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Augmenting antidepressant medication with modular CBT for geriatric generalized anxiety disorder: a pilot study

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Abstract

Objective—Generalized anxiety disorder (GAD) is a prevalent psychiatric condition in older adults with deleterious effects on health and cognition. Although selective serotonin reuptake inhibitor (SSRI) medications have some efficacy as acute treatments for geriatric GAD, incomplete response is the most common outcome of monotherapy. We therefore developed a novel sequential treatment strategy, using personalized, modular cognitive-behavioral therapy (mCBT) to augment SSRI medication.

Method—In an open label pilot study (N =10), subjects received a sequenced trial of 12 weeks of escitalopram followed by 16 weeks of escitalopram augmented with mCBT. We also examined the maintenance effects of mCBT over a 28-week follow-up period following drug discontinuation and termination of psychotherapy.

Results—Results suggest that (1) adding mCBT to escitalopram significantly reduced anxiety symptoms and pathological worry, resulting in full remission for most patients and (2) some patients maintained response after all treatments were withdrawn.

Conclusion—Findings suggest that mCBT may be an effective augmentation strategy when added to SSRI medication and provide limited support for the long-term benefit of mCBT after discontinuation of pharmacotherapy.

Keywords

aged; elderly; cognitive therapy; behavior therapy; drug therapy; psychotherapy; selective serotonin reuptake inhibitor

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Introduction

Generalized anxiety disorder (GAD) is defined by excessive, uncontrollable worry accompanied by somatic and mental symptoms such as restlessness and muscle tension (Association, 2000). The disorder tends to be chronic in the absence of effective treatment, with most patients reporting an unremitting course of illness (Rubio and Lopez-Ibor, 2007).

Several studies in elderly populations have found that the point prevalence of GAD in community-living elderly is high, with estimates ranging from 1.2 to 7.3% (Beekman *et al*., 1998; Schoevers *et al*., 2003; Trollor *et al*., 2007; Gum *et al*., 2009). Younger people often continue to have GAD as they enter the ranks of the aged, and many people develop it late in life (Le Roux *et al*., 2005; Lenze *et al*., 2005; Chou, 2009).

Compared to older adults without psychiatric illness, individuals with late-life GAD have a threefold increased risk of health-related activity limitation and similar decrements in health-related quality of life (de Beurs *et al*., 1999; Wetherell *et al*., 2004; Porensky *et al*., 2009). Older adults are also more vulnerable to worsening health and cognition from chronic anxiety (Lenze and Wetherell, 2009), which may be the result of CNS damage (Sinoff and Werner, 2003) due to chronically elevated cortisol (Mantella *et al*., 2008) or blood pressure (Paterniti *et al*., 1999). Overall, these increased disabilities are on par with those associated with late-life major depressive disorder (MDD) (Beekman *et al*., 1997; Wetherell *et al*., 2004).

Of the few prospective controlled trials for late-life GAD, benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), and to a lesser extent, cognitive-behavioral therapy (CBT), have been shown efficacious acutely (Koepke *et al*., 1982; Schuurmans *et al*., 2006; Lenze *et al*., 2009; Schuurmans *et al*., 2009; Stanley *et al*., 2009). Benzodiazepines, commonly prescribed for late-life GAD, increase risk for falls, fractures, and cognitive impairment, and may accelerate cognitive decline; thus their use as long-term monotherapy is not recommended (Gray *et al*., 2006; Benitez *et al*., 2008; Pariente *et al*., 2008; Wright *et al*., 2009). Moreover, even with an adequate course of SSRI or CBT treatment, most participants fail to achieve high end state functioning (Lenze *et al*., 2009; Stanley *et al*., 2009). In sum, many older adults with GAD will not achieve adequate short-term outcomes with a monotherapy (SSRI or CBT) approach, and little is known about optimal long-term strategies for this chronic disorder.

When monotherapy is inadequate, combination treatments may be more efficacious, particularly SSRIs and CBT (Fava *et al*., 2005), which have different mechanisms and may be able to treat different components of the illness (McNally, 2007; Arce *et al*., 2008). A recent meta-analysis of studies with younger and middle-aged adults indicates that a combination of pharmacotherapy and CBT may be more effective than CBT alone as an acute treatment for anxiety disorders (Hofmann *et al*., 2009).

