

Antihypertensive Agents and Risk of Parkinson's Disease, Essential Tremor and Dementia: A Population-Based Prospective Study (NEDICES)

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Key Words

Parkinson's disease · Essential tremor · Dementia · Epidemiology · Calcium channel blockers · Antihypertensive agents · Hypertension

Abstract

Background: Recent interest in antihypertensive agents, especially calcium channel blockers, has been sparked by the notion that these medications may be neuroprotective. A modest literature, with mixed results, has examined whether these medications might lower the odds or risk of Parkinson's disease (PD) or dementia. There are no data for essential tremor (ET). **Objective:** To examine the association between antihypertensive use (defined broadly and by individual subclasses) and ET, PD and dementia. For each disorder, we used cross-sectional data (association with prevalent disease) and prospective data (association with incident disease). **Methods:** Prospective population-based study in Spain enrolling 5,278 participants at baseline. **Results:** Use of antihypertensive medications (aside from β -blockers) was similar in prevalent ET cases and controls. Baseline use of antihypertensive agents was not associated with reduced risk

of incident ET. Antihypertensive medication use was not associated with prevalent or incident PD. Calcium channel blocker use was marginally reduced in prevalent dementia cases ($OR_{adjusted} = 0.63$, $p = 0.06$) but was not associated with reduced risk of incident dementia ($RR_{adjusted} = 1.02$, $p = 0.95$). **Conclusions:** We did not find evidence of a protective effect of antihypertensive medications in these three neurodegenerative disorders.

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Introduction

The identification of modifiable risk factors for neurodegenerative diseases has important implications in terms of slowing or halting the progression of those diseases. Recent interest in antihypertensive agents, especially calcium channel blockers, has been sparked by the notion that these medications, which inhibit oxidative stress and the inflammatory response, might be neuroprotective [1, 2]. A modest literature, with mixed results, has examined whether the use of these medications might lower the odds or risk of Parkinson's disease (PD) or

Alzheimer's disease (AD) [3–5]. With one exception [6], these studies all have been cross-sectional [3–5]. Essential tremor (ET), associated with mixed degenerative pathologies (cerebellar degeneration in most cases and Lewy bodies in others) [7], is one of the more common neurodegenerative disorders [8], yet the protective role of antihypertensive agents has not been studied in this disease. The current study used a population-based design to examine the association between antihypertensive use (defined broadly as well as by individual subclasses) in each of these three late-life degenerative disorders (PD, dementia, and ET). For each disorder, the study used cross-sectional data to examine the association with prevalent disease as well as prospective data to examine the association with risk of incident disease.

Methods

Study Population

The Neurological Disorders in Central Spain (NEDICES) is a population-based survey of the frequency and determinants of major age-associated conditions of the elderly. The study population comprised subjects ≥ 65 years of age taken from the census of 3 communities in central Spain: Las Margaritas (a working-class neighborhood in greater Madrid), Lista (a professional neighborhood in central Madrid), and Arévalo (an agricultural zone northwest of Madrid) [9]. We have reported elsewhere a detailed account of the background, study population, and methods of the survey [9–11]. Written (signed) informed consent was obtained from all subjects at the time of enrollment.

Study Evaluation

Evaluations were performed at baseline (1994–1995) and at follow-up (1997–1998). As detailed previously [9–13], the evaluations included a demographic and medical questionnaire that screened for neurological disorders (ET, dementia, PD, stroke). Persons who screened positive for neurological disorders underwent a neurologic evaluation that included a standardized medical history (including current medications), a general neurologic examination, and the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) [14], which were performed by senior neurologists. Participants underwent a short neuropsychological test battery. This battery, which was implemented by trained lay interviewers, has been described in previous studies [12, 15].

Diagnoses

Participants were diagnosed as having ET if they had an action tremor of the head or limbs without any other recognizable cause [9, 16]. The tremor had to be of gradual onset (i.e., slow and progressive) and either (1) present for at least 1 year or (2) accompanied by a family history of the same disorder (one or more reportedly affected first-degree relatives) [9, 16]. On an Archimedes spiral, tremor severity had to be moderate or greater (rating ≥ 2 on the handwriting scale of Bain and Findley [17]). Based on their medical history, participants were not considered to have ET if

their tremor was related to alcohol withdrawal, hyperthyroidism, anxiety, or medications. Similarly, based on their neurologic examination, participants with action tremor attributed to PD, dystonia, orthostatic tremor, or other movement disorders were not considered to have ET. Participants initially identified as ET were subsequently independently evaluated by 2 additional neurologists who examined the participant together. Participants were classified as having ET only when the 3 neurologists agreed. If ET was diagnosed, data on age of onset were elicited.

