Published in final edited form as:
Am J Geriatr Psychiatry. 2011 May ; 19(5): 482–490. doi:10.1097/JGP.0b013e3181ec806c.

Elevated cortisol in older adults with Generalized Anxiety Disorder is reduced by treatment: a placebo-controlled evaluation of escitalopram

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Abstract

Background—Generalized Anxiety Disorder (GAD) is a common disorder in older adults which has been linked to hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis in this age group. We examined whether treatment of GAD in older adults with a selective serotonin reuptake inhibitor (SSRI) corrects this HPA axis hyperactivity.

Methods—We examined adults aged 60 and above with GAD in a 12-week randomized controlled trial comparing the SSRI escitalopram to placebo. We collected salivary cortisol at six daily timepoints for two consecutive days to assess peak and total (area under the curve) cortisol, both at baseline and post-treatment.

Results—Compared with placebo-treated subjects, SSRI-treated subjects had a significantly greater reduction in both peak and total cortisol. This reduction in cortisol was limited to subjects with elevated (above the median) baseline cortisol, in whom SSRI-treated subjects showed substantially greater reduction in cortisol than did placebo-treated subjects. Reductions in cortisol were associated with improvements in anxiety. Additionally, genetic variability at the serotonin transporter promoter predicted cortisol changes.

Conclusions—SSRI treatment of GAD in older adults reduces HPA axis hyperactivity. Further research should determine whether these treatment-attributable changes are sustained and beneficial.

Keywords

anxiety; cortisol; aging; health; stress; antidepressant

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Other authors report no financial conflicts.

Introduction

Substantial research suggests that chronic overactivation of the Hypothalamic-Pituitary-Adrenal (HPA) axis incurs wear and tear to the brain and body via toxic effects of elevated cortisol levels.[1] This mechanism may be particularly relevant to older adults, for several reasons. First, aging is associated with changes to HPA axis function, as indicated by reduced basal cortisol rhythmicity, suggesting that aging reduces homeostatic control in this system.[2-5] Second, aging is associated with decreased corticolimbic connectivity, resulting in the functional disruption of large-scale systems involved in cognition and emotion.[6, 7] This results in a decreased ability of prefrontal cortex to modulate the HPA axis response to negative emotions. [8, 9] As a result, emotional states such as anxiety might produce more substantial elevation in cortisol in older adults.[10, 11] Third, aging increases vulnerability to adverse effects of elevated cortisol, because compensatory mechanisms preventing its deleterious effects are diminished.[1] Finally, many of the putative deleterious health outcomes of HPA axis hyperactivity are age-related problems, including Alzheimer's disease, late-life depression, cardiovascular disease, and all-cause functional and cognitive decline and mortality [12-16].

Generalized Anxiety Disorder (GAD) is a common and impairing anxiety disorder in older adults,[17, 18] and it has been associated with elevated cortisol in this age group.[19, 20] Therefore, we hypothesized that elevated cortisol levels in older adults with GAD might be reduced by treatment. In a 12-week trial of the SSRI escitalopram vs. placebo for older adults with GAD, we examined treatment-attributable changes in peak cortisol (30 minutes after waking) and total cortisol (area under the curve measure utilizing all timepoints from morning to nighttime). We compared GAD subjects to matched healthy older adults to demonstrate that these cortisol measures are elevated in GAD. We hypothesized that GAD subjects with elevated baseline peak and total cortisol would have greater reductions in these measures with escitalopram, compared to placebo. We also hypothesized that changes in cortisol would be associated with clinical changes in anxiety scores.

Additionally, we examined genetic variability in the serotonergic system as a contributor to cortisol changes. Genetic variability in the promoter of the serotonin transporter gene, *SLC6A4*, is associated with altered functional connectivity between the amygdala and frontal regions[21, 22] and with altered HPA axis regulation, including in older adults[23, 24]. We therefore genotyped subjects for a haplotype in the *SLC6A4* promoter region consisting of the 5-HTTLPR S/L polymorphism and the rs25531 a/g polymorphism. Subjects with no copies of the La haplotype (La-) have lower SSRI efficacy than those with 1 or 2 copies (La +),[25] as well as a greater increase in cortisol in stress paradigms.[23] We therefore hypothesized that La- subjects would have less reduction in cortisol levels with treatment.

Materials and methods

The study was a 12-week, double-blind, randomized controlled trial comparing escitalopram and placebo.[26] Subjects were age 60 and older, with a principal diagnosis of GAD (according to the Structured Diagnostic Interview for DSM-IV axis I diagnoses (SCID)[27] and a score of 17 or greater in the Hamilton Anxiety Rating Scale.[28] The University of Pittsburgh Institutional Review Board approved the study. Recruitment sources included primary care sites, specialty mental health practices and advertisements. Comorbid unipolar depression or other anxiety disorders were allowed; exclusion criteria included lifetime psychosis or bipolar disorder, dementia, medical instability, exogenous steroid use (including inhaled steroids), and antidepressant or anxiolytic coprescription (with the exception of continuing low-dose benzodiazepines if already in use). Subjects were

randomized to 10mg of escitalopram or placebo, with increase to 20mg after four weeks as needed.

