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Cognitive-Behavioral Therapy Augmentation of SSRI Reduces Cortisol Levels in Older Adults with Generalized Anxiety Disorder: A Randomized Clinical Trial

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Abstract

Objectives—Elevated cortisol in stress and aging, such as has been seen in late-life anxiety disorders, is postulated to accelerate cognitive and physiological decline in this large and increasing population. Selective serotonin-reuptake inhibitors (SSRIs) and cognitive behavior therapy (CBT) are both effective treatments for Generalized Anxiety Disorder (GAD) in older adults. On the other hand, there is very little research examining the effect of combining these therapies on peak cortisol levels. For the current analyses, we examined the effectiveness of CBT augmentation on peak cortisol levels in older adults diagnosed with GAD.

Methods—The sample consisted of 42 individuals with late-life GAD who received an acute course of the SSRI escitalopram and then entered a 16-week randomized phase. Twenty-one participants were randomized to receive 16 sessions of CBT in addition to continuing escitalopram and the remaining 21 participants continued on escitalopram without CBT. Generalized Estimating Equations were performed to assess the effectiveness of CBT augmentation on peak cortisol levels (30 minutes after waking).

Results—Older adults with GAD who received both escitalopram and CBT demonstrated a significant reduction in peak cortisol levels at post-treatment compared to the group who received escitalopram without CBT augmentation.

Conclusions—CBT augmentation of SSRI treatment reduced peak cortisol levels for older adults with GAD. Since persistently high cortisol levels in aging are thought to increase age-related cognitive and medical problems, our findings suggest that there may be a benefit to health and cognition of CBT augmentation for late-life anxiety disorders.

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Keywords

Generalized anxiety disorder (GAD); HPA axis; escitalopram; cognitive behavioral therapy (CBT); cortisol

The prevalence of anxiety disorders is high in the older adult population (see Wolitzky-Taylor, Castriotta, Lenze, Stanley, & Craske, 2010). More specifically, prevalence estimates of Generalized Anxiety Disorder (GAD) in older adults range from 1.2 to 7% (Angst, Gamma, Baldwin, Ajdacic-Gross, & Rossler, 2009; Beekman et al., 1998; Goncalves & Byrne, 2012a; Gum, King-Kallimanis, & Kohn, 2009; Grant et al., 2005) with a peak age of onset around 40–50 years of age (Goncalves & Byrne, 2012a). Further, the prevalence of GAD appears to increase until 50–60 years of age (Ansseau, Fischler, Dierick, Mignon, & Leyman, 2005; Carter, Wittchen, Pfister, & Kessler, 2001). Importantly, the diagnosis of GAD is related to several negative outcomes including an increased likelihood of being diagnosed with other comorbid disorders (e.g., major depressive disorder; Byers, Yaffe, Covinsky, Friedman, & Bruce, 2010; Carter et al., 2001), higher rates of disability (Ansseau et al, 2005; Romera et al., 2010), lower levels of health related quality of life (Wetherell et al., 2004), greater healthcare utilization (Porensky et al., 2009) and poorer cognitive performance (Butters et al., 2011; Mantella et al., 2007; Rosnick, Rawson, Butters, & Lenze, 2013) which has been reported to be related to poorer treatment outcomes (Caudle et al., 2007).

There are effective pharmacological and psychotherapeutic techniques for older adults with GAD (see Goncalves & Byrne, 2012b for review and meta-analysis). For instance, studies have shown that cognitive behavioral therapy (CBT) reduces levels of worry, anxiety, depressive symptoms (Gould, Coulson, & Howard, 2012; Stanley et al., 2003; Stanley et al., 2009) and increases self-reported quality of life in older adults with GAD relative to waiting list (Ayers, Sorrell, Thorp, & Wetherell, 2007; Mitte, 2005) but these changes may not be superior to other comparison interventions (Wetherell, Gatz, & Craske, 2003). For example, relaxation training (RT) has also been reported as having a large positive effect in treating geriatric anxiety (Thorp et al., 2009).

Medication is frequently used to treat older adults with GAD. Serotonergic antidepressant medications such as venlafaxine ER (Katz, Reynolds, Alexopoulos, & Hackett, 2002) and SSRIs such as escitalopram (Lenze et al., 2009), citalopram (Lenze et al., 2005), and sertraline (Schuurmans et al., 2006) have been shown to be effective pharmacological treatments for older adults with GAD. It has been suggested, however, that SSRI monotherapy is not typically sufficient to achieve full remission of GAD for most older adults (Lenze et al., 2009; see also Pinquart & Duberstein, 2007), providing a rationale for augmentation with behavioral therapies.

