Antihypertensive Medications and PTSD Incidence in a Trauma Cohort

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Abstract

Objective: Antihypertensive medications have been examined as agents for posttraumatic stress disorder (PTSD) prevention in trauma-exposed individuals, given well-documented associations between PTSD and increased risk of cardiovascular disease and purported trauma-relevant mechanisms of action for these medications. Evidence regarding the effectiveness of such drugs for this purpose remains mixed.

Methods: We conducted a national population-based cohort study using data from Danish national registries to assess whether 4 classes of antihypertensive drugs (beta-adrenoceptor blockers [beta blockers], angiotensin II receptor blockers [ARBs], angiotensin-converting enzyme [ACE] inhibitors, and calcium channel blockers) were associated with a decreased incidence of PTSD (diagnosed according to *ICD-10*) over a 22-year study period. Data for this study originated from a population-based cohort of over 1.4 million persons who experienced a traumatic event between 1994 and 2016 in Denmark. We calculated the incidence rate of PTSD per 100,000 person-years among persons who filled a prescription for each class of drug in the 60 days prior to a traumatic event and for corresponding unexposed comparison groups. We then used Cox proportional hazards regression to compare the rate of PTSD among persons who filled an antihypertensive medication prescription within 60 days before their trauma to the rate among persons who did not.

Results: We found evidence that calcium channel blockers were associated with a decreased incidence of PTSD (adjusted hazard ratio = 0.63, 95% confidence interval [CI] = 0.34, 1.2); all other antihypertensive medication classes had null or near null associations.

Conclusions: These findings lay a foundation for additional research focusing on antihypertensive medications that appear most effective in reducing PTSD incidence following trauma and for additional replication work aimed at continuing to clarify the disparate findings reported in the literature to date.

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There is a well-documented association between trauma, posttraumatic stress disorder (PTSD), and cardiovascular disease (CVD).[1] Accordingly, drugs for treating hypertension have been examined for reduction in PTSD symptoms and, to a lesser extent, for PTSD prevention in trauma-exposed individuals. Antihypertensive medications include drugs across a variety of classes: beta-adrenoceptor blockers (beta blockers), angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers. Several studies have reported a possible association between antihypertensive medications and posttraumatic stress disorder (PTSD), although results are mixed.[2–5] Much of the evidence documenting associations between antihypertensive drugs and PTSD come from small clinical (not population-based) studies and animal models, and thus, conflicting findings may be due to true etiologic differences or differences between samples and other methodological choices.

Meta-analyses and literature reviews summarizing several small studies have concluded that there is weak evidence for a small protective effect of propranolol, a beta blocker, on incident PTSD prevention.[2–4] It is hypothesized that propranolol interferes with memory reconsolidation at the time of trauma, thereby preventing reactivation of disturbing memories (a key symptom of PTSD[6]). Other beta blockers may also affect PTSD symptoms. For example, atenolol, a non-lipid-soluble beta blocker, is thought to reduce anxiety and is sometimes used to treat PTSD and anxiety disorders.[3,7] Additionally, evidence from animal models suggests that calcium channel blockers (eg, nimodipine, nisoldipine) may also play a role in either interrupting memory reconsolidation[8] or resolving anxiety symptoms.[9,10] A study

Clinical Points

- Evidence regarding a potential association between antihypertensive medications and PTSD is mixed, most likely due to across-study differences in medications examined, focus on PTSD incidence versus prevalence, and other methodological choices.
- Clinicians should be aware that the different antihypertensive medications may have differential effects on posttraumatic psychopathology, with some medications potentially more beneficial than others.

using cross-sectional data from a hospital biorepository did not document differences in use of calcium channel blockers among people with and without prevalent PTSD[5]; however, incidence of PTSD was not examined. More recently, a large cohort study using electronic health registry data found that brain penetrant calcium channel blockers were associated with a decreased risk of many incident psychiatric disorders, including anxiety disorders, when compared with a low brain permeability calcium channel blocker (amlodipine), although PTSD was not specifically assessed as an outcome.[11]