Combination treatment may be introduced sequentially or simultaneously (Fava *et al*., 2006). Potential advantages of a sequential approach of SSRI and CBT are (1) It reflects real-world clinical practice, in which most older adults who receive mental health treatment do so initially in the form of pharmacotherapy; (2) it allows the patient and provider to focus

sequentially on different aspects of treatment, rather than divide focus among multiple treatments and components of illness at once; and (3) it allows for one treatment to be a catalyst for the next. In GAD, for example, SSRI treatment can reduce acute distress and somatic symptoms, paving the way for CBT to address underlying worry control, engage cognitive distortions, and improve coping skills. Thus, by targeting different facets of the illness, the two treatments may lead to optimal acute outcomes and greater long-term reductions in persistent symptoms and risk of relapse.

Adding psychotherapy that targets underlying worry control to medication treatment may provide durable even if medication is eventually discontinued. A recent review of meta-analyses of studies conducted with younger and middle-aged adults concluded that psychotherapies involving cognitive and behavioral strategies for GAD are superior to nondirective therapy and pill placebo and equivalent to pharmacotherapy in the acute phase of treatment, with robust effects extending as far as 10 years following discontinuation of treatment (Butler *et al*., 2006). In MDD, adding CBT to antidepressants reduces relapse (Blackburn and Moore, 1997; Ma and Teasdale, 2004; Bockting *et al*., 2005; Paykel *et al*., 2005), extending years after stopping medication (Fava *et al*., 2006). A recent pilot study, however, suggested that the relapse prevention benefit of CBT in depressed older adults taking antidepressant medication diminished over time (Wilkinson *et al*., 2009). Because GAD has a chronic course, and many older adults do not wish to remain on medication indefinitely, an investigation of the maintenance effects of CBT for late-life GAD is warranted.

In older adults, as in younger adults, GAD is heterogeneous, commonly co-occurring with depression and other anxiety disorders (Schoevers *et al*., 2003). Moreover, efforts to disseminate empirically supported psychotherapies increasingly emphasize the use of flexible treatments that can be individually tailored to meet the needs of diverse patients (McHugh and Barlow, 2010). For these reasons, a modular CBT (mCBT) approach may offer benefits as a treatment for geriatric GAD (Wetherell *et al*., 2009).

The present pilot study examined a sequenced combination therapy strategy for the treatment of GAD in a sample of older adults. The protocol consisted of 12 weeks open-label escitalopram followed by 16 weeks of escitalopram plus mCBT; this active treatment phase was followed by a 28-week maintenance phase after termination of psychotherapy and drug discontinuation.

Method

Participants and procedure

Participants were 10 adults at least 60 years old who were recruited from medical practices at one of three sites: Pittsburgh, PA, San Diego, CA, or St. Louis, MO. All were Caucasian; other demographic information is presented in Table 1. The patients recruited from the Pittsburgh site had previously participated in a randomized, placebo-controlled trial of escitalopram (Lenze *et al*., 2009). All participants met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV (First *et al*., 1996; Association, 2000)) criteria for a principal diagnosis of GAD of at least moderate intensity (Hamilton Anxiety Rating Scale (Hamilton,

1959)) 17 or greater; note that the Ham-A score of one pilot patient had decreased to 14 by the time of first administration of medication). The Structured Clinical Interview for DSM-IV (SCID-IV (First *et al*., 1996)) and Mini-Mental Status Examination (MMSE (Folstein *et al*., 1975)) were administered for diagnostic purposes and to determine study eligibility. Medical comorbidity was quantified using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G (Miller *et al*., 1992)). On this physician-rated scale, higher scores indicate more medical burden, and a score of 10 represents the average for an elderly primary care population. Participants were excluded for conditions that might threaten their safety or limit their ability to participate in the study, including psychosis or substance abuse/dependence in the past 6 months, current suicidal ideation, and cognitive impairment as defined by a score less than 25 on the MMSE. All participants were tapered off other psychotropic medications for at least 2 weeks before enrolling in the study, and all provided written informed consent.

The three phases of study treatment were 12 weeks of open-label escitalopram (acute phase), followed by 16 weeks of continued escitalopram supplemented with 16 individual sessions of mCBT (augmentation phase), after which patients were tapered off the medication and followed for an additional 28 weeks (maintenance phase). The 12 week duration of acute medication was selected because the investigators found a response rate of 69% at 12 weeks in one study of SSRI treatment of geriatric GAD and 60% response at 32 weeks in another, suggesting that most of the benefit occurs within the first 12 weeks (Blank *et al*., 2006; Lenze *et al*., 2009). The duration of CBT was selected to allow adequate coverage of both required and supplemental modules plus sufficient time for older adults to practice new skills. During the 8-week period in which they were tapering off the medication, patients received three booster sessions, intended to help them cope with emergent anxiety symptoms. Patients were started on a dose of 10 mg of escitalopram increased to 20 mg as tolerated after 4 weeks if substantial improvement was not noted. None of the patients took concurrent benzodiazepines. Seven participants were prescribed 20 mg escitalopram, and the remaining three were prescribed 10 mg.