Older adults with anxiety disorders are more reactive to stressors (Chaudieu et al., 2008; Vasiliadis, Forget, & Preville, 2013) and exhibit elevated cortisol levels compared to healthy older adults (Mantella et al., 2008). This is important because chronically high cortisol in older adults is thought to lead to the deleterious health and cognitive effects of stress (Lenze & Wetherell, 2011). Effective cortisol reduction may therefore be an important dimension of treatments' benefits in this age group. Cognitive behavioral interventions have been shown to be effective in reducing cortisol levels in younger and middle-aged adults with other anxiety disorders (e.g., protective mask phobia: Brand, Annen, Holsboer-Trachsler, & Blaser, 2011). More specifically, Tafet, Feder, Abulafia, and Roffman (2005) reported that non-elderly individuals with GAD who underwent 24 weeks of cognitive therapy demonstrated a significant reduction in afternoon cortisol levels but no significant differences were found in morning cortisol levels compared to a control group. Additionally, Lenze and colleagues (2011) reported that escitalopram treatment for late-life GAD reduced peak (i.e., 30 minutes after waking) and total cortisol levels, and that treatment-attributable reduction in peak cortisol levels correlated with improvement in memory (Lenze et al., 2012).

The authors know of no research to date that has examined the effect of psychotherapy on cortisol levels in older adults with an anxiety disorder, either alone or in combination with medication. Recently, Wetherell and colleagues (2013) showed that SSRI medication augmented with CBT led to greater reduction in worry symptoms and a lower rate of relapse in older adults with GAD compared to participants who continued on the SSRI medication without CBT. For the current study, we utilized a subset of the Wetherell and colleagues (2013) dataset and examined the effects of CBT augmentation on peak cortisol levels in older adults diagnosed with GAD. We hypothesized that the individuals who received CBT in addition to escitalopram would show greater decreases in peak cortisol levels compared to the participants who continued on escitalopram without CBT.

Methods

Study participants

The sample consisted of 42 older adults who had a DSM-IV (American Psychiatric Association, 2000) primary diagnosis of GAD. The diagnosis was determined by the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1995) and scoring >/= 17 on the Hamilton Anxiety Rating Scale (Hamilton, 1959) at baseline. The study was carried out in three locations: Pittsburgh, St. Louis, and San Diego. The study was approved by all three institutional review boards and all participants provided informed consent. Individuals with co-morbid major depression and other anxiety disorders were included in the current study so long as GAD was the principal diagnosis. Participants were excluded if they were cognitively impaired (</= 25 on the Mini Mental Status Exam; Folstein, Folstein, & McHugh, 1975), had a lifetime history of psychosis or bipolar disorder, medically unstable (e.g., severe congestive heart failure or metastatic cancer), had current suicidal ideation, or ongoing psychotherapy. The current study only included participants who were able to provide valid cortisol samples at both the beginning and end of the augmentation phase. Additional information about the parent study is reported elsewhere (Wetherell et al., 2013).

Randomization Procedure

After a 12-week phase in which participants received escitalopram 10mg daily (increased to 20mg after 4 weeks as needed and tolerated), all participants entered an augmentation phase lasting 16 weeks. They remained on a stable dose of escitalopram and were randomly assigned (50:50) to receive CBT or no CBT. Briefly, the modular CBT protocol was administered by six doctoral-level therapists, designed around each participant's symptoms, and targeted worry and anxiety (see Wetherell et al., 2013 for a full description). The following modules were given to all participants: relaxation training, cognitive therapy, problem-solving skills, and psychoeducation/ self-monitoring. A total of 70 patients (34 - CBT; 36 - no CBT) completed the 16-week randomized phase. Of those, 21 participants from the CBT group and 20 participants from the no CBT provided valid saliva samples (see Figure 1 for a complete diagram of the randomization process). We conducted several *t*-tests and chi-squares to determine if those who provided valid saliva samples ($n = 41$) differed from the participants who did not have valid saliva samples ($n = 29$). The results (not shown) revealed that the participants who provided valid saliva samples did not differ on any of the background characteristics or baseline measures compared to the participants who did not have valid saliva samples. Importantly, the change in self-reported worry was similar across the two groups.