Both human and animal studies offer some evidence that ARBs and ACE inhibitors may be associated with a decreased frequency of PTSD or lower PTSD symptoms. For example, a study using a small clinical sample[12] and a cross-sectional study using data from a hospital-based biorepository[5] reported that individuals taking either ARBs or ACE inhibitors had a lower prevalence of PTSD symptoms than individuals not taking these drugs and that people on these medications were less likely to have prevalent PTSD.[5,13] ARBs or ACE inhibitors affect the renin-angiotensin system and have been found to be associated with reducing anxiety and stress, possibly via promoting fear extinction.[14–17] ARBs have been more widely studied than ACE inhibitors, with the ARB losartan receiving particular attention.[14,17] However, a recent randomized controlled trial did not find evidence that losartan performed better than placebo in reducing prevalent PTSD symptoms.[18]

Taken together, the literature documents some possible evidence of an effect of antihypertensive medications on PTSD, but research has been mixed with regard to focus on prevalent PTSD maintenance or incidence, and results have been contradictory. Further, population-based studies of PTSD incidence (ie, new onset among people initially free from PTSD) are rare. The present study fills some of the gaps in this literature through the use of a national population-based study to assess whether 4 classes of antihypertensive drugs, captured as a filled prescription within 60 days before a traumatic experience, were associated with a decreased incidence of PTSD over a 22-year study period.

MATERIALS AND METHODS

Data for this study originated from a population-based cohort of over 1.4 million persons who experienced a traumatic event in Denmark between 1994 and 2016. The methods used for this study have been described elsewhere.[19] Briefly, persons in the cohort experienced probable traumatic events including fire/explosion, transportation accident, exposure to a toxic substance/medical complications, traumatic brain injury, assault with or without a weapon, pregnancy-related trauma, suicide death of a family member, and multiple traumatic events (ie, persons experiencing more than one of these events on the same day). Traumatic event data were obtained from registry-based sources including the Danish National Patient Registry,[20] the Danish Psychiatric Central Research Register,[21] the Danish Medical Birth Registry,[22] the Civil Registration System,[20] and the Cause-of-Death Registry.[23] While we were unable to fully assess the severity of these events given the registry-based nature of the data, we took several steps to ensure that we were capturing traumatic experiences rather than stressors (such as requiring a hospital stay following certain events).[19] Previous analyses indicate that we were able to isolate events that were more serious than typical stressors with these definitions; we found that risks of all forms of psychopathology were increased following all but 1 of our defined traumatic events (the exception was pregnancy-related trauma) when compared with risk of psychopathology following a common stressor (nonsuicidal death of a loved one).[19] All traumatic events were the first recorded traumatic event within the study period. The current analysis was restricted to persons with no recorded psychiatric disorders between 1994 and date of the potentially traumatic experience (*International Classification of Diseases*, 10th Edition, or *ICD-10*, F codes).[24]

We defined exposure as redemption of a prescription for one of 4 classes of antihypertensive medication (calcium channel blockers, Anatomical Therapeutic Chemical [ATC] code: C08; ACE inhibitors, ATC code: C09AA; ARBs, ATC code: C09CA; and beta blockers, ATC code: C07) within 60 days prior to a traumatic event. Although other timeframes for medication redemption prior to trauma were possible, we chose 60 days as our timeframe of interest in an effort to balance looking back far enough to capture all of the people who might be on these medications at the time of trauma against looking back so far that some participants may have redeemed the prescription within the time frame but already stopped using it by the time the trauma occurred. Medication data were obtained from the Danish National Prescription Registry covering all Danish pharmacies.[20] Use of Danish registry data for the current population-based study confers a major advantage in that medication variables in the Danish National Prescription Registry indicates a prescription that was filled at a pharmacy, rather than just receipt of a prescription issued by a physician—

