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The Renin-Angiotensin Pathway in PTSD: the association between ACE inhibitor and ARB medications and traumatic stress symptoms

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ABSTRACT

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By Nayla M. Khoury

PTSD is a debilitating stress-related illness associated with trauma exposure. The peripheral and central mechanisms mediating stress response in PTSD are incompletely understood. Recent preclinical data suggest that the renin-angiotensin (RAAS) pathway, essential to cardiovascular regulation, is also involved in mediating stress and anxiety. The treatment of psychiatric conditions with RAAS-modifying medications has not been the focus of clinical trials. In this study, the authors examined the relationship between active treatment with blood pressure medication, including angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs), and PTSD symptom severity within a highly traumatized civilian medical population.

Using data from a larger study that recruited patients from Grady Memorial's outpatient waiting rooms from 2006 to November 2010, multi-variable linear regression models were fit to statistically evaluate the independent association of being prescribed an ACE-I or ARB with PTSD symptoms, using a sub-set of patients for whom medical information was available (n=505). PTSD diagnosis was assessed using the modified PTSD Symptom Scale (PSS) based on DSM-IV criteria with PTSD symptoms based on PSS and Clinician Administered PTSD Scale (CAPS).

A significant association was found between presence of ACE-I / ARB medication and decreased PTSD symptoms (mean PSS score 11.4 vs 14.9 for individuals prescribed vs not prescribed ACE-I/ARBs, respectively ($p = 0.014$)). After adjustment for covariates, ACE-I/ARB treatment remained significantly associated with decreased PTSD symptoms ($p = 0.044$). Notably, other blood pressure medications, including beta-blockers, calcium channel blockers, and diuretics, were not significantly associated with reduced PTSD symptoms.

These data provide the first clinical evidence supporting a role for the renin-angiotensin system in the regulation of stress response in patients diagnosed with PTSD. Further studies should examine whether available medications targeting this pathway should be considered for future treatment and potential protection against PTSD symptoms. Efforts to better understand the disease mechanisms and to improve treatment and prevention strategies have important public health implications to reduce the immediate and long-term impacts of PTSD on individuals and society.

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CHAPTER I: LITERATURE REVIEW

Background

Posttraumatic stress disorder (PTSD) is a debilitating, stress-related psychiatric illness associated with trauma exposure. While the lifetime prevalence of PTSD in the general population is estimated to be 5-10%, the prevalence of PTSD in low-income, urban, primary care patients has been estimated to be as high as 45% (1, 2). Higher still is the prevalence of lifetime trauma exposure within this population, approximately 88% (1). Additional research investigating risk and protective factors for PTSD is essential to improving future prevention efforts.

Chronic stress, involving exposure to frequent and early traumatic events, has been implicated in multiple adverse health outcomes, including cardiovascular-associated diseases, such as hypertension (3-5). "Allostatic load" has been used to refer to the physiologic cost of excess stress on the hypothalamic pituitary adrenal (HPA) axis and autonomic nervous system (3, 5, 6). A number of studies support the finding that individuals with PTSD have increased prevalence of blood pressure dysregulation (7-9). Although the specific mechanisms are still being elucidated, two recent meta-analyses have demonstrated that PTSD is associated with elevations in resting systolic and diastolic blood pressure (10, 11).

Using data from a larger study that recruited patients from Grady Memorial's outpatient waiting rooms from 2006 to November 2010, we conducted an exploratory analysis on blood pressure and PTSD symptoms. Unexpectedly, we found first that individuals with higher PTSD scores, as measured by the modified PTSD Symptom Scale (PSS), had statistically significant decreased blood pressure, as measured on physical exam; these results were no longer significant after controlling for being on a blood pressure medication. Specifically, it appeared that angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs) selectively reduced the risk of PTSD symptom severity. This preliminary finding led to our current research question: does being on blood pressure medications, specifically ACE-I or ARB, independently decrease the risk of PTSD symptoms among individuals who have been exposed to

trauma? The remainder of this chapter explores the burgeoning preclinical and clinical literature related to this question.

Methods

As this is the first study to examine the association of ACE-I or ARBs on PTSD in humans, the goals of this literature review were to determine what is known about: a) the effects of ACE-I and ARB on psychiatric disorders in general and b) the effects of ACE-I, ARBs on anxiety-related disorders in animal studies.

Three approaches were undertaken to comprehensively review the existing literature. First, a PubMed search examined literature on the renin-angiotensin system and psychiatric disorders. Second, a search was conducted examining ACE-I or ARBs and psychiatric disorders. Lastly, related studies were found using references from the most recent literature review on the topic (12).

Limitations imposed on the PubMed search included studies in English and that were one of the following study types: clinical trials, meta-analysis, practice guidelines, RCT, review, comparative study, journal articles, multicenter studies, or validation studies. Review articles were only included if they were published within the last 5 years. Only a limited number of randomized control trials have been published; these were assessed using the Consolidated Standards of Reporting Trials (CONSORT) 22-item checklist (13). The remaining nonrandomized studies were evaluated using Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) guidelines (14).

Results

There has been accumulating evidence over the past five years that the effects of ACE-I or ARBs extend well beyond the reduction of blood pressure (12, 15-17). The bulk of evidence supporting the association of ARB/ACE-I with improvements in affective disorders, such as

depression and anxiety, come from pre-clinical literature (18-21), with a few smaller clinical studies supporting this association (22, 23). The larger RCT and cohort studies on psychiatric disorders and ACE-I/ARB mainly examine (15) cognitive function as their outcome (12, 15-17). A recent study and literature review calls into question other findings over the past five years that ACE-I or ARBs, particularly centrally acting, reduce cognitive decline (24).

a) Preclinical studies

A recent review on RAAS (Renin Angiotensin Aldosterone System)-altering medications highlights numerous preclinical studies demonstrating the therapeutic and protective effects of ARBs on the brain, including the reduction of stress, anxiety, brain inflammation and ischemia (12). Multiple animal studies have demonstrated that blockade of angiotensin II AT1 receptors or angiotensin II formation can reduce the effects of stress on rodent physiology and behavior (25, 26). For example, a study using transgenic rats with excess generation of brain angiotensin II found that blockade of angiotensin II synthesis with Captopril, a centrally-acting ACE inhibitor, reduced the increased anxiety provoked by increased angiotensin II (18).

Preclinical studies examining physiologic stress markers with the RAAS cascade further support the physiologic role for peripheral and brain AT1 receptors during stress. For example, subcutaneous or oral administration of Candesartan, a centrally-acting ARB, has been demonstrated to reduce HPA activation, as well as central and peripheral sympathetic response to isolation stress in rodents (27). ARB decreases isolation-induced stimulation of corticotropin-releasing hormone (CRF) formation, as well as other hormones in the stress cascade, including adrenocorticotropic hormone (ACTH), corticosterone, aldosterone, vasopressin and catecholamine release (27, 28). In addition, Candesartan decreases the transcription of tyrosine hydroxlase, the rate-limiting enzyme in the synthesis of catecholamines in the locus coeruelus (Seltzer et al. 2004; Saavedra et al., 2006; Bregonzio et al., 2008).

These physiologic effects of RAAS-altering medications correlate well with studies of anxiety and depression behavior in rodent models. One experiment comparing a benzodiazepine

and an ARB on rodent behavior in a plus-maze demonstrated that losartan (an ARB) has similar potency to diazepam (a benzodiazepine) in preventing isolation-induced stress (Kaiser et al. 1992;). Saavedra also found that pretreatment with a centrally-acting ARB prevents stress-induced alterations in cortical CRF, benzodiazepine binding, and locus coeruleus TH mRNA, as well as anxiety behavior in the elevated plus-maze (20). Another experiment demonstrated that injecting losartan into the dorsal-medial hypothalamus of "panic-prone" rodents blocked the anxiety-like and physiological components of lactate-induced panic-like responses (19).