Salivary sampling protocol

Participants provided three daily saliva samples while in their home - immediately upon awakening, 30 minutes after waking, and at bedtime - for two consecutive days, both at the beginning and end of the 16-week CBT vs. no-CBT augmentation phase. This method of salivary collection has been shown to provide a reliable marker of adrenocortical activity in humans (Pruessner et al., 1997). Collection was not directly supervised by researchers; the detailed methods used in the current study to maximize adherence and accuracy of collection, including self-report diaries and reminder calls, and of assay information, are published elsewhere (Mantella et al., 2008). Standard procedures were used to measure cortisol in saliva (Salimetrics, LLC, State College, PA) which have been shown to correlate highly with serum cortisol (www.salimetrics.com). The outcome measure of interest was the peak cortisol level, averaged over the two days of collection. We focused on peak cortisol because (1) this is when there is maximal exposure of the glucocorticoid receptor to cortisol; and (2) our prior research showed that peak cortisol levels are most associated with worry severity (Mantella et al., 2008) and with cognitive function (Lenze et al., 2012).

Background Characteristics and Pre-Augmentation Measures

At the beginning of the study, participants were assessed for medical burden using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G: Miller et al., 1992) as an index of medical comorbidity. In addition, participants were given the Penn State Worry Questionnaire (PSWQ: Meyer, Miller, Metzger, & Borkovec, 1990) prior to the augmentation phase.

Statistical Analysis

We began by examining possible group differences in baseline demographic and clinical characteristics, including medical comorbidity, and worry severity prior to the augmentation phase. We used *t*-tests for all continuous variables and χ^2 tests for all categorical variables. Next, we ran correlations among all of the variables of interest by treatment group status to assess possible covariates. Lastly, we conducted a Generalized Estimating Equation (GEE) analysis to examine the between treatment group difference in peak cortisol change over time from pre to-post augmentation. GEE analysis is a type of regression analysis that is similar to repeated measures ANOVA. GEEs provide a practical method to analyze correlated data arising from repeated measures. Liang & Zeger (1986) introduced GEEs as a method of dealing with such correlated data. The SAS procedure PROC GENMOD was used to perform GEE analysis.

Results

Descriptive Analysis

As can be seen in Table 1, the two groups did not differ significantly on any of the background characteristics or variables of interest. It is worth noting that the PSWQ scores between the NO CBT and CBT groups did approach significance. Thus, we conducted a posthoc analysis to examine the change from baseline to pre-augmentation to determine if there was a difference in response to the escitalopram treatment. The results indicated that the NO CBT group started the true baseline (M = 58.0; SD = 9.6) higher on the PSWQ compared to the CBT group (M = 51.3; SD = 11.0). Importantly, both groups showed comparable declines on the PSWQ while on escitalopram prior to the augmentation phase (−4.7 and −4.5, respectively). This would suggest there was a comparable response to the escitalopram treatment across the groups.

Correlations Among All Variables and Cortisol Change

There were no statistically significant relationships among the variables of interest in the CBT group (see Table 2). On the other hand, there was one statistically significant relationship in the No CBT group- higher scores on the CIRS-G were related to higher PSWQ scores. Based on this finding and, although not significant, the descriptive finding that the No CBT group had higher scores on the CIRS-G (see Table 1), the final GEE model predicted the time by CBT group interaction covarying for CIRS-G.

Effects of CBT Augmentation on Peak Cortisol Level Changes

A Generalized Estimating Equation (GEE) analysis was conducted to examine the between treatment group difference in peak cortisol change over time from pre to post- augmentation. The results of the GEE analysis revealed that medical comorbidity ($\beta = -0.002$, $se = 0.005$, 95% $CI = -0.011$ to $+0.007$, $p = 0.6435$) and group status ($\beta = -0.172$, $se = 0.112$, 95% $CI = -0.392$ to $+0.048$, $p = 0.1258$) were not statistically significant predictors of peak cortisol levels. On the other hand, there was a statistically significant effect of time ($\beta = 0.090$, $se = 0.038$, 95% $CI = -0.165$ to -0.016, $p = 0.0174$) indicating that there was an overall decrease in peak cortisol levels. Most importantly, there was a statistically significant interaction between time and group status ($\beta = 0.137$, $se = 0.068$, 95% $CI = +0.003$ to $+0.271$, $p = 0.0445$; see Figure 2). The interaction was characterized by a slight increase in peak cortisol levels for the group that did not receive CBT; in contrast, peak cortisol levels significantly decreased in the group that received CBT.