Table 1.
Descriptive Characteristics of the Samples at the Time of Trauma

Characteristic	Calcium channel blockers		ACE inhibitors		Beta blockers		Angiotensin II receptor blockers	
	Exposed (n = 31441) n (%)	Unexposed (n = 81031) n (%)	Exposed (n = 28303) n (%)	Unexposed (n = 74770) n (%)	Exposed (n = 39004) n (%)	Unexposed (n = 95563) n (%)	Exposed (n = 12244) n (%)	Unexposed (n = 35679) n (%)
Male	14986 (48)	39169 (48)	15299 (54)	39939 (53)	18446 (47)	44846 (47)	5516 (45)	16162 (45)
Female	16455 (52)	41862 (52)	13004 (46)	34831 (47)	20558 (53)	50717 (53)	6728 (55)	19517 (55)
Age group								
< 30 y	215 (0.7)[a]	648 (0.8)	176 (0.6)[a]	520 (0.7)	1138 (2.9)[a]	3411 (3.6)	48 (0.4)	144 (0.4)
30–50 y	1799 (5.7)[a]	5382 (6.6)	1785 (6.3)[a]	5366 (7.2)	3319 (8.5)[a]	9876 (10)	707 (5.8)	2106 (5.9)
50+ y	29427 (94)[a]	75001 (93)	26342 (93)[a]	68884 (92)	34547 (89)[a]	82276 (86)	11489 (94)	33429 (94)
Married/registered partner	15937 (51)[a]	41900 (52)	14554 (51)	40010 (54)	19904 (51)[a]	49762 (52)	6516 (53)	18728 (53)
Single	2605 (8.3)[a]	7642 (9.4)	2578 (9.1)	6993 (9.4)	4177 (11)[a]	11677 (12)	923 (7.5)	3073 (8.6)
Divorced	3794 (12)[a]	10919 (14)	3517 (12)	10086 (14)	4462 (11)[a]	12619 (13)	1494 (12)	4823 (14)
Widowed	9095 (29)[a]	20539 (25)	7649 (27)	17634 (24)	10448 (27)[a]	21441 (22)	3311 (27)	9041 (25)
Unknown	10 (0)[a]	31 (0)	...[b]	47 (0.1)	13 (0)[a]	64 (0.1)	...[b]	14 (0)
Income quartile								
1 (lowest)	7154 (23)[a]	16696 (21)	6371 (23)[a]	15577 (21)	9310 (24)[a]	19695 (21)	2793 (23)	8452 (24)
2	13847 (44)[a]	32718 (40)	12345 (44)[a]	29121 (39)	16187 (42)[a]	36218 (38)	5015 (41)	14126 (40)
3	5682 (18)[a]	15438 (19)	5130 (18)[a]	14441 (19)	7470 (19)[a]	19088 (20)	2307 (19)	6606 (19)
4 (highest)	4686 (15)[a]	15843 (20)	4371 (15)[a]	15265 (20)	5900 (15)[a]	19946 (21)	2099 (17)	6395 (18)
Child (no income)	23 (0.1)[a]	68 (0.1)	22 (0.1)[a]	67 (0.1)	38 (0.1)[a]	114 (0.1)	...[b]	...[b]
Unknown	58 (0.2)[a]	268 (0.3)	64 (0.2)[a]	299 (0.4)	99 (0.3)[a]	502 (0.5)	30 (0.2)	100 (0.3)
Antidepressants[c]	3734 (12)[a]	6893 (8.5)	3208 (11)	6315 (8.4)	4334 (11)[a]	7620 (8.0)	1423 (12)	3211 (9.0)
NSAIDs	4972 (16)	10950 (14)	4150 (15)	10302 (14)	4990 (13)	12577 (13)	1968 (16)	4825 (14)
Statins	7088 (23)[a]	6551 (8.1)	7338 (26)[a]	6110 (8.2)	10087 (26)[a]	7014 (7.3)	3236 (26)[a]	4354 (12)
CCI score								
0	10506 (33)[a]	42027 (52)	7840 (28)[a]	39093 (52)	12807 (33)[a]	52717 (55)	4064 (33)[a]	16771 (47)
1–2	12907 (41)[a]	27332 (34)	12099 (43)[a]	25154 (34)	15243 (39)[a]	30095 (32)	4825 (39)[a]	12508 (35)
3+	8028 (26)[a]	11672 (14)	8364 (30)[a]	10523 (14)	10954 (28)[a]	12751 (13)	3355 (27)[a]	6400 (18)
Type of trauma								
Fire/explosion	982 (3.1)[a]	4045 (5.0)	925 (3.3)[a]	3734 (5.0)	1000 (2.6)[a]	4694 (4.9)	452 (3.7)[a]	1506 (4.2)
Transportation accident	950 (3.0)[a]	3014 (3.7)	800 (2.8)[a]	3094 (4.1)	898 (2.3)[a]	3718 (3.9)	390 (3.2)[a]	1475 (4.1)
Exposure to toxic substance/ medical complications	23025 (73)[a]	51929 (64)	21041 (74)[a]	48008 (64)	27759 (71)[a]	58086 (61)	8962 (73)[a]	24000 (67)
TBI	5808 (19)[a]	18874 (23)	5100 (18)[a]	17379 (23)	7061 (18)[a]	20881 (22)	2217 (18)[a]	7560 (21)
Assault	110 (0.3)[a]	616 (0.8)	119 (0.4)[a]	614 (0.8)	145 (0.4)[a]	791 (0.8)	60 (0.4)[a]	291 (0.8)
Pregnancy-related	209 (0.7)[a]	1156 (1.4)	21 (0.1)[a]	709 (0.9)	1768 (4.5)[a]	5883 (6.2)	...[b]	289 (0.8)
Family suicide	171 (0.5)[a]	758 (0.9)	108 (0.4)[a]	630 (0.8)	166 (0.4)[a]	778 (0.8)	77 (0.6)[a]	271 (0.8)
Multiple events	186 (0.6)[a]	639 (0.8)	189 (0.7)[a]	602 (0.8)	207 (0.5)[a]	732 (0.8)	81 (0.7)[a]	287 (0.8)

