined treatment versus monotherapy. Yet, there are several important caveats regarding their conclusions. First, conclusions regarding the efficacy of combined treatment can only be made about the specific combinations employed in the studies; possibly tests of other combinations might produce different results. For example, in the panic disorder study by Cottraux and colleagues,\textsuperscript{18} buspirone was the medication used; because buspirone is not widely viewed as having anti-panic properties, it is possible that a medication better known for treating panic disorder, such as one of the SSRIs, might have produced different results. Also, several studies, including those by Foa and colleagues (OCD) and Barlow and colleagues (panic disorder), employed a study design in which medication was discontinued posttreatment. In these situations, relapse following medication discontinuation is a well-known complication, and usual clinical practice is to continue medication, often for at least one year in newly treated patients, and indefinitely for patients with chronic or recurrent symptoms. That a psychological treatment proved superior to medication at follow-up is not surprising, and the study design probably does not constitute a fair test of the treatment conditions.

Conclusion

Combined treatment is commonly recommended, but the empirical support for combined treatment is limited. More research is needed. There are few well-designed studies, and data are absent regarding PTSD and specific phobias. Medication may have been stopped prematurely in several studies. In addition, at least one of the studies used as one of the treatment conditions a medication not known to have proven efficacy for the disorder studied.

References