Participants were required to demonstrate at least 20% improvement on the Ham-A to receive psychotherapy; all met this requirement. Psychotherapy, which targeted reduction of persistent symptoms of worry and anxiety and prevention of relapse, was conducted according to a manualized protocol (Wetherell *et al*., 2009). The protocol consisted of modules devoted to education/monitoring, relaxation training, problem-solving skills training, cognitive therapy, and skills practice. To provide personalized, algorithm-driven treatment, patients could receive several supplemental modules based on criteria drawn from patients' baseline SCID and Ham-A data: Patients who reported a major depressive episode within 1 year prior to enrollment based on the SCID or who scored a 3 or 4 on the Ham-A Depressed Mood item for two consecutive assessments during the open-label acute phase received a behavioral activation module; patients who reported specific or social phobia, panic disorder, agoraphobia, or post-traumatic stress disorder within the past year, or who scored a 3 or 4 on the Ham-A Fears item for two consecutive assessments during acute treatment, received a module on exposure therapy; and patients who scored a 3 or 4 on the Ham-A Insomnia item for two consecutive assessments during the acute phase received the

Sleep Hygiene module. Finally, because working with the family is a key component of good geriatric mental health practice, patients with supportive local family members (spouses, adult children) brought a family member to one session that focused on educating the family and making them an ally in the treatment.

Seven doctoral-level therapists were trained at the three sites by Dr Wetherell, who held 2-day inservices at each site with didactic material, videotaped demonstrations of the protocol, and role plays to familiarize therapists with the manual and procedures. They attended weekly meetings at their local site and weekly across-site meetings chaired by Dr Wetherell and conducted by teleconference. An external expert in CBT for geriatric anxiety rated four randomly selected tapes from each therapist for adherence and competence overall and on several specific components. Average overall adherence on a scale of 0 =*unsatisfactory*, 1 =*adequate*, 2 =*good*, 3 =*very good*, and 4 =*excellent* ranged from 2.6 to 4.0 across therapists, and overall competence, also rated from 0 to 4.0, ranged from 2.5 to 4.0.

After the augmentation phase, patients were slowly tapered off the medication according to the following schedule: 10 mg/d × 2 wk, 5 mg/d × 2 wk, 2.5 mg/d × 2 wk, then no medication. During this 6-week taper, subjects also received three booster CBT sessions, in person or by phone, to reinforce their coping skills while coming off of the medication. Clinical management and assessment visits took place biweekly to every 4 weeks throughout the acute, augmentation, and maintenance phases. At each visit, clinicians asked about compliance during the interval between visits and collected unused pills. They also administered a battery of self-report and clinician-administered measures described in more detail below.

Relapse was defined as a Ham-A score increased to at least 14, plus a clinically significant increase (defined as at least five points higher than the lowest point in the augmentation phase) on two consecutive assessments, plus meeting GAD criteria (i.e., hard to control worry with at least three associated symptoms more days than not) for three or more weeks duration. Development of MDD was also considered relapse, regardless of Ham-A score or GAD status. We measured symptomatic improvement and remission during the augmentation phase, and maintenance of improvement and relapse rate during the maintenance phase, using the Ham-A and the Penn State Worry Questionnaire (PSWQ (Meyer *et al*., 1990)). We examined two definitions of remission: Ham-A score of 8 or less, and PSWQ score of 40 or less, based on data from studies in geriatric GAD patients and normal older controls (Hamilton, 1959; Association, 2000; Diefenbach *et al*., 2001; Schoevers *et al*., 2003; Sinoff and Werner, 2003; Hollon *et al*., 2005; Schuurmans *et al*., 2006; Rubio and Lopez-Ibor, 2007).

Analyses

In addition to examining the data on a patient-by-patient basis, we computed paired *t*-tests to compare change on Ham-A and PSWQ scores from baseline to end of acute phase, from end of acute to end of augmentation, and, for the Ham-A, from end of augmentation to end of maintenance, with end of maintenance defined as completion of the study or time of relapse. Because we did not collect PSWQ data at time of relapse for two patients, we did not make statistical comparisons from end of augmentation through end of maintenance.