Subjects were assessed with diurnal cortisol levels at week 0 and week 12 (or exit from the study, if they received at least 6 weeks of study treatment). Sampling occurred for two days, with results averaged for each time point, consistent with recommendations for cortisol collection in geriatric research.[29] Collection occurred on the two consecutive days immediately prior to the assessment, for the following six time points: immediately upon waking, 30 minutes after waking, noon, 4pm, 8pm, and bedtime. Details of instructions for cortisol collection, and cortisol assays, are available from authors on request; they include not eating, drinking, smoking, or brushing teeth for 30 minutes prior to collection, and no alcohol use.[19] We defined peak cortisol as the mean of the two consecutive days at 30 minutes after waking, and total cortisol as an area under the curve utilizing means at all six timepoints as previously recommended.[30]

Cortisol values are reported in ng/ml (to convert to nmol/l, multiply by 2.76). To confirm that cortisol is elevated in late-life GAD, we compared GAD patients (n=95) at baseline to a group of healthy comparison subjects (n=40) who were equated on race, gender, and age and differed only in having no lifetime psychiatric diagnosis per the SCID.

We examined cortisol changes in GAD subjects for whom both pre and post treatment cortisol data were available (n=61). Mixed effect analyses were used to compare peak and total cortisol reduction between the escitalopram and placebo groups. Clinical evaluations included Hamilton Anxiety Rating Scale at weeks 0,1,2,3,4,6,8,10, and 12, and the Penn State Worry Questionnaire[31] at weeks 0,4,8, and 12. Generalized Estimating Equations analyses (GEE) were used to examine relationships between cortisol and clinical improvement. GEE analysis is a type of regression analysis similar to repeated measures ANOVA; it models inherent correlations in time-course data. Several hypothesized relationships were examined. First, peak and total cortisol would show a greater reduction in the escitalopram group compared to the placebo group. Second, this treatment-attributable reduction would be seen in subjects with cortisol above the median at baseline. Third, cortisol reductions would be associated with clinical improvement (i.e., changes in Hamilton Anxiety Rating Scale and Penn State Worry Questionnaire). All p-values reported are two-tailed; significance level for all tests was $p \leq 0.05$.

Additionally, we simultaneously genotyped two promoter polymorphisms in *SLC6A4*: the 5-HTTLPR insertion/deletion resulting in a short (S) vs. long (L) polymorphism, and rs25531, an a/g single nucleotide polymorphism. There was a reduced n for this combined pharmacogenetic and cortisol evaluation, because of subjects who withdrew from the study prior to blood draw for genotyping (n=4), no DNA in samples (n=2), and failure of genotyping (n=1). As only the La haplotype is associated with high *SLC6A4* transcription,[32] we categorized subjects by whether they had no La haplotypes (La-) or 1-2 La haplotypes (La+), and we compared changes in cortisol with treatment in La- subjects to La+ subjects using mixed-effect repeated measures analysis. We hypothesized reduced cortisol changes with treatment in La- subjects. Because of small sample size for this examination, and as escitalopram and placebo groups did not differ in the association of anxiety symptom changes with cortisol changes, we combined the two treatment groups for this analysis.

Results

Figure 1 shows flow of subjects through the study. Ninety-five subjects with GAD and who had usable cortisol data at baseline were compared to 40 non-anxious comparison subjects.

As Figure 2 shows, these subjects had significantly higher peak and total cortisol levels than a healthy comparison group, confirming an interim report in a subset of this sample.[19]

All other analyses pertain to GAD subjects who were randomized to escitalopram or placebo and had usable cortisol data at both pre and post treatment. Table 1 describes baseline characteristics of these subjects, dichotomized at the median for peak cortisol levels (4.74ng/ml). There were no significant differences in any baseline characteristic among subjects above vs. below the median peak cortisol value for the overall group except for race: a significantly greater percentage of European-Americans than African-Americans had higher total cortisol levels, consistent with other research.[33]

Table 2 shows the comparison of changes in cortisol values between the escitalopram and placebo groups. Escitalopram-treated subjects as a whole showed a greater reduction in peak cortisol, and a trend for greater reduction in total cortisol, compared to placebo-treated subjects, as hypothesized. These differences appeared mainly due to greater escitalopram-attributable reductions in subjects with high baseline cortisol values; for example, among subjects in the top quartile of peak cortisol, those receiving escitalopram had a much greater decline than those receiving placebo. Similar results were found for those in the top quartile for total cortisol. In contrast, subjects in the bottom two quartiles of either peak or total cortisol, showed no significant changes over time in cortisol levels in either the escitalopram or placebo group, or any difference between the escitalopram and placebo groups.

