Combined medication and cognitive therapy for generalized anxiety disorder

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The current study assessed efficacy of combined cognitive behavioral therapy (CBT) and venlafaxine XR compared to venlafaxine XR alone in the treatment of generalized anxiety disorder (GAD) within settings where medication is typically offered as the treatment for this disorder. Patients with DSM-IV—diagnosed GAD who were recently enrolled in a long-term venlafaxine XR study were randomly offered (n = 77), or not offered (n = 40), the option of adding 12 sessions of CBT. Of those offered CBT, 33% (n = 26) accepted and attended at least one treatment session. There were no differences between the combined treatment group and the medication only group on primary or secondary efficacy measures in any of the sample comparisons. Many patients who present in medical/psychopharmacology settings seeking treatment for GAD decline the opportunity to receive adjunctive treatment. Of those that receive CBT, there appears to be no additional benefit of combined treatment compared to venlafaxine XR alone.

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1. Introduction

Generalized anxiety disorder (GAD) is a prevalent and chronic disorder with high rates of recurrence. The most recent data on the occurrence of DSM-IV GAD is from the National Comorbidity Survey Replication study (Kessler, Chiu, Demler, & Walters, 2005), which reported lifetime prevalence for DSM-IV GAD of 5.7% and 12-month prevalence of 3.1%. Projected lifetime prevalence revealed that 8.3% of the United States population can be expected to experience GAD at some time if they live to age 75 (Kessler et al., 2005). A large-scale naturalistic study of the course of anxiety disorders found that the probability of recovery from DSM-III-R GAD over a 12 year period was 58%, and the probability of subsequent recurrence among those who did recover was 45% (Yonkers, Dyck, Warshaw, & Keller, 2000; Yonkers, Warshaw, Massion, & Keller, 1996).

Beyond the characteristic chronicity and high rates of recurrence, patients with GAD often experience significant impairments in psychosocial functioning, like poor emotional health (Robins & Regier, 1991), low occupational level (Massion, Warshaw, & Keller, 1993), and increased risk of suicide (Boden, Fergusson, & Horwood, 2007). Role impairment in those with pure GAD (without co-morbidity) is comparable to pure major depressive disorder (MDD) as well as other mood disorders (Grant et al., 2005; Kessler, Stang, Wittchen, Stein, & Walters, 1999; Wittchen, Carter, Pfister, Montgomery, & Kessler, 2000). Moreover, significant disability similar to what would be expected from chronic medical illnesses can result from cases in which anxiety is not successfully treated (Fyer et al., 1994; Kessler, Keller, & Wittchen, 2001).

Both medications and cognitive-behavioral psychotherapy (CBT) have been widely investigated as treatments for GAD. A standard package of CBT for GAD usually includes both cognitive restructuring and applied relaxation, along with education about the nature of anxiety, training in the recognition and monitoring of situational, physiological, cognitive, and behavioral cues associated with anxious responding, training in arousal reduction techniques such as progressive muscle relaxation, pleasant imagery and diaphragmatic breathing, and imaginal exposure to anxiety cues coupled with coping skill rehearsal (Newman & Borkovec, 2002; Roemer & Orsillo, 2002). A meta-analysis reviewed results of 19 studies investigating efficacy of CBT for GAD and found that CBT treatments were superior to wait-list controls, psychological placebos, and pill placebos (Mitte, 2005). CBT currently stands as the only psychotherapy method for GAD that has empirical support (Chambless et al., 1996). However, despite empirical support for CBT in treatment of GAD, amount of clinically significant change has only been moderate, with approximately half of patients displaying some ongoing clinical symptoms after treatment (Chambless & Gillis, 1993).

Psychopharmacological treatments have also been found to be effective in the treatment of GAD. The most investigated medications for GAD are benzodiazepines (Rickels & Rynn, 2002), but...
selective serotonin reuptake inhibitor (SSRI) and serotonin norepinephrine reuptake inhibitor (SNRI) antidepressants have been found to be efficacious (Mitte, Noack, Steil, & Hautzinger, 2005), and are now considered first-line pharmacotherapies for GAD. Similar to CBT, a satisfactory response to short-term SSRI/SNRI treatment occurs for only about 60% of patients and full remission in only about 37% of patients (Gelenberg et al., 2000; Pollack et al., 2001).

Given that both CBT and psychopharmacological treatments are commonly used in the treatment of GAD, yet neither alone results in a high rate of clinical response to treatment, it is remarkable that little research attention has been devoted to the efficacy of the combination of medication and psychotherapy. Only two studies have examined combinations of psychosocial and medication treatments for GAD; neither of these used SSRI or SNRI medications now accepted as front-line pharmacological treatments for GAD. In a study by Power et al. (1990), five treatments were compared: CBT, diazepam, pill placebo, diazepam plus CBT, and pill placebo plus CBT. Patients (about 20 per condition) met DSM-III GAD criteria, although no structured interview was employed. Results indicated that the combined treatment fared the best, with 90.5% of patients in combined treatment showing clinically significant change. However, this study is difficult to interpret because sample sizes were small, diagnosis was not established by structured interview, DSM-III diagnoses were used, and no assessment of adequacy of implementation of CBT was performed. In another study, 60 patients with GAD were randomized to receive buspirone plus anxiety management training; buspirone and non-directive therapy; placebo and anxiety management training; and placebo and non-directive therapy (Lader & Bond, 1998). There were no differences among the four groups, all of whom showed improvement. In summary, no studies have examined the efficacy of SSRI/SNRI medications and psychotherapy for GAD.