Most relevant to the current study is an experimental finding that ARBs can prevent a stress-induced disorder in rodents (21). As stress has been shown to reduce gastric blood flow and produces acute gastric lesions (29), spontaneously hypertensive rats in the study were pretreated for 14 days with Candesartan (ARB) before cold-restraint stress. Results demonstrated that AT1 blockade increased gastric blood flow by 40-50%, prevented gastric ulcer formation by 70-80% after cold-restraint stress, and had multiple effects on hormones of the HPA axis (21). Candesartan's protective effect was due to preventing stress-induced reduction on gastric blood flow and ischemia, as well as reducing central and peripheral sympathoadrenal stimulation and direct anti-inflammatory effects in the gastric mucosa (21). Meanwhile, Candesartan did not block the protective effects of glucocorticoid release from the cold-restraint-induced-HPA axis stimulation.

b) Affective disorders and the RAAS system

The clinical literature on the RAAS and affective disorders such as depression and anxiety is limited, with no existing randomized studies and with most studies having relatively small sample sizes. Nevertheless, there is some clinical evidence to support the hypothesis that RAAS activity may be associated with affective disorders, such as depression (23, 30, 31). For example, Saab and colleagues examined polymorphisms of genes encoding for components of the RAAS in Lebanese patients and their first-degree relatives and found that angiotensin receptor type 1 (A1166C) CC genotype was significantly associated with depression ($p< 0.05$) (31).

Similarly, a recent study examined genotypes of 194 depressed patients and 541 "mentally healthy subjects" with coping styles in response to stressful situations (30). Coping styles have been hypothesized to be a moderator of the stress reaction and may render an individual more vulnerable to stress-related disorders, such as depression and cardiovascular disease (32). The finding of specific SNPs associated with positive coping styles suggests that the ACE gene may be involved in the development of coping strategies (30).

While the effect of RAAS-modifying medications on affective disorders has not been evaluated in any randomized controlled studies, a cross-sectional study examined 378 patients diagnosed with hypertension in a primary care clinic. Results demonstrated that 20% of patients taking a RAAS-modifying medication were on an anti-depressant compared to 34% of those not taking a RAAS-modifying medication (P=0.003, (22)). The highest usage of anti-depressants occurred in the group of patients taking beta-blockers alone for treatment of their hypertension.

Moreover, a smaller but more direct study examined 17 patients with Diabetes Mellitus type II aged 40-65 who were treated with Candesartan, an ARB known to cross the blood brain barrier. Preliminary results revealed that cortisol response was decreased significantly as was depression scores, while interpersonal sensitivity showed significant improvement (23). Nevertheless, the small sample size and lack of controls were limitations of these findings.

c) Studies on Cognitive impairment

While the literature on the effect of RAAS-modifying medications on cognitive impairment and cognitive decline is more robust than their effects on affective disorders, results have been inconsistent (16, 24, 33, 34)). A number of reviews of clinical trials over the past five years lent evidence for the potential use of centrally- acting ACE-I and/or ARBs for the treatment of hypertension and cognitive protection in the elderly (16) or in the prevention of Alzheimer's disease (35-37). However, the most recent two studies and subsequent meta-analysis examining the effects of RAS-blockade on cognitive function in patients at-risk patients found no significant

differences between individuals on a Ramipril (an ACE-I), Telmisartan (an ARB), or a combination of both medications (24).

The TRANSCEND trial examined an at-risk population of patients 55 years and older with established cardiovascular disease or diabetes with end-organ damage, modeled after the HOPE trial (38). Patients were randomly assigned to Telmisartan 80 mg daily or placebo (24). Patients were followed-up with physical measurements, demographic and medical information after 6 weeks, 6 months, then every 6 months until the end of the study. More extensive assessments were taken at baseline, 2 years and at penultimate visits, including a cognitive function assessment using a Mini-mental Status exam (MMSE). Two of the main outcomes were a) cognitive impairment, defined by either an investigator-reported and specialist-confirmed diagnosis of dementia, or cognitive impairment by an MMSE score of 23 or less during follow-up in patients without dementia or CI at base and b) cognitive decline, defined by a drop in at least 3 points on the MMSE (24).

Neither cognitive impairment nor cognitive decline differed significantly between treatment groups, even after adjusting for various factors, including age, gender, history of hypertension, previous stroke or TIA, use of English version of MMSE, systolic blood pressure, education, ethnicity, history of CAD, smoking, use of antiplatelets, statins, beta blockers and consumption of alcohol (24). When pooling these results into a larger meta-analysis, results showed that treatment with a RAAS-modifying medication is not significantly more effective than placebo in reducing risk of cognitive impairment (relative risk 0.97, 95% CI 0.92-1.01) and cognitive decline (0.97, 0.93-1.01) (24). However, although the trends were not significant, meta-regression suggested reductions in the risks of cognitive impairement and cognitive decline (3.4%, 95% CI -4.6 to 10.9, p =0.40 and 1.0%, -3.4 to 5.2, p =0.66, respectively) associated with each 5 mm Hg reduction in systolic blood pressure that were consistent with the size of overall observed treatment effects (24).

The authors note methodological limitations that may account for the study's lack of effect, including insufficient power to detect small treatment effects requiring longer periods of exposure to manifest on cognition than expected for primary vascular events (24). While the potential use of ARBs and ACE-I on cognition improvement in certain populations still exists, the most recent data concludes that in a population of patients with established CV disease or complicated DM, different approaches and degrees of RAAS blockade using Telmisartan and Ramipril alone or in combination in addition to background treatment does not appear to significantly affect cognitive function (24).

Conclusions

A common approach for the treatment of hypertension involves the pharmacological inhibition of the renin-angiotensin aldosterone system (RAAS) by angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs). ACE inhibitors prevent the de novo synthesis of angiotensin II, while ARB's block interaction between angiotensin II and its receptor. Many studies have demonstrated that the therapeutic actions of both ACE-I and ARBs, particularly the latter, extend beyond blood pressure reduction (39, 40). The wide-ranging effects of the RAAS are due in part to the systemic and local paracrine and autocrine functions of the RAAS within individual organs, such as the brain (41) or kidney (42) .

Preclinical studies of the effect of RAAS-altering medications on affective disorders, including a stress-induced disorder have done much to elucidate our current understanding of the relation of the RAAS with the stress response. In addition, they have demonstrated the potential therapeutic and protective effects of such medications, which have yet to be examined carefully in clinical trials. While a few small clinical trials have begun to examine the effect of the RAAS on affective disorders, the bulk of the literature has been focused on cognitive impairment. While evidence has been mixed, recent data failed to show significant differences in cognitive function between different RAAS-modifying medications and placebo.

With the exception of studies examining cognition, the treatment or prevention of psychiatric conditions with ARBs or ACE inhibitors has not been the focus of clinical trials. Further research is clearly needed to elucidate the role of ARBs and ACE inhibitors as therapy in a wide range of stress-related disorders, including PTSD. Using data that has been collected through the Grady Trauma Project from 2006-2010, this analysis examines the cross-sectional, independent association of ACE-I or ARB intake with PTSD symptoms in a highly traumatized population.

CHAPTER II

4 tables, 1 figure

The Renin-Angiotensin Pathway in PTSD: ACE inhibitor and ARB medications are associated with fewer traumatic stress symptoms

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Abstract:

Objective: PTSD is a debilitating stress-related illness associated with trauma exposure. The peripheral and central mechanisms mediating stress response in PTSD are incompletely understood. Recent data suggest that the renin-angiotensin pathway, essential to cardiovascular regulation, is also involved in mediating stress and anxiety. In this study, the authors examined the relationship between active treatment with blood pressure medication, including angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs), and PTSD symptom severity within a highly traumatized civilian medical population.

Method: Cross-sectional, observational data was analyzed from a larger study, recruiting patients from Grady Memorial Hospital's outpatient population from 2006 to November 2010. Multi-variable linear regression models were fit to statistically evaluate the independent association of being prescribed an ACE-I or ARB with PTSD symptoms, using a sub-set of patients for whom medical information was available (n=505). PTSD diagnosis was assessed using the modified PTSD Symptom Scale (PSS) based on DSM-IV criteria with PTSD symptoms based on PSS and Clinician Administered PTSD Scale (CAPS).