Next, we examined association of clinical improvements with cortisol changes among those above the median for these cortisol measures. For subjects above the median in baseline cortisol measures, there was a significant association of Hamilton Anxiety Rating Scale change with both peak (GEE parameter estimate 1.01, 95% CI 0.58-1.43, z=4.66, p<0.0001) and total cortisol (estimate 0.10, 95% CI 0.03-0.18, z=2.76, p=0.006), while for those below the median in baseline cortisol, there was no association (for peak: estimate -0.91, 95% CI -2.1-0.25, z=-1.53 p=.12; for total: estimate -0.05, 95% CI -0.25-0.15, z=-0.50, p=.62). Findings were similar for association of cortisol changes with Penn State Worry Questionnaire change. For subjects above the median, there was a significant association (for peak: estimate 1.95, 95% CI 0.67-3.25, z=2.97, p=0.003; for total: estimate 0.22, 95% CI 0.03-0.41, z=2.28, , p=0.02.. For those below the median, there was no association (for peak: estimate -.037, 95% CI -3.10-2.34, z=-.27, , p=0.79; for total: estimate -0.10, 95% CI -0.47-0.26, z=-0.57, p= 0.57).

Finally, we examined association of serotonin transporter promoter haplotype with treatment-attributable changes in cortisol among 54 subjects who had both genotyping data and pre and post treatment cortisol data. Among this group, haplotype frequencies were as follows: La/La n=14, La/Sa n=18, Sa/Sa n=12, Lg/Sa n=7, La/Lg n=2. Subjects were categorized as La+ (n=34) or La- (n=20). In terms of treatment-attributable changes, Figure 3 shows that the La+ group showed a reduction in peak and total AUC cortisol levels, compared to no reduction in the La-group. There appeared to be no significant differences in this effect between drug and placebo, though small sample size precluded a formal evaluation. La+ vs. La- proportions did not differ by treatment group (La+, 15 escitalopram, 19 placebo; La-, 8 escitalopram, 12 placebo, exact p=.99), and the genotype groups did not differ in pretreatment peak or total AUC cortisol levels: means for peak cortisol were: La+ 4.70ng/ml (SD 1.86), La- 4.59ng/ml (SD 1.89; t=0.45, df=52, p=0.65), for AUC cortisol La+ 27.0 (SD 13.4), La- 26.9 (SD 10.5; t=0.25, df=52, p=0.81).

Discussion

This study demonstrated that treatment of an anxiety disorder in older adults reduces elevated cortisol levels. The reduction in cortisol was treatment-attributable, as it was seen to a much greater extent with escitalopram than with placebo. The findings are noteworthy, given the great public health potential of translating neurobiological links between stress, health, and aging to clinical conditions.

Older adults with GAD had elevated total and peak cortisol levels – approximately 40-70% higher than an equated non-anxious sample. It remains unknown how GAD is associated with elevated cortisol in older adults. A possible explanation comes from observations that a sense of control appears to modulate the cortisol response to stress,[34] given that a sense of loss of control centrally defines GAD. However, it is unclear why cortisol levels would be elevated only in some subjects with GAD; other explanations regarding medical, cognitive, and/or brain changes[35] in older adults with GAD should be examined. Additionally, it should be noted that cortisol levels in late life GAD were not supraphysiologic, as would be found in Cushing's disease.

Among those with elevated baseline cortisol, both peak and total cortisol were reduced with escitalopram compared to placebo. This drug-placebo difference suggests that the cortisol reduction was due to the SSRI treatment rather than practice effects, expectancy, or regression to the mean. Further, reduction in cortisol was associated with reductions in anxiety (i.e., those with a better treatment response also had a greater drop in cortisol). Together, these findings suggest that late-life anxiety disorder treatment can correct elevated cortisol, particularly when the treatment is successful at reducing anxiety symptoms. It is also possible that cortisol reduction was a direct SSRI effect (rather than an effect of treating the anxiety); other treatments (e.g., Cognitive-Behavioral Therapy[36]) should be examined to clarify their effects on the HPA axis.

Our finding of elevated cortisol in late-life GAD which reverses with treatment are notable in light of the somewhat more variable findings in late-life depression, in which both elevated and suppressed cortisol have been reported.[37, 38] as well as both reversal and non-reversal of hypercortisolemia with recovery from depression.[39, 40] This raises the question of whether comorbid anxiety, common in late-life depression [41] might be associated with a treatment-relevant neurobiological subtype of late-life depression, as has been suggested in young adults.[42] However, the present study is unable to address this issue, as no subjects with depression alone were included. Further research investigating relationships between anxiety disorders and depression in older adults may benefit from examination of the HPA axis.