Based on the information reported by Mantella and colleagues (2008), it appears that the No CBT group had peak cortisol levels slightly below a group of untreated late-life GAD participants (see dashed line in Figure 2). Moreover, it appears that the CBT group had peak cortisol levels significantly below the untreated GAD group but the peak cortisol levels were still above the nonanxious older adult comparison group (see solid line in Figure 2).

We conducted a post hoc analysis to determine if the changes in peak cortisol within each group were related, ultimately, to changes in self-reported worry. We examined the bivariate relationship between peak cortisol change and worry change within each group. The results revealed that the two outcomes were not related in either group [CBT group – $r(18) = -0.339$, $p = 0.144$; No CBT group- $r(17) = 0.336$, $p = 0.160$].

Discussion

A treatment strategy of augmenting SSRI medication with CBT reduced peak salivary cortisol in older adults with Generalized Anxiety Disorder, relative to SSRI medication alone. This is the first study to demonstrate a physiological benefit using CBT augmentation of SSRI in older adults with GAD. These findings are important because they demonstrate that there may be a physiological, as well as psychological, benefit for older adults with GAD to receive combined treatments.

The diagnosis of GAD is related to a multitude of poor cognitive (Butters et al., 2011; Mantella et al., 2007; Rosnick et al., 2013) and health outcomes (e.g., Ansseau et al, 2005; Romera et al., 2010) including elevated cortisol levels (Mantella et al., 2008). Cortisol-reduction strategies may be one pathway to reducing accelerated cognitive and health-related burdens of stress and the aging process. The current findings have demonstrated one way of doing this via CBT augmentation of SSRIs for late-life GAD. Further, the current findings are in line with the research demonstrating the beneficial effects of CBT for younger individuals with GAD (Tafet et al., 2005) and extend them to older adults in the context of augmentation of SSRI, a common indication for CBT, as antidepressant monotherapy typically yields partial response.

One possible explanation for the current findings is that the participants who received CBT may have been able to exert more control and/or developed better coping strategies (Abelson, Khan, Liberzon, Erickson, & Young, 2008; Tafet et al., 2005), thereby reducing peak cortisol levels. Abelson and colleagues (2005, 2008) found that young adult and middle-aged patients with panic disorder and healthy participants who were made to feel more in control and/or given access to coping mechanisms with a physiologically arousing injection had significantly lower cortisol levels compared to individuals with access to neither. Further, the participants in the current study who did not receive the CBT augmentation began the study and pre-augmentation phase with higher levels of worry compared to the participants in the CBT group. It is possible the participants in the NO CBT group had more persistent (and possibly pernicious) anxiety thereby demonstrating the slight increase in cortisol. In support of this idea, Dierckx and colleagues (2012) found a dose response effect of treatment status (early responder, late responder, and non-response) and cortisol changes in a sample of children and adolescents in which those who were anxious longer exhibited larger cortisol changes (see also Sunderland, Wong, Hilvert-Bruce, & Andrews, 2012).

In addition, Wetherell and colleagues (2013) recently revealed that CBT augmentation to escitalopram treatment reduced pathological worry and others (Donegan & Dugas, 2012) have reported that changes in worry were related to changes in somatic anxiety. So, it is possible that the reduction in worry is responsible for the decreases in cortisol that we found in the current study. However, based on our post hoc analysis, it appears that the reductions in worry and cortisol with CBT augmentation are not related to each other. Although others have reported a relationship between worry severity and cortisol levels (Chaudieu et al., 2008; Mantella et al., 2008), the findings from the post hoc analysis are consistent with literature suggesting there is no relationship between self-reported stress and cortisol levels (e.g., Kirschbaum, Klauer, Filipp. & Hellhammer, 1995) or other biomarkers of stress such as alpha amylase (e.g., Nater, Rohleder, Scholtz, Ehlert, & Kirschbaum, 2007) in healthy samples. Further, Campbell and Ehlert (2012) reported that only approximately 25% of the studies in their review found a relationship between salivary cortisol and subjective stress.