Results: A significant association was determined between presence of ACE-I / ARB medication and decreased PTSD symptoms (mean PSS score 11.4 vs 14.9 for individuals prescribed vs not prescribed ACE-I/ARBs, respectively ($p = 0.014$)). After adjustment for covariates, ACE-I/ARB treatment remained significantly associated with decreased PTSD symptoms ($p = 0.044$). Notably, other blood pressure medications, including beta-blockers, calcium channel blockers, and diuretics, were not significantly associated with reduced PTSD symptoms.

Conclusions: These data provide the first clinical evidence supporting a role for the renin-angiotensin system in the regulation of stress response in patients diagnosed with PTSD. Further studies should examine whether available medications targeting this pathway should be considered for future treatment and potential protection against PTSD symptoms.

Introduction

Posttraumatic stress disorder (PTSD) is a debilitating, stress-related psychiatric illness associated with trauma exposure. While the lifetime prevalence of PTSD in the general population is estimated to be 5-10%, the prevalence of PTSD in low-income, urban, primary care patients has been estimated to be as high as 45% (1, 2). Higher still is the prevalence of lifetime trauma exposure within this population, approximately 88% (1). Additional research investigating risk and protective factors for PTSD is essential to improving future prevention efforts.

Chronic stress, involving exposure to frequent and early traumatic events, has been implicated in multiple adverse health outcomes, including cardiovascular-associated diseases, such as hypertension (3-5). For example, individuals with PTSD have increased prevalence of blood pressure dysregulation (7-9). Although results from previous studies have been mixed, meta-analyses have demonstrated that PTSD is associated with elevations in resting systolic and diastolic blood pressure (10, 11).

A common approach for the treatment of hypertension involves the pharmacological inhibition of the renin-angiotensin system (RAS) by angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs). ACE inhibitors prevent the de novo synthesis of angiotensin II, while ARB's block interaction between angiotensin II and its receptor. Many studies have demonstrated that the therapeutic actions of both ACE-I and ARBs, particularly the latter, extend beyond blood pressure reduction (39, 40). The wide-ranging effects of the RAS are due in part to the systemic and local paracrine and autocrine functions of the RAS within individual organs, such as the brain (41) or kidney (42) .

A recent review highlights numerous preclinical studies showing the therapeutic and protective effects of ARBs on the brain, including the reduction of stress, anxiety, brain inflammation and ischemia (12, 40, 43-46). Moreover, recent animal studies have demonstrated that blockade of angiotensin II AT1 receptors or angiotensin II formation can reduce the effects of stress on rodent physiology and behavior (25, 26). These data provide evidence that in animal

models, inhibition of brain AT1 receptor activity, by oral or ICV brain injection of ARBs, leads to improvement in stress-related behavior and associated brain pathology (25).

Clinical reports have also described the protective effects of ARBs on cognition (34, 40, 47), quality of life improvements and reductions in depression and anxiety (44, 48). Moreover, a genetic variation in ACE has been identified as altering the risk for major depression, as well as ACE and cortisol plasma levels (49). However, the treatment of psychiatric conditions with ARBs or ACE inhibitors has not been the focus of clinical trials. Further research is clearly needed to elucidate the role of ARBs and ACE inhibitors as therapy in a wide range of stress-related disorders, including PTSD. Using data that has been collected through the Grady Trauma Project from 2006-2010, this analysis examines the cross-sectional, independent association of ACE-I or ARB intake with PTSD symptoms in a highly traumatized population.

Methods:

The study was approved by Emory University Institutional Review Board. All procedures of the study were discussed thoroughly with each participant, and all participants provided written informed consent and received monetary compensation for their participation.

Subjects and sample recruitment

This secondary analysis examined data on 505 individuals, who were part of a larger cross-sectional study investigating the genetic and environmental factors that contribute to PTSD. From 2006 to 2010, participants were recruited from the waiting rooms of primary care, obstetric-gynecological clinics or the pharmacy at Grady Memorial Hospital. One of the largest public hospitals in the United States, Grady serves a primarily African American and highly traumatized, low-income, inner-city population. Recruitment took place Monday-Friday during regular clinic hours. Those subjects who agreed to participate completed a number of self-report measures, taking 45-75 minutes to complete.

All 4,803 participants who completed the initial interview were asked if they would consent to subsequent study phases. A scheduler, blinded to the participant's information, randomly contacted these participants. 663 returned for subsequent parts of the study, which included a physician-administered medical exam, permission to examine the electronic medical records, and additional self-report measures and structured clinical interviews, including the Clinician Administered PTSD Scale (CAPS).

The primary exposure of interest was taking an ACE-I or ARB; therefore, individuals whose information on blood pressure medications was missing were excluded from analysis (93 subjects (14% of the sample)). Patients who had missing information on the PTSD symptom scale (PSS) were also excluded from the analysis (28 or 4.9% of the remaining sample). To examine the association of ACE-I or ARB with PTSD symptoms among individuals exposed to traumatic events, only individuals who reported one or more traumatic events on the childhood questionnaire (CTQ) or traumatic event inventory (TEI) were included in the analysis, leaving a sample of 505 individuals. A flow chart of the selection process for the sample is provided (Fig. 1).

Measurements

Trauma exposure was measured using the TEI, a 14-item screening instrument for lifetime history of traumatic events (50, 51). For each traumatic event, experiencing and witnessing of the event is assessed separately. The TEI also assesses frequency of trauma exposure within each trauma type. Measured as a continuous variable, frequency of exposure to traumatic events was used as a potential covariate. As previous studies have shown associations between chronic stress and blood pressure (4, 5, 10, 52), there may be an indirect association between being on a blood pressure medication and chronic stress, which may be partly measured by frequency of traumatic events.

The primary outcome of interest in this study was PTSD symptom severity; therefore the principal measurement used for analysis was the PSS, a psychometrically valid 17-item self-

report scale that measures PTSD symptom severity during the two-week period immediately prior to study assessment (50, 53-55). PSS frequency items (measured as "0: not at all" to "3: 5 or more times a week) were summed to obtain a continuous measure of PTSD symptom severity. We also examined the major subtypes of post-traumatic stress symptoms, including hyperarousal symptoms, avoidance or numbing symptoms and intrusive thoughts, using the symptom-specific subscales of the PSS (54). The categorical diagnosis of PTSD was initially determined based on DSM-IV A-E criterion responses to the PSS questionnaire.

Additionally, information from the CAPS was also used to examine the effect of ACE-I or ARBs on the severity of both current and lifetime PTSD symptoms. An interviewer-administered diagnostic instrument with excellent psychometric properties, the CAPS uses DSM-IV scoring criteria to generate a categorical diagnosis of PTSD, as well as a continuous measure of the extent and severity of lifetime and current post-traumatic stress symptoms (56, 57). While both the PSS and CAPS can generate symptoms to assess PTSD severity, CAPS adds additional information about lifetime PTSD symptoms. For each of the 17 diagnostic criteria, the CAPS rates frequency and intensity scores on a scale of 0 (absent) to 5 (extremely severe). This analysis used the CAPS to obtain both continuous lifetime and current PTSD variables (scores from 0 to 170).

The primary exposure of interest in this study, collected by physicians based on participants' reports, was whether an individual was prescribed an ACE-I or ARB. The data on ACE-I and ARBs were pooled since there were a small number of individuals on ARBs (17 or 3.16% of the sample) and because of similar mechanisms of action.

Potential covariates assessed in the analysis included: other blood pressure medications, (categorized into beta-blockers, calcium channel blockers (CCBs), diuretics, and other for medications with another mechanism of action), whether an individual was currently on a psychiatric medication, current substance abuse, body mass index (BMI), frequency of adult trauma (as assessed by the TEI), and childhood trauma. Childhood trauma was assessed using the

Childhood Trauma Questionnaire (CTQ), a self-report inventory assessing three types of childhood abuse: sexual, physical and emotional. Studies have established internal consistency, stability overtime and criterion validity of both the original 70-item CTQ and the current brief version (58, 59).