[a]Standardized difference compared exposed to unexposed for overall category was greater than 0.1.
[b]Values under 10 not displayed.
[c]Although we restricted the sample to persons without psychiatric disorders prior to trauma, some cohort members had been prescribed pre-trauma antidepressants (for, eg, nonpsychiatric indications such as chronic pain and smoking cessation).
Abbreviations: ACE = angiotensin-converting enzyme, CCI = Charlson Comorbidity Index, NSAID = nonsteroidal anti-inflammatory drug, TBI = traumatic brain injury.

the norm in most population-based registry-based data sources. To create an unexposed comparison cohort, we matched each exposed person, without replacement, to up to 3 persons who did not fill an antihypertensive medication prescription within 60 days prior to their traumatic experience (matched on year of birth, month and year of trauma, and sex). Follow-up ended for unexposed persons if they filled an antihypertensive medication prescription in the study period. Sample sizes are presented in Table 1. The outcome was an incident diagnosis of PTSD (*ICD-10* code: F43.1)[24] over the 22-year follow-up period, as indicated in the Danish National Patient Registry[20] (covering all inpatient and outpatient contacts at nonpsychiatric hospitals in Denmark) and/or the Danish Psychiatric Central Research Register[21] (covering all inpatient and outpatient care at psychiatric hospitals in Denmark). We included all primary and secondary diagnoses in the present analysis. A validation study of PTSD diagnoses in the Psychiatric Central Research Registry showed high validity when compared with independent symptom reassessment.[25] Confounders were chosen for adjustment based on the existing literature. They included marital status and income at the time of trauma, obtained from the Civil Registration System[20]; filled prescriptions for an antidepressant (ATC code: N06A), an NSAID (ATC code: M01A), or a statin (ATC code: C10AA) within 60 days prior to the traumatic event; Charlson Comorbidity Index (CCI) score at any time before trauma[26] (based on diagnoses recorded in the Danish National Patient Register); and traumatic event type.

We conducted descriptive analyses comparing demographic characteristics (sex, age group, marital

status, income quartile, and type of trauma) and individual CCI diagnoses in the exposed and matched unexposed groups and calculated standardized differences between the groups for each variable. Next, we calculated the incidence rate of PTSD per 100,000 person-years, and the cumulative incidence of PTSD over the entire study period, among persons in the exposed and unexposed groups. Incidence rates are a measure of the number of outcome cases that occur over a period of time that is equivalent across all groups (ie, 100,000 person-years) and can be interpreted as the number of cases that would occur if you followed 100,000 people for 1 year or 50,000 people for 2 years, etc. Finally, we conducted Cox proportional hazards regression to compare the PTSD rate among persons who filled an antihypertensive medication prescription within 60 days prior to their traumatic experience to matched persons who did not fill a prescription for these medications. We estimated associations based on age-, trauma date–, and sex-matched groups (ie, the minimally adjusted models), and associations additionally adjusted for the confounders noted above. In accordance with recent scientific recommendations against using null-hypothesis significance testing to determine the importance of results,[27,28] and concerns raised regarding the role of null-hypothesis significance testing in the reproducibility crisis,[29,30] we evaluate our results without regard to whether their confidence intervals include the null. Rather, we present confidence intervals as information regarding the range of likely values for the evaluated associations. Further, we interpret our results with regard to the level of evidence provided by these point estimates and confidence intervals. That is, point estimates and confidence intervals that indicate a range of consistent estimates as most likely (either protective or harmful) will be interpreted as potential findings, while near null point estimates and confidence intervals that provide relatively equal evidence of protective and harmful associations will be interpreted as less informative evidence. Importantly, we provide all results so that readers can make their own determinations about our findings. All analyses were conducted in SAS version 9.4. This work was approved by the Institutional Review Board at Boston University Medical Campus and the Danish Data Protection Agency (2015-57-0002). Given data security requirements, all data and code can be accessed only by request to the Danish government.