There are several possible public health implications of the current findings. We recently showed that cortisol levels in older adults with GAD were negatively related to cognitive functioning (Rosnick et al., 2013), and others (Caudle et al., 2007) have reported that older adults with GAD who commit more cognitive errors are more likely to have poor treatment outcomes. These findings would suggest that we could potentially improve therapeutic outcomes and cognitive functioning by lowering cortisol levels in older adults with GAD. This idea has been supported by Lenze and colleagues (2012), who found that cortisol reduction after escitalopram treatment was related to memory improvements. Similarly, Mohlman (2013) reported that participants whose executive skills increased after CBT demonstrated the best response to treatment as indicated by significant worry reduction (see also Mohlman & Gorman, 2005). Future research should determine if there is any added cognitive or other health benefit of combined therapy above individual therapies.

Limitations

First, we do not know what the participants' cortisol levels were prior to starting the escitalopram treatment that they received for 12 weeks before randomization to CBT vs. no CBT. Therefore, we cannot determine the level of cortisol reduction from baseline (i.e., how much did cortisol levels decrease - if any – simply from the escitalopram treatment). Second, due to the small sample size, the current lack of a relationship between changes in cortisol and changes in worry should be interpreted with caution, although it is buttressed by similar findings in healthy adults (see Campbell & Ehlert, 2012 for review; Kirschbaum et al., 1995). Future research should examine this question with a larger sample. This would allow more intricate analyses as to the mechanism for the decrease (or increase in the No CBT group) in cortisol levels for the group who received CBT augmentation. Third, this was a single pre-post design which did not allow us to examine the long-term effects on cortisol levels for the combined treatment. In other words, what happens to cortisol levels when the patients discontinue CBT? If they continue CBT, will cortisol levels continue to decrease to the level of non-GAD older adults? In addition, including multiple measurement points after treatment would allow future researchers to better assess the relationship between cortisol and worry change. It is possible that the long-term association between these two variables is very different than the short-term effects that were assessed here (for more information on acute vs. long term effects of combined therapies for anxiety disorders see Würz & Sungur, 2009). Fourth, we do not know if cortisol reduction is a good thing and we did not have a psychotherapy or CBT only control group. Lastly, we did not collect other physiological measures such as alpha amylase. Since a relationship has been demonstrated between other biomarkers of stress (e.g., salivary alpha amylase: Fisher & Newman, 2013; nesfatin-1: Gunay, Tutuncu, Aydin, Dag, & Abasli, 2012) and GAD in college students, future research should examine if there are similar beneficial effects of combined therapies on these markers.

Conclusions

Previous research has highlighted the individual -- and somewhat limited -- benefits of pharmacotherapy and CBT for older adults with GAD. Combination strategies may therefore be most beneficial for relieving the burden of this disorder. The current study provides support for a physiological benefit using CBT augmentation of SSRI in older adults with GAD. If in fact chronically high cortisol is causally influencing the range of deleterious health and cognitive outcomes of late-life anxiety and other stress disorders, this behavioral strategy could mitigate these outcomes via cortisol reduction. This assertion requires proof with a direct test, as has been done with cholesterol reduction and cardiac outcomes. Such a study would be desirable but, given the large sample size and long-term follow-up needed, probably not feasible. Until such a time, patients may be motivated by knowing the physiological effects of this behavioral treatment.