Results

Changes over time for each patient are displayed in Figures 1 and 2. Over the acute escitalopram phase, the mean HAMA score decreased from 23.3 (SD =9.1) to 13.0 (SD =13.0), $t(9) = 5.01$, $p < 0.001$, an effect size of $d = 0.93$; the mean PSWQ decreased from 55.5 (15.8) to 49.8 (10.9), $t(9) = 1.82$, $p > 0.10$, $d = 0.43$. Three of the 10 patients achieved remission according to the Ham-A criteria of 8 or less. One patient scored in the remission range on the PSWQ at baseline; no additional patients reached remission as defined by this measure with escitalopram monotherapy.

Following 16 sessions of CBT in conjunction with continued escitalopram, the mean Ham-A decreased further to 8.2 (6.4), $t(9) = 3.77$, $p = 0.004$, $d = 0.49$, with seven patients achieving remission. The mean PSWQ decreased to 40.9 (14.0), $t(9) = 3.92$, $p = 0.003$, $d = 0.71$, with six patients achieving remission according to this measure.

Three patients relapsed during the maintenance phase, one each at weeks 10, 16, and 20. Two of them met criteria for MDD in addition to GAD. After discontinuation of the medication, combining the non-relapsers' scores from the end of the maintenance phase and the relapsers' scores from the time of relapse, the mean Ham-A was 13.3 (8.6), which represents a marginally significant increase, $t(9) = 2.19$, $p = 0.06$, relative to the score at the end of the augmentation phase. Four patients remained in remission according to Ham-A criteria. According to PSWQ criteria, only two patients remained in remission at the end of maintenance.

The three pilot patients who relapsed were followed after they were put back on the medication. After resumption of the medication, Ham-A scores declined to 28, 2, and 13, all of which were clinically improved from scores at time of relapse. PSWQ scores for two of the patients remained elevated after resumption of escitalopram monotherapy: 65, 34, and 54.

Discussion

In this pilot study of 10 older adults with GAD, we found support for a planned sequential treatment approach of SSRI augmented by modular CBT. Following SSRI monotherapy, subjects showed significant reductions in anxiety symptoms but evidenced less reduction in worry severity, and few patients achieved full remission status. Further reductions in anxiety symptoms and particularly worry severity followed augmentation with mCBT. Most individuals achieved full remission with this sequential SSRI/mCBT approach. Moreover, the finding that anxiety symptoms as measured by the Ham-A appeared to respond well to medication whereas worry as measured by the PSWQ appeared to respond to mCBT is consistent with the model of sequential treatment targeting different aspects of the illness.

We found partial evidence for the maintenance effects of mCBT following drug discontinuation: Although only three of 10 relapsed, and symptom scores remained below pre-treatment levels, few patients remained at the level of remission. By comparison, the only existing study of maintenance pharmacotherapy in GAD (in younger adults) found a relapse rate of 56% for patients following discontinuation of escitalopram (Allgulander *et*

al., 2006). Preliminarily, it appears that some but not all patients can be tapered from SSRI after receiving augmentation CBT.

One important feature of the protocol was the integration of psychotherapy with pharmacotherapy. We emphasized open communication between pharmacotherapists and psychotherapists, with weekly consultations to ensure optimal care. This experience led to the qualitative realization that the treatments did not seem to interfere with each other, and in fact many patients were appreciative of the opportunity to benefit from two different types of therapy. This collaborative approach to care does not often occur in usual clinical practice at present, but success with this model in treating geriatric depression (Unutzer *et al*., 2002) suggests that it may represent a promising strategy in the management of anxiety as well as mood disorders.

In terms of optimizing relapse prevention, we found that patients did not typically experience increased distress during the 6-week medication taper immediately after mCBT augmentation but rather appeared to be at risk for relapse months later. Furthermore, we learned that some patients stopped engaging in the skills taught in mCBT following termination of treatment. These patients were at particularly high risk for return of symptoms in the face of stressful life events. Thus, going forward, one enhancement to the treatment strategy is using the booster sessions when they are needed during maintenance treatment, as triggered by elevations in anxiety symptom scores or self-reported distress.

Limitations of this study include its small size and the open-label treatment design, in which raters as well as patients were aware of patients' treatment status. Furthermore, this design cannot rule out the possibility that improvement after 12 weeks was due to the continued administration of escitalopram rather than to mCBT, or that patients who remained well during the maintenance phase would have done so absent psychotherapy. Controlled research with blind raters is needed to more definitively examine the augmentation and/or relapse prevention benefits of mCBT added to SSRI treatment in late-life GAD; a randomized, controlled trial of this strategy is underway.