RESULTS

Descriptive characteristics of the sample are presented in Table 1. The sample as a whole was relatively evenly split by sex, and the large majority of persons were over 50 years of age. This is consistent with the general timing of prescriptions for antihypertensive medications. Among persons exposed and unexposed to one of the 4 types of antihypertensive medications, the biggest differences were in CCI score at the time of trauma—persons receiving antihypertensive medications had more comorbid conditions. The average length of follow-up time for participants in the sample was 5–6 years and varied slightly based on the type of antihypertensive medication.

Table 2.

Associations (With 95% CIs) Between Categories of Prescribed Antihypertensive Medications at the Time of Trauma and Incident PTSD

	Calcium channel blockers	ACE inhibitors	Beta blockers	Angiotensin II receptor blockers
Minimally adjusted models[a]	0.70 (0.41, 1.2)	1.1 (0.70, 1.8)	0.94 (0.66, 1.3)	0.72 (0.36, 1.5)
Adjusted models[b]	0.63 (0.34, 1.2)	1.2 (0.67, 2.1)	0.88 (0.60, 1.3)	1.1 (0.48, 2.4)

[a]Minimally adjusted models are adjusted for age, sex, and trauma date due to the matching used to create the analytic cohorts.
[b]Adjusted models additionally controlled for marital status; prescriptions for antidepressants, non-steroidal anti-inflammatory drugs, or statins; and Charlson Comorbidity Index score.
Abbreviations: ACE = angiotensin-converting enzyme, PTSD = posttraumatic stress disorder.

Results of all regression analyses are presented in Table 2. For persons who received calcium channel blockers within 60 days prior to trauma, the rate of PTSD was 10.9/100,000 person-years and the cumulative incidence in the study period was 0.06%. The PTSD rate among the matched unexposed cohort was 15.7/100,000 person-years, and the cumulative incidence in the study period was 0.08%. This corresponded to a minimally adjusted association of 0.70 (95% confidence interval [CI] = 0.41, 1.2). After adjusting for marital status, income, other medications prescribed and redeemed at the time of trauma, CCI score, and trauma type, the observed association was 0.63 (95% CI = 0.34, 1.2).

In contrast, we found weak or no evidence of an association with PTSD incidence for ACE inhibitors, ARBs, and beta blockers. Among persons who received ACE inhibitors, the rate of PTSD was 17.2/100,000 person-years and the cumulative incidence was 0.09%, while among the matched unexposed group the rate of PTSD was comparable, at 17.4/100,000 person-years, with a cumulative incidence of 0.09%. The minimally adjusted association between ACE inhibitors and PTSD incidence was 1.1 (95% CI = 0.70, 1.8), and after adjusting for additional confounders, the observed association was 1.2 (95% CI = 0.67, 2.1). Among persons who received beta blockers, the rate of PTSD was 20.9/100,000 person-years, with a cumulative incidence of 0.12%. In the matched unexposed comparison group, the rate of PTSD was 24.5/100,000 person-years, with a cumulative incidence of 0.13%. These rates corresponded to a minimally adjusted association of 0.94 (95% CI, 0.66, 1.3) and an

association of 0.88 (95% CI, 0.60, 1.3), after adjusting for additional confounders. Finally, persons who filled a prescription for ARBs within 60 days of their trauma had a PTSD rate of 15.9/100,000 person-years with a cumulative incidence of 0.08%, while the matched comparison group without a prescription for any antihypertensive medication had a PTSD rate of 21.8/100,000 person-years and a cumulative incidence of 0.10%. This corresponded to a minimally adjusted association of 0.72 (95% CI, 0.36, 1.5) between ARBs and PTSD incidence and an adjusted association of 1.1 (95% CI, 0.48, 2.4).