The diagnosis of dementia was made by consensus of 2 neurologists based on medical, neurological and, if available, neuropsychological information [15]. The medical records of all participants who received a diagnosis of dementia were also reviewed by a senior neurologist (F.B.P.) with the aid of a psychologist (F.S.-S.; see Acknowledgments). If there were doubts about any aspect of the dementia diagnosis, additional information (mainly from family doctors) was elicited. For the diagnosis of dementia, we applied the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria [18] and required evidence of cognitive deficit (neuropsychological test battery, clinical mental status examination) as well as evidence of impairment in social or occupational function. If dementia was diagnosed, data on age at onset were elicited.

Parkinsonism was diagnosed when at least 2 cardinal signs (resting tremor, rigidity, bradykinesia, and impaired gait/postural reflexes) were present [19, 20]. PD was diagnosed in patients without secondary causes or atypical features. A second neurologist reexamined all diagnosed PD patients. All diagnoses were then discussed and adjudicated by a panel composed of 3 senior neurologists. If PD was diagnosed, data on age at onset were elicited.

Data Analyses

Statistical analyses were performed by E.D.L. using SPSS version 16.0 (SPSS, Inc., Chicago, Ill., USA). Baseline characteristics of participants (table 1) were compared using Student's *t* tests and χ^2 tests. Antihypertensive agents were first treated as a single class of medication and then divided into subclasses: angiotensin-converting enzyme (ACE) inhibitors, β -blockers, calcium channel blockers, diuretics, nitrates and vasodilators (table 2). We also distinguished between 'any antihypertensive agent' and 'any antihypertensive agent excluding β -blockers' because of the propensity of ET cases to be treated with β -blockers [21]. In cross-sectional analyses (table 3), logistic regression models were used to examine the relationship between antihypertensive agent use (yes vs. no, independent variable) and diagnosis (ET, PD, dementia, in different models), yielding odds ratios (ORs) with 95% confidence intervals (CIs). We adjusted for variables that were associated with diagnosis in univariate analyses. Given the emphasis on calcium channel blockers in previous literature [3, 5], we highlighted this subclass of antihypertensives in these analyses. Attributable risk was calculated by subtracting the risk of the non-exposed group from the risk for the exposed group (e.g., the proportion of antihypertensive medication users with ET – the proportion of non-users with ET). In prospective analyses, we used Cox proportional hazards models to estimate the relative risk of incident disease (ET, PD, or dementia, in different models); this generated relative risks (RRs) with 95% CIs (table 4). Person-years for participants who developed incident disease were calculated as the time between the baseline evaluation and the reported date of disease

Table 1. Baseline characteristics of 5,278 participants

Baseline characteristics	Essential tremor	Parkinson's disease	Dementia	Controls
Participants	256	81	306	4,663
Age, years (mean \pm SD)	75.5 \pm 7.1 ^c	77.0 \pm 5.6 ^c	82.6 \pm 7.2 ^c	73.7 \pm 6.6
Female gender	149 (58.2%)	38 (46.9%)	209 (68.3%) ^c	2,662 (57.1%)
Educational level				
Illiterate	50 (19.5%) ^b	15 (18.5%)	95 (31.0%) ^c	564 (12.1%)
Can read and write	104 (40.6%)	29 (35.8%)	110 (35.9%)	1,857 (39.8%)
Primary studies	68 (26.6%)	26 (32.1%)	65 (21.2%)	1,566 (33.6%)
Secondary studies	33 (12.9%)	10 (12.3%)	28 (9.2%)	639 (13.7%)
Unknown	1 (0.4%)	1 (1.2%)	8 (2.6%)	37 (0.8%)
Community				
Las Margaritas	115 (44.9%) ^b	22 (27.2%)	106 (34.6%)	1,546 (33.2%)
Lista	64 (25.0%)	24 (29.6%)	87 (28.4%)	1,398 (30.0%)
Arévalo	77 (30.1%)	35 (43.2%)	113 (36.9%)	1,719 (36.9%)
Diabetes mellitus ¹	44 (17.4%)	14 (17.7%)	44 (16.4%)	744 (16.0%)
Heart disease ¹	26 (10.2%)	2 (2.6%) ^a	32 (11.8%)	451 (9.7%)
Self-reported depression ¹	97 (41.5%) ^c	35 (45.5%) ^c	82 (33.3%) ^b	954 (20.5%)