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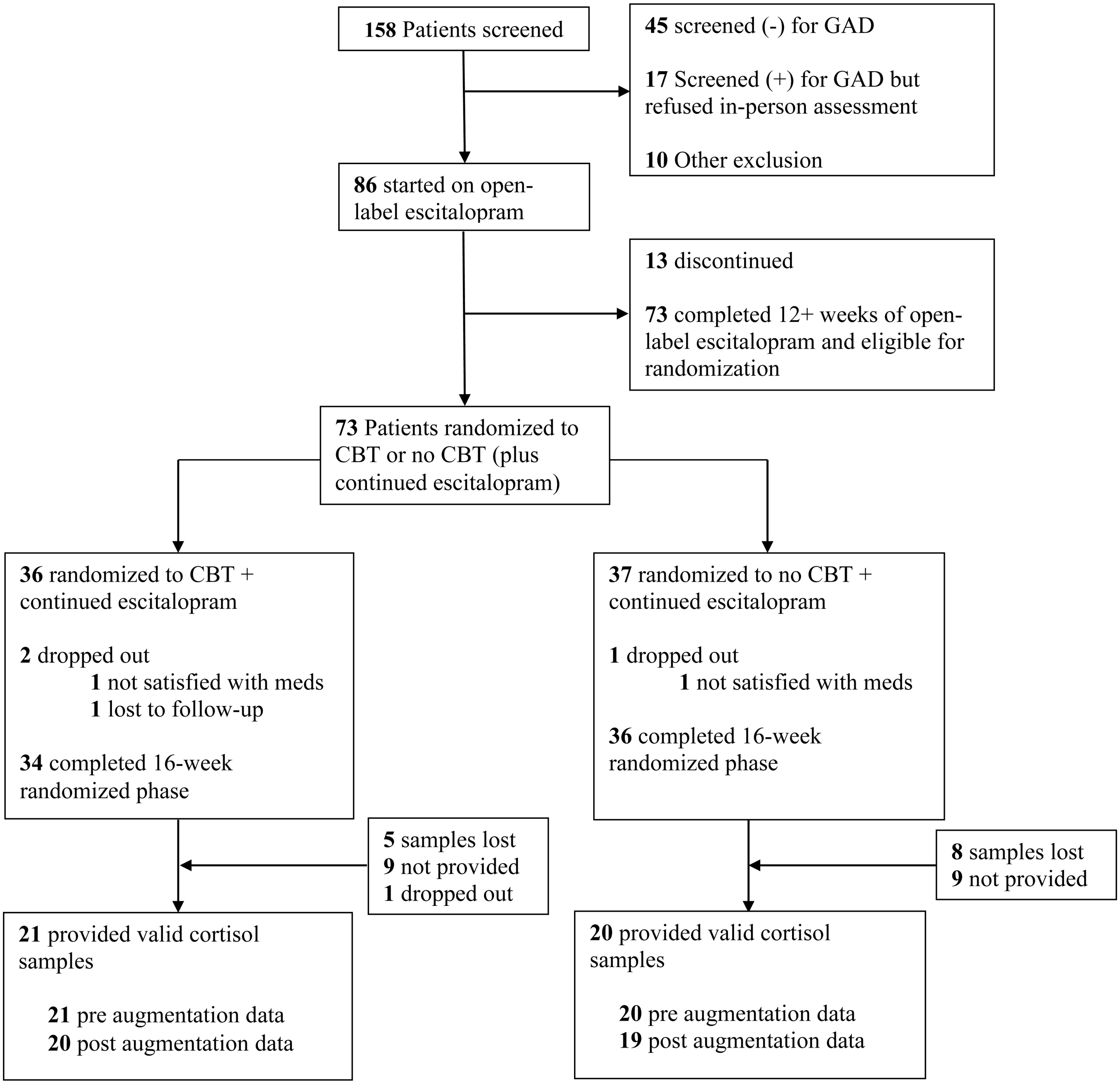

Figure 1.
Diagram for a Trial of Cognitive-Behavioral Therapy Augmentation of SSRI Treatment in Older Adults with Generalized Anxiety Disorder