Demographic information assessed as potential covariates included: sex, age, current employment, household income level ($0-249, $250-499, $500-999, $1,000-1999, or >$2,000 per month), education (categorized into <12th, high school graduate or GED, some college or technical school, or college graduate and higher education) and race (dichotomized into "African American" and "other," due to the small number of non-African American subjects in the analysis).

Missing data included information on race (3 or .6% of the sample), income (12 or 2.4% of the sample), employment (3 or .6% of the sample), education (3 or .6% of the sample), current psychiatric medications (247 or 48.9% of the sample), current substance abuse (9 or 1.8% of the sample), adult traumatic experiences (6 or 1.2% of the sample), and childhood traumatic experiences (19 or 3.8% of the sample). Since close to half of the sample had missing data on current psychiatric medication and BMI (247 or 48.9% of the sample and 244 or 48.3% of the sample, respectively), these variables were excluded as potential covariates from modeling analysis.

Analysis

All analysis was performed using SAS 9.2 (Cary, NC) statistical software. To statistically evaluate the independent effect of ACE-I and ARB medication on PTSD symptom severity among patients exposed to trauma, linear regression models were fit with PTSD symptoms, measured by the total PSS score as the continuous outcome variable. Two-way multiplicative interaction between the categorical variable of active treatment with an ACE-I or ARB medication and other covariates were assessed in a full model. Potential confounders were assessed using multiple approaches. First, directed acyclic graphs were constructed using

information from previous literature. Second, a two-table approach was used, in which the association of each potential confounder was examined in relation to both PTSD symptoms and active treatment with an ACE-I or ARB. Finally, a backward regression modeling approach was used, in which variables were removed one at a time and assessed for statistical significance and effect on the beta estimate for the main exposure of interest.

Descriptive analysis of the variables was performed, stratified by categorical PTSD diagnosis. Chi-square tests were used to assess the association of PTSD diagnosis with: ACE-I or ARBs, beta-blockers, calcium channel blockers (CCBs), diuretics, sex, race, income, employment, education, current psychiatric medications, and current substance abuse. Two sampled T-tests were used to assess the association of PTSD diagnosis with BMI, age, and adult and childhood trauma (as assessed by the TEI and CTQ, respectively).

To evaluate the effect of different categories of blood pressure medications, including ACE-I and ARBs, on PTSD symptoms, univariate analysis of variance was performed. To statistically evaluate the independent effect of ACE-I and ARBs on PTSD symptoms, multi-variable linear regression models were constructed, using potential confounders, which were previously identified. Co-linearity between the covariates was assessed and linear regression assumptions were checked.

To analyze the effect of treatment with different types of blood pressure medications on the severity of PTSD symptom subtypes, multi-variable linear regression models were created and tested using continuously scaled PTSD symptoms among each subtype as the outcome. A p-value of ≤ 0.05 was considered statistically significant for analysis.

Results:

Among the 505 individuals exposed to at least one traumatic event, 180 met criteria for PTSD diagnosis based on PSS score. In the sample, 98 individuals were on ACE-I or ARBs, 63 were on beta-blockers, 53 were on CCBs, 109 on diuretics and 12 were on other blood pressure

medications. A significant univariate association was found between PTSD diagnosis and ACE I or ARBs status (Table 1). Of 98 individuals on an ACE-I or ARB, 26 met criteria for PTSD diagnosis using PSS; of 407 individuals not on an ACE-I or ARB, 154 met criteria for PTSD diagnosis (Chi-Square T-value = 4.40, p = 0.036). Covariates demonstrating significant differences based on PTSD diagnosis included: being on a CCB, employment, current psychiatric medication, current substance abuse, total adult trauma experienced and childhood trauma (Table 1). Significantly different potential confounders stratified by ACE-I or ARB included age, education, beta-blockers, CCB and diuretics (Table 2).

Mean PSS scores (total and by subtype) for individuals receiving different blood pressure medications are shown in Table 3. A significant difference in mean total PSS score was only found based on ACE-I or ARB status (11.41 +/- 11.1 (S.D.) for ACE-I/ARB treated and 14.9 +/- 12.9 for non-ACE-I or ARB treated, F = 6.12, p = 0.014). When examined by PTSD subtype, individuals on ACE-I or ARB and/or beta-blockers demonstrated significant differences in mean hyperarousal score (3.90 +/- 4.0 (S.D.) and 5.20 +/- 4.6 on and off ACE-I or ARBs, respectively; 3.88 +/- 3.6 and 5.10 +/- 4.6 on and off beta blockers, respectively). No significant differences in mean avoidance/numbing score were found for any blood pressure medications. Lastly, significant differences in mean intrusive thoughts score were limited to comparisons of individuals on versus not on ACE-I or ARBs (2.48 +/- 3.3 (S.D.) for ACE-I/ARB treated and 3.75 +/- 4.1 for non-ACE-I/ARB treated). Given the comorbidity of depression with PTSD, we also examined the effect of ACE-I / ARB status on depressive symptoms. In the analyzed traumatized sample, individuals on ACE-I/ARBs were found to have lower total BDI scores than individuals not on ACE-I/ARBs, but the results were not statistically significant (13.42 +/- 12.2 (S.D.) compared with 16.19 +/- 12.6, p > 0.05).

In multivariate linear regression, there were no statistically significant interactions between treatment status with an ACE-I or ARB and covariates. Covariates that were independently associated with PTSD symptoms were childhood trauma, adult trauma, being male,

and unemployed. In backward stepwise regression, beta-blockers and age remained in the model, as these variables confounded the association of ACE-I or ARB with PTSD symptoms. After adjusting for the above covariates, individuals treated with an ACE-I or ARB had significantly decreased risk of current PTSD symptoms compared to individuals not receiving an ACE-I or ARB (β -2.83, S.E 1.4, P=0.044; Table 4).

Frequency of childhood and adult trauma were independently associated with all the outcomes of interest, therefore they were included in every model. Unemployment was also independently associated with hyperarousal symptoms, as assessed by the PSS, and current and lifetime PTSD symptoms, as assessed by the CAPS. After adjustment for the above covariates, individuals receiving an ACE-I or ARB had a significantly decreased risk of current PTSD symptoms (β -7.16, S.E 2.78, P=0.010). Age and diuretics also remained in the model examining hyperarousal symptoms as the outcome, as they were found to be confounders. After adjusting for the above covariates, individuals on ACE-I or ARBs had a significantly decreased risk of PTSD hyperarousal symptoms (β -1.22, S.E 0.56, P=0.028; Table 4).

Beta-blockers, age and diuretics were included in the model examining lifetime PTSD symptoms as the outcome, as they were found to be confounders. After adjustment for the above covariates, individuals on an ACE-I or ARB had a significantly decreased risk of lifetime PTSD symptoms (β -1.22, S.E 0.56, P=0.028; Table 4).

Age, beta blockers, other BP medications and income level all remained in the model examining avoidance/numbing symptoms as the outcome, as they were found to be confounders. After adjustment for the above covariates, the effect of being on an ACE-I or ARB remained insignificant.

Lastly, being male was independently associated with intrusive symptoms and remained in the model. Beta-blockers and age were also included, as their presence confounded the effect of ACE-I or ARB on intrusive symptoms. After adjustment for the above covariates, individuals

treated with an ACE-I or ARB had a significantly decreased risk of PTSD intrusive thoughts symptoms (β -1.01, S.E 0.46, P=0.029; Table 4).

Discussion

Results from this study suggest that ACE-inhibitors and ARB medications have protective effects on PTSD symptoms among individuals exposed to trauma. After adjustment, the effect of ACE-inhibitors and ARBs on the reduction of PTSD symptoms remained significant, both using the PSS and the CAPS measurements (P=0.028 and P=0.010, respectively), the latter of which is thought to be a more thorough measurement of current and lifetime PTSD symptoms.