Some participants had more than one neurological disease: there were 3 with essential tremor and Parkinson's disease, 12 with essential tremor and dementia, and 13 with Parkinson's disease and dementia. Unless otherwise indicated the values are the number of participants with percentages in parentheses.

^a $p < 0.05$ compared to controls; ^b $p < 0.01$ compared to controls; ^c $p < 0.001$ compared to controls.

¹ In some cells, data are missing and percentage reflects total available data.

Table 2. Use of antihypertensive agents in essential tremor, Parkinson's disease, dementia and controls

Antihypertensive agent	Essential tremor	Parkinson's disease	Dementia	Controls
Any antihypertensive agent	129 (50.4%) ^a	41 (50.6%)	131 (42.8%)	2,063 (44.2%)
Any antihypertensive agent (excluding β -blockers)	122 (47.7%)	38 (46.9%)	130 (42.5%)	1,998 (42.8%)
ACE-inhibitors	31 (12.1%)	10 (12.3%)	33 (10.8%)	592 (12.7%)
β -Blockers	17 (6.6%) ^b	3 (3.7%)	6 (2.0%) ^a	187 (4.0%)
Calcium channel blockers	27 (10.5%)	11 (13.6%)	23 (7.5%) ^a	514 (11.0%)
Diuretics	54 (21.1%)	16 (19.8%)	65 (21.2%)	861 (18.5%)
Nitrates	10 (3.9%)	3 (3.7%)	25 (8.2%) ^b	231 (5.0%)
Vasodilators	41 (16.0%) ^d	8 (9.9%)	39 (12.7%)	461 (9.9%)

Some participants were taking more than one antihypertensive agent. Values are given as the number of participants with percentages in parentheses.

^a $p < 0.10$ compared to controls; ^b $p < 0.05$ compared to controls; ^c $p < 0.01$ compared to controls; ^d $p < 0.001$ compared to controls.

onset. When the date of onset of disease was unknown, person-years were calculated as the midpoint between the first evaluation and the follow-up evaluation. We began with an unadjusted model and then, in adjusted models, included as confounders those variables that were associated with disease in univariate analyses. Due to the emphasis on calcium channel blockers in previous literature [3, 5], we highlighted this subclass of antihypertensives in these analyses.

Results

Cross-Sectional Analyses

There were 5,278 participants at baseline. The baseline characteristics of participants with prevalent ET, prevalent PD, and prevalent dementia were compared to those of participants with none of these disorders (controls);

Table 3. Cross-sectional analyses (odds of prevalent disease with antihypertensive medication use)

Antihypertensive agent	Essential tremor	Parkinson's disease	Dementia
Any antihypertensive agent	1.28 (0.995–1.64), 0.055 1.15 (0.88–1.50), 0.32	1.28 (0.83–1.99), 0.27 1.17 (0.74–1.86), 0.50	0.93 (0.73–1.17), 0.53 0.88 (0.66–1.16), 0.36
Any antihypertensive agent (excluding β -blockers)	1.21 (0.94–1.56), 0.14 1.09 (0.83–1.42), 0.54	1.17 (0.75–1.81), 0.49 1.05 (0.66–1.66), 0.84	0.97 (0.77–1.23), 0.81 0.89 (0.67–1.19), 0.43
Calcium channel blockers	0.97 (0.64–1.45), 0.87 0.87 (0.57–1.33), 0.52	1.30 (0.68–2.46), 0.43 1.13 (0.59–2.17), 0.71	0.65 (0.42–1.01), 0.06 0.63 (0.39–1.01), 0.06

In logistic regression models, use of an antihypertensive agent was the independent variable, and diagnosis (essential tremor, Parkinson's disease, dementia, in different models) was the dependent variable. Unadjusted models are reported (upper row in each cell) and then models that adjusted for age, gender, education

and self-reported depression (lower row in each cell). Results are given as OR (95% CI) and p values. For any antihypertensive agent, the attributable risk was: -1.1% (essential tremor); 0.4% (Parkinson's disease), and -0.4% (dementia).