In designing a study of combined medication and psychotherapy for a psychiatric disorder, an important consideration is the context in which patients are seeking treatment. Some patients pursue treatment for symptoms from a primary care physician, or psychiatrist, and have a preference for receiving medication. Depending on patient preferences, the treating physician may then refer the patient for psychotherapy rather than prescribing medication, or perhaps more commonly as an adjunct to medication. Other patients may seek help for anxiety symptoms directly from a psychotherapist, who may or may not refer the patient for adjunctive medication treatment depending on patient preference, severity of illness, and other clinical considerations. Patients seeking treatment by a non-psychotherapist physician compared to a psychotherapist may differ in important characteristics, such as severity of symptoms, degree of psychic vs. somatic symptoms, and/or treatment preference, and these characteristics may be associated with differential responsiveness to medication compared to psychotherapy.

The issue of treatment context is particularly salient for the treatment of GAD because patients with GAD commonly show up in primary care medical practices and often are specifically seeking medication for their symptoms. The 12-month prevalence rate for GAD in primary care is approximately 4%, and much higher prevalence rates are apparent when DSM-IV symptom criteria are used without a duration criterion (Wittchen et al., 2002). When individuals with GAD present to a primary care physician, only 13% of them report a chief complaint of anxiety (Wittchen et al., 2002). More common complaints of GAD patients in primary care include somatic symptoms (48%), pain (35%), sleep disturbance (33%), and depression (16%) (Wittchen et al., 2002). Overall, use of medications for anxiety disorders has been increasing in both primary care and psychiatric settings (Harman, Rollman, Hanusa, Lenze, & Shear, 2002). Thus, in clinical practice, psychotherapy, if it is offered at all, will therefore frequently be offered in the context of medication treatment for GAD and its occurrence is based on the presumption that the combination is likely more efficacious than either CBT or medication alone.

The current preliminary study was designed with these issues in mind. The availability of an ongoing study (Rickels et al., 2010) of long-term venlafaxine XR treatment of GAD being conducted at primary care sites and a psychopharmacology clinic allowed us to ask the following questions: (1) what percent of patients who have initially sought medication for their GAD symptoms would be interested in combining medication with CBT, and (2) for patients who receive at least one session of CBT, does the combination of medication plus 12 weeks of CBT result in greater improvements in GAD symptoms, depression, and functioning compared to medication alone among patients who initially sought medication treatment (and received at least one dose of medication)?

2. Method

2.1. Study design

The medication study was an 18-month, relapse prevention one consisting of three treatment phases (Rickels et al., 2010). The first phase was a 6-month open-label venlafaxine flexible-dose treatment phase (75 mg–225 mg/day). The second and third phases were each 6-month randomized, double-blind, placebo-controlled relapse phases. Only data from the first phase are included in the current report. Most patients (n = 239) enrolled in the medication trial were recruited and seen in one of four primary care practices by research psychiatrists who were placed into the primary care sites. An additional group (n = 95) of patients was enrolled in a psychopharmacology clinic in a university setting. Further details of the parent trial are available elsewhere (Rickels et al., 2010).

After the parent medication study was ongoing, the current combined treatment study was initiated. Patients who were enrolled in the medication study were randomly selected to be offered the option of adding 12 weeks of CBT in addition to venlafaxine XR. Patients were generally approached to consider the addition of CBT at the first study visit (week 2) after beginning medication. A 2:1 (CBT:medication) randomization scheme was used because of the existence of the large comparison group of patients on venlafaxine XR alone (n = 159) that was already available from the parent study. Study visits occurred at baseline, biweekly for 8 weeks and monthly thereafter. This medication trial was conducted from 2005 to 2009 with approval and oversight by the local Institutional Review Board (IRB). The CBT addition was also approved by the IRB and was conducted from October, 2006 to March, 2008. Patients provided written informed consent for participation in the medication trial, and separately for the CBT addition study.

2.2. Participants

Patients were recruited through community outreach presentations, mailings, media advertising, and referrals from health care professionals including the primary care physicians at the primary care sites. To be eligible, patients needed to be over the age of 18, meet DSM-IV criteria for GAD (based on a diagnostic interview at baseline) and obtain scores ≥4 on the Clinical Global severity scale (CGI: Guy, 1976) and ≥20 on the Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959). To eliminate patients with co-morbid disorders, patients were excluded if they had a score >18 on the Hamilton Depression Scale (HAM-D; Hamilton, 1960), an episode of major depressive disorder in the previous six months, or any other current DSM-IV anxiety diagnoses. Patients also could not have any regular use of buspirone, anticonvulsants, neuroleptics,
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