DISCUSSION

We found evidence that a specific class of antihypertensive medications—calcium channel blockers—was associated with a decreased incidence of PTSD following trauma, while ACE inhibitors, ARBs, and beta blockers showed little to no effect on PTSD incidence in our sample. This is in contrast to a recent study by Seligowski et al (2021) using data from a hospital biorepository which found that people on ACE inhibitors and ARBs were less likely to have prevalent PTSD, but not those on calcium channel blockers.[5] There may be methodological explanations for these discrepant findings. While we were able to confirm that participants had at least filled a prescription for an antihypertensive medication within 60 days prior to their traumatic experience, the study by Seligowski et al[5] used electronic health record data to confirm medications but did not explore timing of medications relative to traumatic experiences. Further, our study used longitudinal data to observe PTSD incidence (ie, the sample was PTSD free at the time of trauma and at the time they filled the antihypertensive prescription) while the study by Seligowski et al (2021) was a cross-sectional assessment of the co-occurrence of medication prescriptions and PTSD diagnosis.[5] Consistent with our findings, recent work by Colbourne and Harrison (2022) found that brain permeating calcium channel blockers were protective against incident anxiety disorders when compared with ARBs among a sample with no prior psychiatric disorders, although PTSD was not examined as a specific outcome.[11] Taken together, these findings provide a foundation for additional longitudinal research on antihypertensive medications that appear most effective in reducing PTSD incidence following trauma and for additional work aimed at clarifying the disparate findings regarding these associations in the literature to date.

Knowledge is accumulating regarding the potential mechanisms through which antihypertensive medications may impact PTSD incidence. There is a growing literature implicating the renin-angiotensin system, which is involved in blood pressure regulation, in the link between PTSD and CVD.[5] Studies have found that circulating levels of renin are higher in people who are trauma-exposed, and persons who are on ACEs and ARBs report fewer PTSD symptoms.[12] In addition, recent work has highlighted differences in the brain permeability of antihypertensive medications as a potential mechanism through which some antihypertensive medications prevent psychopathology while others do not.[11] In tandem with research that is needed to elucidate the nuances of these associations in population-based and clinical samples, additional mechanistic research will be an important component in furthering our understanding of differences in the effects of these medications on PTSD incidence. The strengths of this study include its large population-based design, allowing us to examine 4 antihypertensive medication classes within the same sample; use of Danish registries in which comprehensive data captured for a full population minimize selection bias; and access to a prescription registry that documents prescription redemption rather than prescription receipt. There are also several important limitations to consider. We focused on prescriptions received in the 60 days prior to the traumatic event in an effort to balance sensitivity and specificity of this classification, but it is possible that there are other etiologically important time frames for antihypertensive medication prescription fills prior to trauma. In addition, while data on prescription redemption rather than prescription receipt provide an additional layer of confidence regarding medication consumption compared with traditional population-based registry data, we cannot be sure that persons in the study were taking these medications routinely at the time when the traumatic event occurred. In addition, despite the large original cohort, the variable definitions required for our analysis decreased the sample size considerably, making some estimates imprecise (ie, with large confidence intervals). Although the captured traumatic events were the first in the period of this study, it is possible that participants had trauma history before the study period and we were unable to capture these data. Relatedly, this study relies strictly on diagnostic codes, and it is possible that some participants had subsyndromal psychopathology that would not be captured. "New user" designs have become an important methodological approach in pharmacoepidemiology, but we were unable to implement this approach because the proportion of people who started an antihypertensive medication and happened to experience a traumatic event within the same 60 days was small, even within our large sample. For these reasons, replication of our findings using other larger samples from diverse populations and more rigorous causal methods (eg, propensity score matching) is warranted. In addition, certain characteristics of Denmark (eg, universal health care) may limit generalizability of these findings, calling for replication in different populations.

Despite these limitations, this study contributes to the literature as the first longitudinal examination of associations between 4 classes of antihypertensive medications and PTSD incidence in a single population-based sample and can fruitfully point the way to future research in the field.

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