Another treatment-relevant neurobiological subtype examined in this study was genetic variability in the serotonin transporter promoter, which we found was associated with cortisol changes during treatment. It has been hypothesized that genetic variability accounts for much of the heterogeneity in cortisol responsiveness, with serotonergic modulation being a key contributor.[43] This is supported by prior research in serotonin transporter genetic variability, showing that La- individuals have more reactivity of anxiety to daily stressors[44] and a more robust HPA axis response to stress.[23] We found that La- individuals had no reduction in cortisol levels with treatment, versus a significant reduction in La+ individuals. Our finding is consistent with the hypothesis of serotonergic regulation of the HPA axis, which is an important issue in older adults as it has been posited as a mechanism for late-life depression pathogenesis.[45] However, the relationship is likely bidirectional, and can be impacted by illness chronicity, ongoing or early-life stress, other age-related neurobiological changes, and other factors. Additionally, our finding is exploratory and limited by small

sample size; further research in larger samples is needed to clarify the interaction between serotonergic genetic variability, treatment effects, and HPA axis function.

There are caveats to these findings. First, the effects of SSRI treatment on cortisol reduction were large but not necessarily sustained or beneficial; evidence of this would require longer-term evaluations. Second, it is unclear whether these findings are generalizable to other ethnic groups. African-Americans and Latinos are large and growing sections of the U.S. older adult population, with differential cortisol responses to stress, compared to European-Americans. Further research should investigate ethnic differences in cortisol in late-life anxiety.[46, 47] Finally, cortisol is a marker of one neurobiological pathway; other markers in the myriad of biological pathways related to health in older adults[15, 48] should also be investigated in clinical trials.

In summary, cortisol in older adults with GAD was reduced by SSRI treatment, in those with elevated cortisol prior to treatment. Further research should examine connections between treatment of anxiety disorders and modulation of neurobiological stress pathways in older adults and clarify whether alterations in the HPA axis have resultant implications for health.[49] Anxiety disorders in older adults are common and at present are typically unrecognized or poorly-managed; if treatment corrects HPA axis disturbance, with subsequent benefits to health and cognition, this would increase the already high public health importance of late-life anxiety.

Acknowledgments

This research was supported by National Institutes of Health grant R01 MH070547, the Center for Mental Health Services Research (P30 MH068579; principal investigator: Enola Proctor, Ph.D.), the Advanced Center for Interventions and Services Research in Late-life Mood Disorders (P30 MH71944; principal investigator: Charles F. Reynolds III, M.D.), and the John A. Hartford Center of Excellence in Geriatric Psychiatry (principal investigator: Reynolds). Forest Laboratories Inc., which holds the U.S. patent for escitalopram, provided escitalopram and matching placebo for the study. Neither NIH nor Forest had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Financial Disclosure

Dr. Lenze is a consultant for Fox Learning Systems, was a consultant for the Veteran's Medical Research Foundation from 2007-2008, and has received research support from Forest Laboratories (current), Pfizer, Novartis and OrthoMcNeill Neurologics (until 2007). Dr. Mantella is an employee of Abbott Laboratories; she carried out this research while at University of Pittsburgh (until 2007).

References

1. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med. Jan 15; 1998 338(3):171–179. [PubMed: 9428819]
2. Van Cauter E, Leproult R, Kupfer DJ. Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. J Clin Endocrinol Metab. Jul; 1996 81(7):2468–2473. [PubMed: 8675562]
3. Lupien S, Lecours AR, Lussier I, Schwartz G, Nair NP, Meaney MJ. Basal cortisol levels and cognitive deficits in human aging. J Neurosci. May; 1994 14(5 Pt 1):2893–2903. [PubMed: 8182446]
4. Ferrari E, Magri F, Dori D, et al. Neuroendocrine correlates of the aging brain in humans. Neuroendocrinology. Apr; 1995 61(4):464–470. [PubMed: 7783860]
5. Deuschle M, Gotthardt U, Schweiger U, et al. With aging in humans the activity of the hypothalamus-pituitary-adrenal system increases and its diurnal amplitude flattens. Life Sci. 1997; 61(22):2239–2246. [PubMed: 9393943]