In addition, this analysis suggests that ACE-I and ARBs may preferentially affect the severity of hyperarousal and intrusive PTSD symptoms. Other medications that have been shown to decrease these symptoms include: Prazosin, Clonidine, Guanfacine, and Propanolol, all of which target the noradrenergic system (60). As the renin-angiotensin system is linked with the noradrenergic system, it may not be surprising that ACE-I and ARBs would affect these specific symptoms (61). Among other effects, angiotensin II activity in the brain has been shown to increase transcription of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis (12, 60).

Results from this analysis did not demonstrate any interaction in individuals taking both beta-blockers and ACE-I/ARB on PTSD symptoms. In fact, while univariate associations demonstrated a significant effect of beta-blockers on hyperarousal symptoms, these effects did not remain after adjustment for confounders. This was somewhat surprising, given that propanolol has also been used both to ameliorate PTSD symptoms, and, in some studies, to prevent PTSD (60). Nevertheless, the present literature on chemoprophylaxis for individuals exposed to trauma is controversial. Equivocal data exists for the use of alcohol, cortisol, morphine, and propanolol to prevent PTSD in at-risk patients and no conensus exists about when, for whom, and at what dose prophylaxis would be indicated or cost-effective (62). Additional

studies that are better designed to examine whether ACE-I and ARBs can prevent PTSD or reduce symptom severity in at-risk populations are warranted. These include longitudinal cohort or randomized controlled studies that focus on at-risk individuals or those already diagnosed with PTSD and on specific medications.

Limitations of this study include collapsing ARBs and ACE-I categories; this was done for convenience due to the small number of individuals on ARBs, but it may mask important mechanistic subtleties. In addition, the cross-sectional design makes causation difficult to evaluate. Notably, if co-linearity between being on a blood pressure medication and stress-related hypertension were the case in this cohort, we would expect greater PTSD symptom severity to associate with taking blood pressure medications. In contrast, with the ARB/ACE-I class, we find the unexpected decrease in PTSD symptoms associated with medication use. As with many large cross-sectional studies of convenience, we have a number of variables with missing data and the missing values from certain variables such as BMI and psychiatric medication excluded them from analysis. Lastly, chart extraction may not be ideal for determining if individuals are taking medications on a regular basis.

In summary, the present analysis supports the burgeoning preclinical literature describing a role for the renin-angiotensin pathway in stress-related disorders (12, 40, 43-46). While animal models have demonstrated that inhibition of brain AT1 receptor activity reduces of stress-related behaviors (25), this is the first analysis examining the effect of these medications on PTSD symptoms in individuals exposed to trauma. Since ACE-I and ARB medications are safe and widely used to treat hypertension, they may be novel and important targets to consider for treatment and potential protection against PTSD symptoms among certain populations.

Clinical Points: Certain anti-hypertensive medications may have protective effects on stress-related disorders, such as PTSD. Results from this preliminary study suggest that targeting the renin-angiotensin system through available medications may have protective effects on PTSD symptoms among patients exposed to traumatic events. Further research is needed to examine whether ACE-I and ARBs can prevent PTSD or reduce symptom severity in at-risk populations.

TABLES AND FIGURES

Table 1| Descriptive Overview of Variables Stratified by PTSD diagnosis (N=505)

Variables	PTSD (N=180)		No PTSD (N=325)		Analysis			Missing values	
Discrete	**N**	**%**	**N**	**%**	**DF**	**χ^2**	**P**	**N**	**%**
ACE I or ARB	26	14.4	72	22.2	1	4.40	0.036	None	0
Beta Blocker	17	9.4	46	14.2	1	2.35	0.125	None	0
CCB	12	6.7	41	12.6	1	4.36	0.037	None	0
Diuretics	32	17.8	77	23.7	1	2.39	0.122	None	0
Other BP med	2	1.1	10	3.1	1	***	***	None	0
Sex (Male)	114	63.3	189	57.2	1	1.79	0.181	None	0
Race (Black)	159	89.3	297	91.7	1	0.76	0.385	3	0.6
Income / month					4	5.30	0.258	12	2.4
$0-249	72	41.1	105	33.0					
$250-499	16	9.1	39	12.3					
$500-999	48	27.4	82	25.8					
$1,000-1,999	28	16.0	70	22.0					
≥$2,000	11	6.3	22	6.9					
Employed	30	16.9	85	26.2	1	6.72	0.017	3	0.6
Education					3	3.98	0.264	3	0.6
<12th grade	43	23.9	73	22.5					
HS Grad/GED	76	42.2	144	44.3					
Some college	52	28.9	78	24.0					
≥ College	9	5.0	30	9.23					
Psych. Med	28	33.7	30	17.1	1	8.89	0.003	247	48.9
Sub. Abuse	17	9.7	11	3.4	1	8.25	0.004	9	1.8
Continuous	**μ**	**SD**	**μ**	**SD**	**DF**	**T**	**P**	**N**	**%**
BMI μ (SD)	32.68	8.4	32.94	9.5	259	0.22	0.826	244	48.3
Age μ (SD)	42.28	11.6	41.97	13.1	497	-0.26	0.796	6	1.2
TEI* μ (SD)	4.85	2.44	2.96	2.3	487	-8.53	<.001	6	1.2
CTQ μ (SD)**	51.48	20.6	38.93	14.5	263	-7.10	<.001	19	3.76

*TEI: traumatic events inventory **CTQ: childhood trauma questionnaire ***Chi-Square assumptions not met

Table 2| Potential Confounders, Stratified by ACE-I or ARB (N= 505)

Potential Confounders	ACE-I or ARB (N=112)		Not on ACE-I or ARB (N=458)		Analysis		
Discrete	**N**	**%**	**N**	**%**	**DF**	**χ^2**	**P**
Sex (Male)*	55	56.1	245	60.2	1	0.54	0.461
Race (Black)*	90	92.8	366	90.4	1	0.55	0.459
Income (per month)					4	4.01	0.405
$0-249	34	35.4	143	36.0			
$250-499	8	8.3	47	11.8			
$500-999	31	32.3	99	24.9			
$1,000- 1,999	15	15.6	83	20.9			
≥$2,000	8	8.3	25	6.3			
Employed*	16	16.5	99	24.4	1	2.80	0.094
Education*					3	7.94	0.047
<12th grade	19	19.4	97	23.8			
High School grad/ GED	36	36.7	184	45.2			
Some college	30	30.6	100	24.6			
College grad. or higher	13	13.3	26	6.4			
Psych. Med.*	17	30.9	41	20.2	1	2.85	0.091
Sub. Abuse*	5	5.2	23	5.8	1	0.05	0.816
BB	35	35.7	28	6.9	1	60.14	<.0001
CCB	23	23.5	30	7.4	1	21.79	<.0001
Diuretics	53	54.1	56	13.8	1	75.87	<.0001
Continuous	**μ**	**SD**	**μ**	**SD**	**DF**	**T**	**P**
BMI*	33.73	8.5	32.61	9.28	259	-0.82	0.414
Age*	51.45	8.0	39.81	12.5	223	-11.3	<.0001
TEI*	5.49	3.6	5.42	3.6	487	-0.17	0.865
CTQ*	42.43	15.8	43.56	18.4	484	0.54	0.588

*Variables contain missing values.