In conclusion, we found preliminary evidence for the benefits of modular CBT as augmentation treatment with SSRI for geriatric GAD, particularly in the short term. Given the aging of the global population, such treatments will be increasingly needed to avoid the detrimental effects of anxiety disorders in this age group.

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Key Points

- In a pilot sample of older adults with generalized anxiety disorder, adding a modular form of cognitive-behavioral therapy to escitalopram significantly reduced anxiety symptoms and pathological worry, resulting in full remission for most patients.
- Some patients maintained response after all treatments were withdrawn, suggesting the possibility that behavioral therapy may have relapse prevention benefits for some patients.

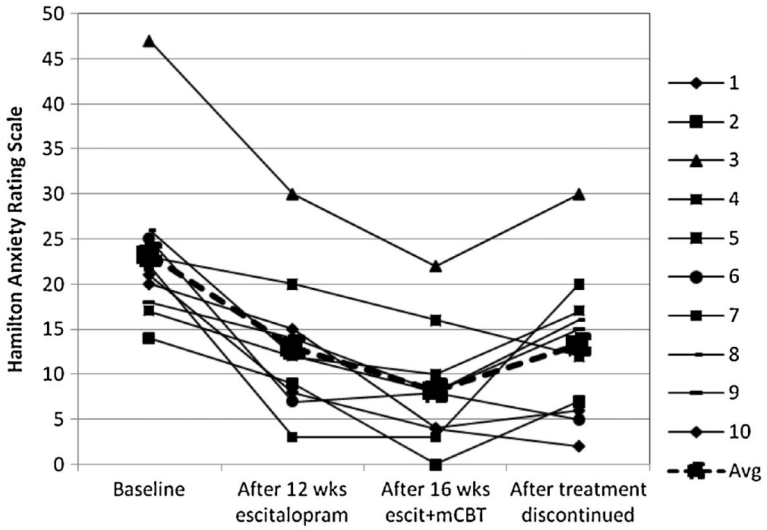

Figure 1.

Effects of escitalopram augmented with modular cognitive-behavioral therapy (mCBT) on anxiety symptoms in geriatric generalized anxiety disorder (*N*=10).

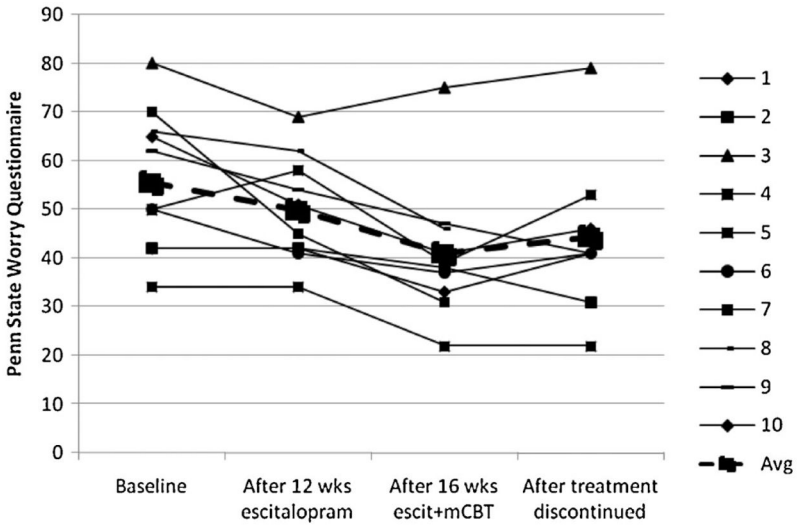

Figure 2.

Effects of escitalopram augmented with modular cognitive-behavioral therapy (mCBT) on worry severity in geriatric generalized anxiety disorder (*N*=10).

Table 1

Participant demographics

ID	Gender	Age	Education (years)	Age of onset of GAD	Axis I comorbidity	Health status (CIRS-G)	Cognitive status (MMSE)
1	F	75	15	75	None	9	Missing
2	M	65	19	65	None	10	30
3	M	61	12	5	Current major depression, agoraphobia, specific phobia, obsessive-compulsive disorder	7	28
4	M	78	17	5	None	15	30
5	F	87	10	87	Current panic disorder, social phobia; past major depression	7	27
6	M	67	19	66	Past major depression and alcohol abuse	13	30
7	F	65	12	10	Current panic disorder	9	28
8	F	64	19	5	Current specific phobia; past major depression and alcohol abuse	9	29
9	F	61	14	55	None	10	30
10	F	63	12	5	Current social phobia	13	30

GAD, generalized anxiety disorder; CIRS-G, Cumulative Illness Rating Scale—Geriatrics; MMSE, Mini Mental State Examination.