6. Andrews-Hanna JR, Snyder AZ, Vincent JL, et al. Disruption of large-scale brain systems in advanced aging. Neuron. Dec 6; 2007 56(5):924–935. [PubMed: 18054866]
7. Pfefferbaum A, Adalsteinsson E, Sullivan EV. Frontal circuitry degradation marks healthy adult aging: Evidence from diffusion tensor imaging. Neuroimage. Jul 1; 2005 26(3):891–899. [PubMed: 15955499]
8. Urry HL, van Reekum CM, Johnstone T, et al. Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. J Neurosci. Apr 19; 2006 26(16):4415–4425. [PubMed: 16624961]
9. Kern S, Oakes TR, Stone CK, McAuliff EM, Kirschbaum C, Davidson RJ. Glucose metabolic changes in the prefrontal cortex are associated with HPA axis response to a psychosocial stressor. Psychoneuroendocrinology. May; 2008 33(4):517–529. [PubMed: 18337016]
10. Otte C, Hart S, Neylan TC, Marmar CR, Yaffe K, Mohr DC. A meta-analysis of cortisol response to challenge in human aging: importance of gender. Psychoneuroendocrinology. Jan; 2005 30(1): 80–91. [PubMed: 15358445]
11. Seeman TE, Singer B, Wilkinson CW, McEwen B. Gender differences in age-related changes in HPA axis reactivity. Psychoneuroendocrinology. Apr; 2001 26(3):225–240. [PubMed: 11166486]
12. Catania C, Sotiropoulos I, Silva R, et al. The amyloidogenic potential and behavioral correlates of stress. Mol Psychiatry. Jan; 2009 14(1):95–105. [PubMed: 17912249]
13. Csernansky JG, Dong H, Fagan AM, et al. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. Am J Psychiatry. Dec; 2006 163(12):2164–2169. [PubMed: 17151169]
14. Lupien SJ, Nair NP, Briere S, et al. Increased cortisol levels and impaired cognition in human aging: implication for depression and dementia in later life. Rev Neurosci. 1999; 10(2):117–139. [PubMed: 10658955]
15. Gruenewald TL, Seeman TE, Ryff CD, Karlamangla AS, Singer BH. Combinations of biomarkers predictive of later life mortality. Proc Natl Acad Sci U S A. Sep 19; 2006 103(38):14158–14163. [PubMed: 16983099]
16. Lee BK, Glass TA, McAtee MJ, et al. Associations of salivary cortisol with cognitive function in the Baltimore memory study. Arch Gen Psychiatry. Jul; 2007 64(7):810–818. [PubMed: 17606815]
17. Bryant C, Jackson H, Ames D. The prevalence of anxiety in older adults: methodological issues and a review of the literature. J Affect Disord. Aug; 2008 109(3):233–250. [PubMed: 18155775]
18. Wetherell JL, Thorp SR, Patterson TL, Golshan S, Jeste DV, Gatz M. Quality of life in geriatric generalized anxiety disorder: a preliminary investigation. J Psychiatr Res. May-Jun;2004 38(3): 305–312. [PubMed: 15003436]
19. Mantella RC, Butters MA, Amico JA, et al. Salivary cortisol is associated with diagnosis and severity of late-life generalized anxiety disorder. Psychoneuroendocrinology. Jul; 2008 33(6):773–781. [PubMed: 18407426]
20. Chaudieu I, Beluche I, Norton J, Boulenger JP, Ritchie K, Ancelin ML. Abnormal reactions to environmental stress in elderly persons with anxiety disorders: evidence from a population study of diurnal cortisol changes. J Affect Disord. Mar; 2008 106(3):307–313. [PubMed: 17727959]
21. Pezawas L, Meyer-Lindenberg A, Drabant EM, et al. 5-HTTLPR polymorphism impacts human cingulate-amygdala interactions: a genetic susceptibility mechanism for depression. Nat Neurosci. Jun; 2005 8(6):828–834. [PubMed: 15880108]
22. Heinz A, Braus DF, Smolka MN, et al. Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. Nat Neurosci. Jan; 2005 8(1):20–21. [PubMed: 15592465]
23. Gotlib IH, Joormann J, Minor KL, Hallmayer J. HPA axis reactivity: a mechanism underlying the associations among 5-HTTLPR, stress, and depression. Biol Psychiatry. May 1; 2008 63(9):847–851. [PubMed: 18005940]
24. O'Hara R, Schroder CM, Mahadevan R, et al. Serotonin transporter polymorphism, memory and hippocampal volume in the elderly: association and interaction with cortisol. Mol Psychiatry. Jun; 2007 12(6):544–555. [PubMed: 17353910]
25. Alessandro S, Kato M. The serotonin transporter gene and effectiveness of SSRIs. Expert Rev Neurother. Jan; 2008 8(1):111–120. [PubMed: 18088204]