Table 3 | Uni-variable Analysis of Variance of PTSD symptoms by PSS total score and by symptom subtype

	Mean PSS Score	**SD**	**F**	**Mean Hyperarousal Score**	**SD**	**F**	**Mean Avoid/Numb Score**	**SD**	**F**	**Mean Intrusive Score**	SD	F
ACE-I orARB												
On (N=98)	11.41	11.1	6.12*	3.90	4.0	6.69*	5.03	5.4	2.51	2.48	3.3	8.16**
Off (N=407)	14.90	12.9		5.20	4.6		5.97	5.7		3.75	4.1	
Beta Blocker												
On (N=63)	11.42	9.4	3.60	3.88	3.6	4.11*	4.84	4.7	2.05	2.70	2.8	2.97
Off (N=442)	14.64	13.0		5.10	4.6		5.92	5.7		3.62	4.1	
CCB												
On (N=53)	12.26	11.7	1.45	4.55	4.4	0.48	4.53	5.2	2.97	3.19	3.6	0.37
Off (N=452)	14.47	12.8		5.00	4.5		5.94	5.7		3.54	4.0	
Diuretic												
On (N=109)	13.18	12.0	0.97	4.65	4.4	0.63	5.40	5.5	0.65	3.13	3.9	1.21
Off (N=396)	14.53	12.8		5.03	4.5		5.90	5.7		3.61	4.0	

*P<0.05 **P<0.01

Table 4 | Multi-variable Linear Regression of PSS and CAPS Score

Outcome: PSS Total Score (N=467)	ACE-I or ARB β Estimate	S.E	T	P
Unadjusted effect	-3.51	1.4	-2.47	0.014
Adjusted* effect	-2.83	1.4	-2.02	0.044
PSS Hyperarousal Score (N=467)				
Unadjusted effect	-1.30	0.5	-2.59	0.010
Adjusted** effect	-1.22	0.6	-2.20	0.028
PSS Avoidance Numb Score (N=459)				
Unadjusted effect	-0.94	0.6	-1.49	0.138
Adjusted *** effect	-0.92	1.1	-1.12	0.161
PSS Intrusive Score (N=467)				
Unadjusted effect	-1.27	0.4	-2.86	0.005
Adjusted**** effect	-1.01	0.5	-2.20	0.029
Lifetime CAPS Score (N=467)				
Unadjusted effect (ACE-I or ARB)	-4.90	3.95	-1.24	0.216
Adjusted¥ effect (ACE-I or ARB)	-1.22	0.56	-2.20	0.028
Current CAPS Score (N=417)				
Unadjusted effect (ACE-I or ARB)	-5.05	2.91	-1.74	0.083
Adjusted¥¥ effect (ACE-I or ARB)	-7.16	2.78	-2.57	0.010

*Adjusted for childhood trauma, adult trauma, age, sex, employment, and beta blocker. R^2=0.29, F=27.20 ** 2 Adjusted for childhood trauma, adult trauma, age, diuretics, employment and beta blocker. R^2=0.22, F=18.20 ***Adjusted for childhood trauma, adult trauma, age, other BP meds., bet blockers, and income. R^2=0.27, F=16.20 ****Adjusted for childhood trauma, adult trauma, age, sex, and beta blockers. R^2=0.22, F=21.17 ¥Adjusted for childhood trauma, adult trauma, age, diuretics, employment and beta blockers. R^2=0.22, F=18.20. ¥¥ Adjusted for childhood trauma, adult trauma, and employment. R^2= 0.190, F=22.07

505 Participants remained in sample for analysis

Figure 1 | Recruitment and Selection of Study Participants

CHAPTER III

Summary

Using data that has been collected through the Grady Trauma Project from 2006-2010, this analysis examined the cross-sectional, independent association of ACE-I or ARB intake with PTSD symptoms in a highly traumatized population. Results from this study suggest that ACE-inhibitors and ARB medications have protective effects on PTSD symptoms among individuals exposed to trauma. After adjustment, the effect of ACE-inhibitors and ARBs on the reduction of PTSD symptoms remained significant, both using the PSS and the CAPS measurements (P=0.028 and P=0.010, respectively), the latter of which is thought to be a more thorough measurement of current and lifetime PTSD symptoms.

In addition, this analysis suggests that ACE-I and ARBs may preferentially affect the severity of hyperarousal and intrusive PTSD symptoms. Other medications that have been shown to decrease these symptoms include: prazosin, clonidine, guanfacine, and propanolol, all of which target the noradrenergic system (60). As the renin-angiotensin system is linked with the noradrenergic system, it may not be surprising that ACE-I and ARBs would affect these specific symptoms (61). Among other effects, angiotensin II activity in the brain has been shown to increase transcription of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis (12, 60).

Results from this analysis did not demonstrate any interaction in individuals taking both beta-blockers and ACE-I/ARB on PTSD symptoms. In fact, while univariate associations demonstrated a significant effect of beta-blockers on hyperarousal symptoms, these effects did not remain after adjustment for confounders. This was somewhat surprising, given that propanolol has also been used both to ameliorate PTSD symptoms, and, in some studies, to prevent PTSD (60). Propanolol has received much attention in the literature as a potential medication to treat PTSD; however evidence for its effectiveness remains unclear (62). For example, in a recent randomized control study in an emergency department, Pitman and colleagues found physiological arousal differences on 3-month follow-up in traumatized

individuals administered propanolol compared to placebo; however, these results did not extend to overall PTSD measures (63). Equivocal data also exists for the use of alcohol, cortisol, and morphine to prevent PTSD in at-risk patients and no census exists about when, for whom, and at what dose prophylaxis would be indicated or cost-effective (62).

In summary, the present analysis supports the burgeoning preclinical literature describing a role for the renin-angiotensin pathway in stress-related disorders (12, 40, 43-46). While animal models have demonstrated that inhibition of brain AT1 receptor activity reduces of stress-related behaviors (25), this is the first analysis examining the effect of these medications on PTSD symptoms in individuals exposed to trauma. Since ACE-I and ARB medications are safe and widely used to treat hypertension, they may be novel and important targets to consider for treatment and potential protection against PTSD symptoms among certain populations.

Public Health Implications and Possible Future Directions

PTSD has important independent effects on functional limitations and quality of life in many individuals exposed to trauma, above and beyond the physical impacts of trauma (64, 65). While a substantial proportion of traumatized individuals will recover without any type of treatment, at least one third of individuals who initially develop traumatic stress symptoms remain symptomatic for at least 3 years and are at high risk of developing secondary problems, including substance abuse (2). Important for the current study population, the risk of PTSD may be higher still in individuals exposed to intentional acts of interpersonal violence compared to accidents or disasters (2).

To reduce the immediate and long-term impacts of PTSD on individuals and society, it is necessary to continue efforts to better understand the disease mechanisms and to improve treatment and prevention strategies. Most PTSD prevention efforts in the field focus on secondary prevention, which targets individuals already exposed to violence but before they have developed persistent PTSD symptoms (62). Possible future strategies to identify individuals at risk for PTSD

include utilizing physiologic measures, such as heart rate data, in emergency room and ICU settings among individuals presenting with trauma (62). Clearly, identifying at-risk individuals who are likely to need PTSD treatment is more cost-effective than treating chronic PTSD at a later stage (66). However, in the current study population, where the majority of traumas are unpredictable, multiple and across varying time courses, targeting individuals immediately after trauma exposure may be difficult. Furthermore, treating individuals suffering from PTSD even years after the trauma may be both necessary and beneficial, as treatment efficacy does not appear to decrease as a function of time elapsed since the traumatic event (67)

Indeed, while prevention and early intervention may be ideal from a public health standpoint, some studies have found that PTSD treatment is actually most efficacious in individuals who already exhibit PTSD symptoms (68). For example, a recent meta-analysis of 25 studies that examined a range of psychological interventions found no significant difference between any intervention and standard care for all individuals exposed to trauma. However, for individuals already exhibiting symptoms of PTSD, trauma-focused cognitive behavioral therapy (TFCBT) was more effective than either waiting list or supportive counseling (68). It is unknown if this finding would extend to pharmacologic interventions.

While it is still unclear exactly what time frame is most effective for intervening, current recommendations are to practice "watchful waiting" after a traumatic event, to monitor an individual for at least one month and encourage them to use existing support systems and strategies (66). Identification of full-blown PTSD can occur in a variety of settings; however, results from this study and others support the pursuit of PTSD identification in primary care medical settings, since a high number of individuals suffer from PTSD, even if it is not their presenting complaint. Primary care settings have also been shown to be effective for PTSD reduction, particularly when using combined collaborative care interventions (65, 66).

Although a major area of research interest, pharmacotherapy currently is still recommended only as adjunctive therapy to TFCBT, or if TFCBT cannot be conducted for a

variety of reasons (69). In terms of medications, SSRIs are considered first-line and are the most commonly investigated class of agents in placebo-controlled trials; paroxetine and sertraline are the only medications approved by the FDA and the European Medicines Agency for PTSD treatment (69, 70). A recent meta-analysis of medications found that SSRIs and venlafaxine had the largest body of evidence supporting their efficacy in treating PTSD over the short-term, with responses reported as early as 2-4 weeks of treatment (70).

