Can Cognitive-Behavioral Therapy for Anxiety and Depression Be Improved with Pharmacotherapy? A Meta-Analysis

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KEYWORDS

• Cognitive-behavioral therapy • Drug treatment • Antidepressants
• Anxiety disorders • Depression

KEY POINTS

- Antidepressant and anxiolytic medications do not consistently or markedly enhance the effects of CBT for patients with anxiety or depressive disorders.
- Antidepressant medications may be efficacious second-line treatments for patients failing to respond to CBT.
- Novel agents that are thought to potentiate the neurobiological mechanisms of CBT are promising but await further study.

ROOM FOR IMPROVEMENT IN COGNITIVE-BEHAVIORAL THERAPY

The efficacy of cognitive-behavioral therapy (CBT) is well established in the treatment of anxiety and depressive disorders. Meta-analyses of controlled trials indicates a moderate-sized superiority for CBT versus placebo (PBO) treatment,[1,2] and small to moderate-sized superiority over alternative psychological treatments such as psychodynamic therapy.[3] However, there is clearly room for improvement: across trials, as many as half of patients receiving CBT are considered nonresponders at posttreatment.[4–7]

THE POTENTIAL FOR PHARMACOLOGIC AUGMENTATION

Thus, an important question is whether pharmacologic treatment, added to CBT, can improve outcomes over CBT alone. The efficacy of medications as monotherapies for

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anxiety and depressive disorders is reasonably well established, although significant concerns about reporting standards (some of which could apply to CBT trials as well as pharmacotherapy trials) have been raised.[8,9] Across studies, antidepressant medications, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and monoamine oxidase inhibitors (MAOIs) show superiority over PBO for depression,[10–12] although the overall effect is small,[13] and may be clinically meaningful only in more severe cases.[14,15] Among the anxiety disorders, the antidepressant medications, as well as anxiolytic medications including benzodiazepines and azapirones, also show a superiority to PBO across studies, with medium effects overall.[16] When medications and CBT have been compared directly, across studies the effects are roughly equivalent, at least in the short term.[2,16–21]

THE NEED TO EXAMINE PLACEBO-CONTROLLED TRIALS OF PSYCHOPHARMACOLOGIC AUGMENTATION

Previous systematic reviews have examined whether the combination of these treatments is better than CBT alone. These reviews have generally shown a small advantage of combined treatment over CBT alone, although there may be an increased risk of relapse when medications are withdrawn.[22–27] Importantly, however, an examination of CBT + medications versus CBT alone cannot facilitate an adequate understanding of the incremental efficacy of medications. In the absence of a PBO control condition, there is no way to determine the effects of the medication, either positive or negative. The PBO response rate in anxiety disorders is substantial[28]; in one systematic review, pill PBO was demonstrated to increase the probability of response in panic disorder with agoraphobia (PD/A) by 26%.[29]

However, the PBO effect also may have the reverse effect in some cases: when patients with PD/A treated with alprazolam (ALP) versus PBO plus CBT rated the extent to which they believed that their treatment gains were attributable to medication or to their own efforts, those who attributed their gains to medication exhibited a greater loss of gains following discontinuation than did those who had attributed their gains to their own efforts during treatment.[30] Additionally, when patients with specific phobia (SpP) treated with exposure plus pill PBO were told that the pill had anxiolytic properties that would make exposure easier, they were more likely to relapse (39%) after treatment than were patients who were told that the pill had stimulating properties that would make exposure more difficult (0%), or those who were told that the pill had no effect on exposure (0%).[31] Thus, there may be both PBO and "nocebo"[32] effects of adding medications to CBT, beyond the specific pharmacologic effects of the medication itself. The aim of the present review was to examine the efficacy of pharmacologic augmentation of CBT by synthesizing studies that randomized patients to CBT + medications versus CBT + PBO.

The present review considers 3 distinct methods of pharmacologic augmentation of CBT. *First*, studies in which CBT was applied concurrently with a medication also used as a monotherapy (eg, CBT plus an SSRI) were examined. *Second*, studies in which pharmacologic treatment was administered following CBT nonresponse, rather than concurrent administration for all patients, were examined. This strategy relates to the practice of stepped care,[33,34] in which treatments are added sequentially only after nonresponse to the initial trial. *Third*, the analysis examines studies that used novel agents, not prescribed as monotherapies, to augment CBT. These studies were limited to the anxiety disorders, in which there has been increasing interest in compounds that do not treat the anxiety directly, but rather are thought to potentiate the