26. Lenze EJ, Rollman BL, Shear MK, et al. Escitalopram for older adults with Generalized Anxiety Disorder: a placebo-controlled trial. JAMA. 2009; 301(3):296–303.
27. First, MB.; Spitzer, RL.; Gibbon, M. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID), Clinician Version: Administration Booklet. Washington, DC: 1996.
28. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959; 32(1):50–55. [PubMed: 13638508]
29. Kraemer HC, Giese-Davis J, Yutsis M, et al. Design decisions to optimize reliability of daytime cortisol slopes in an older population. Am J Geriatr Psychiatry. Apr; 2006 14(4):325–333. [PubMed: 16582041]
30. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology. Oct; 2003 28(7):916–931. [PubMed: 12892658]
31. Meyer TJ, Miller ML, Metzger RL, Borkovec TD. Development and validation of the Penn State Worry Questionnaire. Behav Res Ther. 1990; 28(6):487–495. [PubMed: 2076086]
32. Zalsman G, Huang YY, Oquendo MA, et al. Association of a triallelic serotonin transporter gene promoter region (5-HTTLPR) polymorphism with stressful life events and severity of depression. Am J Psychiatry. Sep; 2006 163(9):1588–1593. [PubMed: 16946185]
33. Chong RY, Uhart M, McCaul ME, Johnson E, Wand GS. Whites have a more robust hypothalamic-pituitary-adrenal axis response to a psychological stressor than blacks. Psychoneuroendocrinology. Feb; 2008 33(2):246–254. [PubMed: 18082975]
34. Abelson JL, Khan S, Liberzon I, Erickson TM, Young EA. Effects of Perceived Control and Cognitive Coping on Endocrine Stress Responses to Pharmacological Activation. Biol Psychiatry. Jun 19.2008
35. Mohlman J, Price RB, Eldreth DA, Chazin D, Glover DM, Kates WR. The relation of worry to prefrontal cortex volume in older adults with and without generalized anxiety disorder. Psychiatry Res. Aug 30; 2009 173(2):121–127. [PubMed: 19559575]
36. Stanley MA, Beck JG, Novy DM, et al. Cognitive-behavioral treatment of late-life generalized anxiety disorder. J Consult Clin Psychol. Apr; 2003 71(2):309–319. [PubMed: 12699025]
37. Bremmer MA, Deeg DJ, Beekman AT, Penninx BW, Lips P, Hoogendijk WJ. Major depression in late life is associated with both hypo- and hypercortisolemia. Biol Psychiatry. Sep 1; 2007 62(5): 479–486. [PubMed: 17481591]
38. Penninx BW, Beekman AT, Bandinelli S, et al. Late-life depressive symptoms are associated with both hyperactivity and hypoactivity of the hypothalamo-pituitary-adrenal axis. Am J Geriatr Psychiatry. Jun; 2007 15(6):522–529. [PubMed: 17545451]
39. Beluche I, Chaudieu I, Norton J, et al. Persistence of abnormal cortisol levels in elderly persons after recovery from major depression. J Psychiatr Res. Dec 1.2008
40. O'Brien JT, Lloyd A, McKeith I, Gholkar A, Ferrier N. A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. Am J Psychiatry. Nov; 2004 161(11):2081–2090. [PubMed: 15514410]
41. Beekman AT, de Beurs E, van Balkom AJ, Deeg DJ, van Dyck R, van Tilburg W. Anxiety and depression in later life: Co-occurrence and communality of risk factors. Am J Psychiatry. Jan; 2000 157(1):89–95. [PubMed: 10618018]
42. Young EA, Abelson JL, Cameron OG. Effect of comorbid anxiety disorders on the hypothalamic-pituitary-adrenal axis response to a social stressor in major depression. Biol Psychiatry. Jul 15; 2004 56(2):113–120. [PubMed: 15231443]
43. Ising M, Holsboer F. Genetics of stress response and stress-related disorders. Dialogues Clin Neurosci. 2006; 8(4):433–444. [PubMed: 17290801]
44. Gunthert KC, Conner TS, Armeli S, Tennen H, Covault J, Kranzler HR. Serotonin transporter gene polymorphism (5-HTTLPR) and anxiety reactivity in daily life: a daily process approach to gene-environment interaction. Psychosom Med. Nov; 2007 69(8):762–768. [PubMed: 17942837]
45. O'Hara R. Stress, aging, and mental health. Am J Geriatr Psychiatry. Apr; 2006 14(4):295–298. [PubMed: 16582037]

46. Gallagher-Thompson D, Shurgot GR, Rider K, et al. Ethnicity, stress, and cortisol function in Hispanic and non-Hispanic white women: A preliminary study of family dementia caregivers and noncaregivers. Am J Geriatr Psychiatry. Apr; 2006 14(4):334–342. [PubMed: 16582042]

47. McCallum TJ, Sorocco KH, Fritsch T. Mental health and diurnal salivary cortisol patterns among African American and European American female dementia family caregivers. Am J Geriatr Psychiatry. Aug; 2006 14(8):684–693. [PubMed: 16861373]

48. Epel ES, Blackburn EH, Lin J, et al. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci U S A. Dec 7; 2004 101(49):17312–17315. [PubMed: 15574496]

49. Comijs HC, Gerritsen L, Penninx BWJH, et al. The association between serum cortisol and cognitive decline in older persons. Am J Geriatr Psychiatry. Jan; 2010 18(1):42–56. [PubMed: 20094017]