Nevertheless, there is a continued need to better understand the neurobiology of PTSD and find more effective medications that can secondarily prevent and/or treat PTSD in traumatized individuals. Results of this study demonstrate that the renin-angiotensin pathway may be an important component to PTSD neurobiological dysregulation that has not previously been explored. Additional studies that are better designed to examine whether ACE-I and ARBs can prevent PTSD or reduce symptom severity in at-risk populations are warranted. These include longitudinal cohort or randomized controlled studies that focus on at-risk individuals or those already diagnosed with PTSD and on specific medications.

REFERENCES

1. Gillespie CF, Bradley B, Mercer K, Smith AK, Conneely K, Gapen M, et al. Trauma exposure and stress-related disorders in inner city primary care patients. Gen Hosp Psychiatry 2009;31:505-514.
2. Kessler R, Sonnega A, Bromet E. Posttraumatic stress disorder in the National Comorbidity survey. Arch Gen Psychiatry 1995;52:1048-1060.
3. McFarlane AC. The long-term costs of traumatic stress: intertwined physical and psycholgical consequences. World Psychiatry 2010;9:3-10.
4. Hepner PS, Crawford EF, Haji UA, Afari N, Hauger RL, Dashevesky BA, et al. The association of posttraumatic stress disorder and metabolic syndrome: a study of increased health risk in veterans. BMC Medicine 2009;7.
5. Lehman BJ, Taylor SE, Kiefe CI, Seeman T. Relationship of Early Life Stress and Psychological Functioning to Blood Pressure in the CARDIA Study. Health Psychol 2009;28(3):338-346.
6. McEvan B, Stellar E. Stress and the individual: Mechanisms leading to disease. Arch. Intern Med 1993;157:2259-2268.
7. Kibler JL. Posttraumatic stress and cardiovascular disease risk. J Trauma Dissociation 2009;10(2):135-50.
8. Tucker P, Jeon-Slaughter H, Pfefferbaum B, Khan Q, Davis NJ. Emotional and biological stress measures in Katrina survivors relocated to Oklahoma. American Journal of Disaster Medicine 2010;5(2):113-25.
9. Ulmer CS, Calhoun PS, Edinger JD, Wagner HR, Beckham JC. Sleep disturbance and baroreceptor sensitivity in women with posttraumatic stress disorder. Journal of Trauma Stress 2009;22(6):643-7.
10. Buckley T, Kaloupek D. A meta-analytic examination of basal cardiovascular activity in posttraumatic stress disorder. Psychosom Med 2001;63:585-594.
11. Pole N. Psychophysiology of Posttraumatic Stress Disorder: A Meta-Analysis. Psychol Bull 2007;133(5):725-746.
12. Saavedra JM, Sanchez-Lemus E, Benicky J. Blockade of brain angiotensin II AT1 receptors ameliorates stress, anxiety, brain inflammation and ischemia: Therapeutic implications. Psychoneuroendocrinology 2010.
13. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parrallel-group randomized trials. Lancet 2001;357:1191-1194.
14. Des Jarlais DC, Lyles C, Crepaz N, Group T. Improving the Reporting Quality of Nonrandomized Evaluations of Behavioral and Public Health Interventions: The TREND Statement. Am Journal of Public Health 2004;94(3):361-366.
15. Ciobica A, Bild W, Hritcu L, Haulica I. Brain renin-angiotensin system in cognitive function: pre-clinical findings and implications for prevention and treatment of dementia. Acta Neurobiologiae Belg. 2009;109:171-180.
16. Hanes D, Weir M. Usefulness of ARBs and ACE inhibitors in the prevention of vascular dementia in the elderly. Am Journal of Geriatric Cardiology 2007;16(3):175-182.
17. Fournier A, Oprisiu-Fournier R, Serot JM, Godefroy O, Archard JM, Faure S, et al. Preventino of dementia by antihypertensive drugs: how AT1-receptor-blockers and dihydropyridines better prevent dementia in hypertensive patients than thiazides and ACE-inhibitors. Expert Review Neurotherapy 2009;9(1413-1431).
18. Wilson W, Voigt P, Bader M, Marsden CA, Fink H. Behavior of the transgenic (mREN2)27 rat. Brain Res 1996;729:1-9.

19. Shekhar A, Johnson PI, Sajdyk TJ, Fitz SD, Keim SR, Kelley PE, et al. Angiotensin-II Is a Putative Neurotransmitter in Lactate-Induced Panic-Like Responses in Rats with Disruption of GABAergic Inhibition in the Dorsomedial Hypothalamus. The Journal of Neuroscience 2006;26(36):9205-9215.
20. Saavedra JM, Armando I, Bregonzio C, Juorio A, Macova M, Pavel J, et al. Centrally Acting, Anxiolytic Angiotensin II AT1 Receptor Antagonist Prevents the Isolation Stress-Induced Decrease in Cortical CRF1 Receptor and Benzodiazepine Binding. Neuropsychopharmacology 2006;31:1123-1134.
21. Bregonzio C, Armando I, Ando H, Jezova M, Baiardi G, Saavedra JM. Anti-inflammatory effects of angiotensin II AT1 receptor antagonism prevent stress-induced gastric injury. American Journal of Gastrointestional Liver Physiology 2003;285:414-423.
22. Nasr S, Crayton J, Agarwal B, Wendt B, Kora R. Lower frequency of antidepressant use in patients on renin-angiotensin-aldosterone system modifying medications. Cell Molecular Neuorbiology 2011;4:615-618.
23. Pavlatou MG, Mastorakos G, Lekakis I, Liatis S, Vamvakou G, Zoumaki E, et al. Chronic administration of an angiotensin II receptor antagonist resets the hypothalamic-pituitary-adrenal (HPA) axis and improves the affect of patients with diabetes mellitus type 2: prelminary results. Stress 2008;11:62-72.
24. Anderson C, Tea K, Goa P, Arima H, Dans A, Unger T, et al. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. Lancet Neurology 2011;10:43-53.
25. Benicky J, Sanchez-Lemus E, Honda M, Pang T, Orecna M, Wang J, et al. Angiotensin II AT1 Receptor Blockade Ameliorates Brain Inflammation. Neuropsychopharmacology 2011;36:857-870.
26. Chen D, Grecca LL, Head GA, Walther T, Mayorov DN. Blood pressure reactivity to emotional stress is reduced in AT1A- receptor knockout mice on normal, but not high salt intake. Hypertens Res 2009.
27. Armando I, Carranza A, Nishimura Y, Hoe KL, Barontini M, Terro´n JA, et al. Peripheral administration of an angiotensin II AT(1) receptor antagonist decreases the hypothalamic-pituitary-adrenal response to isolation Stress. Endocrinology 2001;142:3880-3889.
28. Armando I, Volpi S, Aguilera G, Saavedra JM. Angiotensin II AT1 receptor blocakde prevents the hypothalamic coticotropin-releasing factor response to isolation stress. Brain Res 2007;1142:92-99.
29. Overmier JB, Murison R. Anxiety and helplessness in the face of stress predisposes, precipitates, and sustains gastric ulceration. Behavioral Brain Research 2000;110:161-174.
30. Heck A, Lieb R, Ellgas A, Pfister H, Lucae S, Erhardt. A, et al. Polymorphisms in the angiotensin-converting enzyme gene region predicting coping styles in healthy adults and depressed patients. . Am J Med Genet 2009;150(1):104-114.
31. Saab YB, Gard PR, Yeoman MS, Mfarrej B, El-Moalem H, Ingram MJ. Renin-angiotensin-system gene polymporphisms and depression. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:1113-1118.
32. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. Arch Intern Med 1993;153:2093-2101.
33. McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairement and dementia. Cochrane Database of Systematic Reviews 2009;4.