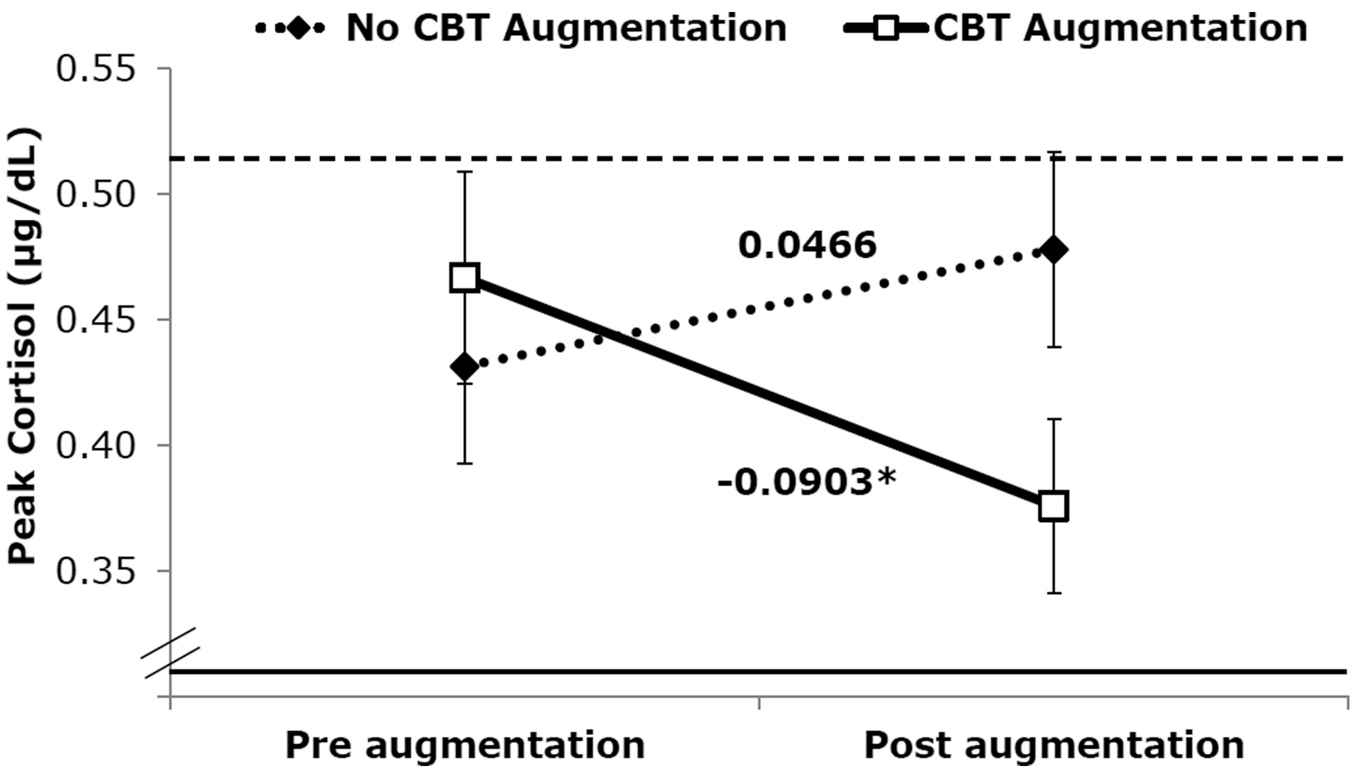

Figure 2.

Line graph showing the significant interaction between treatment group status (no CBT vs. CBT) and time (pre-post augmentation) such that peak cortisol levels decrease significantly in the CBT group and increase slightly in the group that did not receive CBT. Ultimately, peak cortisol levels were reduced with combined SSRI and CBT treatment in late-life GAD. Vertical lines represent the standard errors. The dashed horizontal line represents the approximate average wake +30 cortisol levels of older adult GAD participants who were NOT receiving any treatment and the solid horizontal line represents the approximate average wake +30 cortisol levels of an older adult comparison group without GAD (taken from Mantella et al., 2008).

Table 1

Comparison of Background and Clinical Characteristics of the GAD Participants Who Received CBT Augmentation and Those Who Did Not.

	NO CBT (n=21)	CBT (n=21)	Test Statistics
	Mean (SD)	Mean (SD)	
Age	68.71 (7.97)	71.19 (8.68)	$t = -0.96$, $df = 40$, $p = 0.3414$
White	81%	86%	$\chi^2 = 1.03$, $df = 2$, $p = 0.5979$
Female	76%	81%	$\chi^2 = 0.14$, $df = 1$, $p = 0.7069$
Baseline CIRS	9.95 (3.98)	8.86 (3.84)	$t = 0.90$, $df = 39$, $p = 0.3762$
PSWQ (prior to augmentation)	53.33 (9.97)	46.81 (12.53)	$t = 1.87$, $df = 40$, $p = 0.0692$

Note: CIRS- Cumulative Illness Rating Scale; PSWQ- Penn State Worry Questionnaire. Higher scores on both measures indicate poorer health and more worry, respectively.

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Table 2

Correlations Among Selected Variables and Cortisol Change by Group Status.

	Cortisol Δ	Age	CIRS-G	PSWQ
Cortisol Δ	---	0.11	0.14	0.35
Age	0.31	---	0.30	−0.22
CIRS	−0.12	−0.14	---	−0.14
PSWQ	−0.11	−0.06	0.52*	---

Note: CIRS- Cumulative Illness Rating Scale; PSWQ- Penn State Worry Questionnaire. The correlations within the No CBT group are presented below the diagonal and the correlations within the CBT group are presented above the diagonal;

* $p = 0.0193$