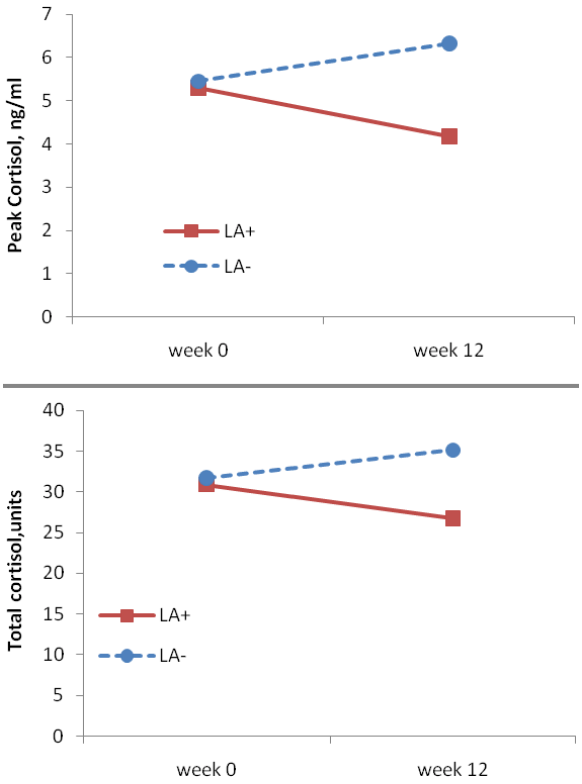

Figure 1. Study flowchart
(no legend)

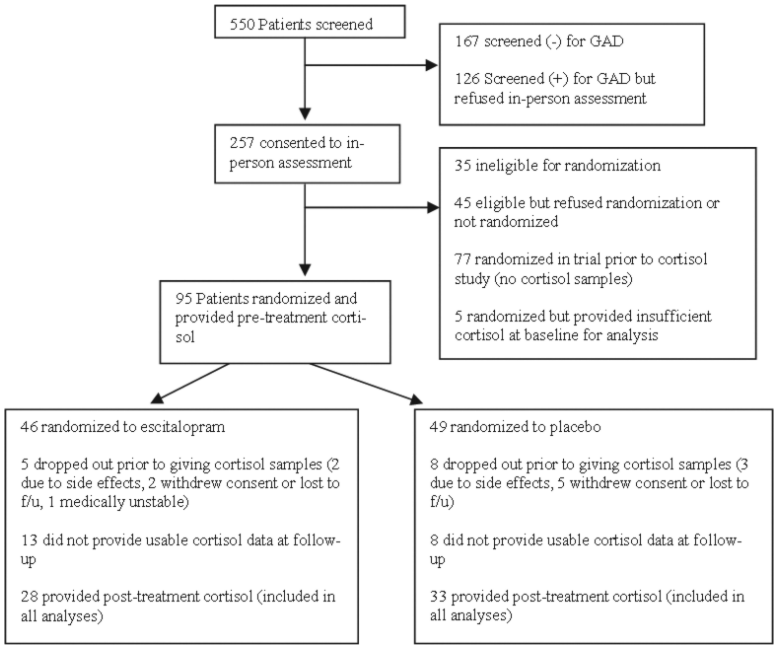

Figure 2. Baseline cortisol values in older GAD subjects vs. healthy comparisons

Note: total cortisol = area under the curve for all six time points from waking to bedtime. T-tests compared the groups at each time point and for a total area under the curve (AUC) cortisol. Means and SD bars are shown.

*Asterisks indicate significantly elevated cortisol in GAD at the *$p<0.01$ or **$p<0.001$ level (df=133 for all significant comparisons).

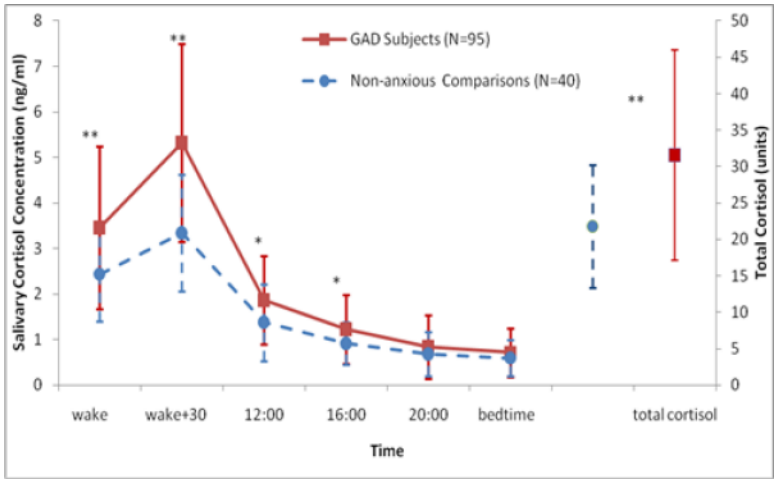

Figure 3. Changes in peak and total cortisol by serotonin transporter promoter genotype

Note: Compared to La- subjects (n=20), La+ subjects (n=34) show a decline in peak (genotype group × time interaction β=-0.17 [SE 0.05], df=54, t-statistic=-3.45, p=0.0011) and total total (genotype group × time interaction β=-0.61 [SE 0.30], df=52, t-statistic=-2.05, p=0.0456) cortisol values. All results are from mixed effect models. Data shown are predicted values from the mixed effect models.