34. Saxby BK, Harrington F, Wesnes KA, McKeith IG, Ford GA. Candesartan and cognitive decline in older patients with hypertension: a substudy of the SCOPE trial. Neurology 2008;70:1858-1866.
35. Gard PR, Rusted JM. Angiotensin and Alzheimer's disease: therapeutic prospects. Expert Review Neurotherapy 2004;4(1):87-96.
36. Takeda S, Sato N, Ogihara T, Morishita R. The renin-angiotensin system, hypertension and cognitive dysfunction in Alzheimer's disease: new therapeutic potential. Frontier Bioscience 2008;13:2253-65.
37. Kehoe P, Miners S, Love S. Angiotensins in Alzheimer's disease- friend or foe? . Trends Neuroscience 2009;32(12):619-28.
38. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Daganais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation study investigators. N Engl J Med 2000;342:145-153.
39. Barra S, Vitagliano A, Cuomo V, Vitagliano G, Gaeta G. Vascular and metabolic effects of angiotensin II receptor block-ers. Expert Opinion Pharmacotherapy 2009;10:173-189.
40. Anderson C. More direct evidence of potential neuroprotective benefits of Angiotensin receptor blockers. Hypertension 2010;28(429).
41. Grobe JL, Grobe CL, Beltz TG, Westphal SG, Morgan DA, Xu D, et al. The brain Renin-angiotensin system controls divergent efferent mechanisms to regulate fluid and energy balance. Cell Metabolism 2010;12(5):431-42.
42. Yu Y, Wang Y, Zhou LN, Zheng F. ARB Treatment Prevents the Decrease in Endothelial Progenitor Cells and the Loss of Renal Microvasculature in Remnant Kidney. Am Journal of Nephrology 2011;33(6):550-7.
43. Papdemetriou V, Farsang C, Elmfeldt D, Hofman A, Lithell H, Olofsson B, et al. Study on Cognition and Prognosis in the Elderly study group. Stroke Prevention with the angiotensin II type 1-receptor blocker candesartan in eldelry patients with isolated systolic hypertension: the Study on Cognition and Prognosis in the Elderly (SCOPE). Journal of American College of Cardiology 2004;44:1175-1180.
44. Zanchetti A, Elmfeldt D. Findings and implications of the Study on Cognition and Prognosis in the Elderly (SCOPE)--A review. Blood Press 2006;15:71-79.
45. Matsumoto S, Shimodozono M, Miyata R, Kawahira K. The Angiotensin II type 1 receptor antagonist olmesartan preserves cerebral blood flow and cerebrovascular reserve capacity, and accelerates rehabilitative outcomes in hypertensive patients with a history of stroke. Int J Neurosci 2010;120:372-380.
46. Dandona P, Kumar V, Aljada A, Ghanim H, syed T, Hofmayer D, et al. Angiotensin II receptor blocker valsartan suppresses reactive oxygen species generation in leukocytes, nuclear factor-kappa B, in mononuclear cells of normal subjects: evendence of an anti-inflammatory action. J. Clin. Endocrinal. Metab. 2003;88:4496-4501.
47. Li NC, Lee A, Whitmer RA, Kivipelto M, Lawler E, Kazis LE, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. BMJ 2010;340.
48. Weber MA. Angiotensin-II receptor blockers for hypertension and heart failure: quality of life and outcomes. Managed Care and Interface 2005;18:47-54.
49. Baghai T, Binder E, C. S, D. S, Eser D, Lucae S, et al. Polymorphisms in the angiotensin-converting enzyme gene are associated with unipolar depression, ACE activity and hypercortisolism. Mol Psychiatry 2006;11:1003-1015.
50. Schwartz AC, Bradley R, Penza KM, Sexton M, Jay D, Haggard P. Pain medication use among patients with posttraumatic stress disorder. Psychosomatics 2006;47(2):136-142.

51. Schwartz AC, Bradley R, Ressler KJ, Sexton M, Sherry A. Treating posttraumatic stress disorder in urban African American mental health patients. Journal of American Psychoanal. Assoc. 2004;53(2):464-465.
52. Pike JL, Smith TL, Hauger RL, Nicassio PM, Patterson TL, McClintick J, et al. Chronic Life Stress Alters Sympathetic, Neuroendocrine, and Immune Responsivity to an Acute Psychological Stressor in Humans. Psychosom Med 1997;59:447-457.
53. Schwartz AC, R.G. B, Sexton M, Sherry A, Ressler KJ. Posttraumatic stress disorder among African Americans in an inner city mental health clinic. Psychiatr Serv 2005;56(2):212-215.
54. Foa E, DF T. Comparison of the PTSD Symptom Scale-Interview Version and the Clinician Administered PTSD Scale. J Trauma Stress 2000;13:181-191.
55. Coffey SF, Dansky BS, Falsetti SA, Saladin MF, K.T. B. Screening for PTSD in a substance abuse sample: psychometric properties of a modified versionof the PTSD Symptom Scale Self-Report. Posttraumatic Stress Disorder. Journal of trauma stress 1998;11(2):393-399.
56. Weathers FW, Keane TM, Davidson JRT. Clinician-administered PTSD scale: a review of the first ten years of research. Depress Anxiety 2001;13(132-56).
57. Blake DD, Weathers FW, Nagy LM, Kaloupek D, Klauminzer G, Charney DS. A clinician rating scale for assessing current lifetime PTSD: the CAPS-1. Behavior Therapy 1990;13:187-88.
58. Bernstein D, Fink I, Handelsman L, al. e. Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am J Psychiatry 1994;151:1132-1136.
59. Bernstein D, Ahluvalia T, Pogge D, Handelsman L. Validity of the Childhood Trauma Questionnaire in an adolescent psychiatric population. Journal of American Academic Child Adolescent Psychiatry 1997;36:340-348.
60. Strawn JR, Geracioti Jr TD. Noradrenergic Dysfunction and the Psychopharmacology of Posttraumatic Stress Disorder. Depress Anxiety 2008;25:260-271.
61. Reid IA. Interactions between ANG II, sympathetic nervous system, and baroreceptor reflexes in regulation of blood pressure. Am J Physiol 1992;262(6):763-78.
62. Fletcher S, Creamer M, Forbes D. Preventing post traumatic stress disorder: are drugs the answer? Aust N Z J Psychiatry 2010;44:1064-1071.
63. Hogue E, Worthington J, Nagurney J, Chang Y, Kay E, Feterowski C, et al. Effect of Acute Posttrauma Propranolol on PTSD Outcome and Physiological Responses During Script-Driven Imagery. In: CNS Neuroscience Thearpy. Boston: Blackwell Publishing Ltd.; 2011.
64. Ramchand R, Marshall GN, Schell TL, Jaycox LH. Posttraumatic Distress and Physical Functioning: A Longitudinal Study of Injured Survivors of Community Violence. Consulting and Clinical Psychology 2008;76(4):668-676.
65. Zatzick D, Rivara F, Jurkovich G, Russo J, Trusz SG, Wang J, et al. Enhancing the population impact of collaborative care interventions: mixed methods development and implementaiton of stepped care targetting posttraumatic stress disorder and related comorbidities after acute trauma. Gen Hosp Psychiatry 2011;33:123-134.
66. Guidance NIfHaCE. Post-Traumatic Stress Disorder: The Management of PTSD in Adults and Children in Primary and Secondary Care. In: Health NCCfM, editor. UK: The Royal College of Psychiatrists & The British Psychological Society; 2005.
67. Gillespie K, Duffy M, Hackmann A, al e. Community based cognitive thearpy in the treatment of posttraumatic stress disorder following the Omagh bomb. Behavior Research and Therapy 2002;40:345-357.
68. Roberts NP, Kitchiner NJ, Kenardy J, Bisson JI. Systematic Review and Meta-Analaysis fo Multiple-Session Early Interventions Following Traumatic Events. Am J Psychiatry 2009;166:293-301.

69. Forbes D. Post-traumatic stress disorder: Best practice GP guidelines. Aust Fam Physician 2009;38(3):106-111.
70. Ipser JC, Stein DJ. Evidence-based pharmacotherapy of post-traumatic stress disorder (PTSD). International Journal of Neuropsychopharmacology 2011:1-16.