Table 1

Baseline sociodemographic and clinical variables of GAD subjects with pre and post-cortisol data (N=61)

Variable	Peak pre-treatment cortisol below median (n=28)	Peak pre-treatment cortisol above median (n=33)	p-value
Demographic characteristics			
Age, mean (SD), years	72.1 (7.7)	72.3 (8.2)	0.9360
Caucasian race/ethnicity, No. (%)	21 (75%)	32 (97%)	0.0190
Male gender, No. (%)	7 (25%)	16 (49%)	0.0593
Education, mean (SD), y	13.3 (2.1)	14.5 (2.5)	0.0451
Recruitment site:			
Self-referral/advertisements	10 (36%)	13 (39%)	0.8572
Mental health setting	3 (11%)	2 (6%)	
Primary care site	15 (54%)	18 (55%)	
Clinical characteristics			
Hamilton Anxiety Rating Scale, mean (SD)	22.3(4.2)	21.2 (3.4)	0.3163
Hamilton Depression Rating Scale, mean (SD)	10.6 (3.2)	10.6 (3.2)	0.9958
Cumulative Illness Rating Scale for Geriatrics (medical comorbidity score), mean (SD)	9.1(4.6)	7.9 (3.3)	0.2433
Mini-mental State Examination, mean (SD)	28.7 (1.5)	28.1(1.6)	0.0981
Penn State Worry Questionnaire, mean (SD)	53.2 (11.4)	52.0(13.7)	0.7280
Current comorbidity, No (%)			
-Major depressive disorder	4 (14%)	4 (12%)	1.0000
-Any depressive disorder (including major)	5 (18%)	5 (15%)	1.0000
-Any anxiety disorder (other than GAD)	5 (19%)	6 (18%)	1.0000
Clinical history			
Age of onset of GAD, mean (SD), y	40.8 (29.3)	50.8(26.2)	0.2413
Duration of current GAD, mean (SD), mo	348.1(326.4)	262.0 (328.4)	0.2396
Concomitant benzodiazepine use at randomization, No (%)	4 (15%)	2 (6%)	0.3943

Note: The Two Sample t-test was used for age, HRSD, CIRSG-Score, and PSWQ (df=59). The Mann-Whitney test was used for education, HRSA, MMSE Score, age at onset, and duration. The Chi Square test was used for gender (df=1). Fisher's Exact test was used for geographic ancestry, recruitment site, major depressive disorder, any depressive disorder, anxiety disorder, and benzodiazepine use. All analyses were conducted with SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

Table 2

Changes in peak and total Cortisol, by treatment group and by baseline values

	n	Escitalopram		Placebo		Analysis of changes between groups *	
		Baseline Mean (SD)	Change Mean (SD)	Baseline Mean (SD)	Change Mean (SD)	F (time × group)	p-value
Peak Cortisol, ng/ml							
Entire group	61	5.2(1.8)	-0.8(2.7)	5.5(2.3)	0.2(2.2)	5.39(1,60)	0.0237
Top quartile	16	7.9(1.7)	-3.3(2.0)	8.3(1.8)	-0.8(3.1)	11.65(1,15)	0.0039
Top 2 quartiles	33	6.5(1.7)	-1.6(3.3)	7.0(1.9)	-0.4(2.4)	7.13(1,32)	0.0118
Bottom 2 quartiles	28	3.9(0.8)	-0.02(1.7)	3.6(0.8)	1.0(1.7)	0.11(1,27)	0.7409
Total Cortisol, units							
Entire group	61	29.3(10.2)	-3.4(13.7)	32.0(15.6)	2.4(12.8)	3.58(1,60)	0.0633
Top quartile	13	47.5(9.2)	-19.3(1.9)	51.8(12.8)	-5.8(13.9)	11.25(1,12)	0.0057
Top 2 quartiles	33	36.3(8.4)	-7.2(15.3)	42.7(12.9)	-3.0(13.9)	6.45(1,32)	0.0161
Bottom 2 quartiles	28	21.2(4.1)	1.0(10.6)	19.1(5.0)	8.9(7.6)	0.04(1,27)	0.8429

Note: Peak Cortisol = value 30 minutes after waking; total Cortisol = area under the curve for all six time points from waking to bedtime.

* Analytic results are for comparisons of change from baseline to post-treatment. At baseline, the escitalopram and placebo groups did not differ in peak or total cortisol, in the entire group or any subgroup (p-values ranged 0.11-0.65 for baseline comparisons between treatment groups).