Table 4. Prospective analyses (risk of incident disease with antihypertensive medication use)

Antihypertensive agent	Essential tremor	Parkinson's disease	Dementia
Any antihypertensive agent	1.46 (0.95–2.26), 0.09 1.46 (0.92–2.31), 0.11	0.90 (0.44–1.85), 0.77 1.11 (0.51–2.39), 0.80	1.21 (0.89–1.64), 0.24 0.98 (0.71–1.36), 0.91
Any antihypertensive agent (excluding β -blockers)	1.41 (0.91–2.16), 0.12 1.59 (0.98–2.57), 0.06	0.96 (0.47–1.97), 0.91 1.17 (0.54–2.53), 0.69	1.25 (0.90–1.71), 0.15 0.99 (0.71–1.38), 0.96
Calcium channel blockers	1.60 (0.90–2.84), 0.11 1.62 (0.91–2.90), 0.10	1.24 (0.43–3.55), 0.69 1.24 (0.43–3.60), 0.69	1.26 (0.80–1.97), 0.32 1.02 (0.64–1.62), 0.95

In Cox proportional hazards models, diagnosis (essential tremor vs. control, Parkinson's disease vs. control, dementia vs. control, in different models) was the outcome variable and use of an antihypertensive agent was the predictor variable. Unadjusted

models are reported (upper row in each cell) and then models that adjusted for age, gender, education, and depressive symptoms (lower row in each cell). Results are given as the risk ratio (95% CI) and p values.

differences in age, gender, educational level, and self-reported depression were apparent (table 1).

Participants who used an antihypertensive agent ($n = 2,352$ [44.6%]) were older than those who did not (mean \pm SD = 74.9 ± 6.9 vs. 73.9 ± 7.0 years; $p < 0.001$). A larger proportion of women than men used an antihypertensive agent (1,524/3,040 [50.1%] women vs. 828/2,238 [37.0%] men; $p < 0.001$). Use of an antihypertensive agent was highest in Lista and lowest in Las Margaritas ($p < 0.001$) but did not differ by educational level ($p = 0.84$). A larger proportion of participants with diabetes mellitus ($p < 0.001$), heart disease ($p < 0.001$), and self-reported depression ($p = 0.002$) used an antihypertensive agent when compared to their counterparts without each condition.

A marginally larger proportion of ET cases than controls were on an antihypertensive agent (50.4 vs. 44.2%; table 2); however, this difference was largely due to the higher proportion of ET cases taking β -blockers (presumably for tremor). When β -blockers were excluded, use of an antihypertensive medication did not differ between ET cases and controls (table 2). A larger proportion of ET cases were taking vasodilators, but ET cases and controls did not differ with regard to each of the other subclasses of antihypertensives. PD cases and controls did not differ with regard to antihypertensive medication use. A marginally lower proportion of demented cases were taking β -blockers and calcium channel blockers; a higher proportion was taking nitrates (table 2).

In logistic regression models, use of antihypertensive agents was not associated with odds of ET or PD after ad-

justing for age, gender, education and depressive symptoms (table 3). In similar adjusted analyses, only use of calcium channel blockers was marginally lower in demented cases (table 3).

Prospective Analyses

We excluded participants with prevalent ET, PD or dementia at baseline and those for whom follow-up data were unavailable. Of the 3,942 remaining participants, there were 83 incident ET cases, 30 incident PD cases and 161 participants with incident dementia. In unadjusted and adjusted Cox models, baseline use of antihypertensive agents was not associated with reduced risk of incident ET; in fact, it was marginally associated with increased risk of incident ET (table 4). Baseline use of these medications was not associated with reduced risk of incident PD or incident dementia in Cox models (table 4).

Discussion

Several recent studies have related calcium channel blockers and ACE inhibitors to possible neuroprotective effects [1–3]. Calcium channel blockers, for example, have been shown to reduce degeneration of dopaminergic neurons in mesencephalic neuron-glia cultures in a dose-dependent manner [2].

In the current study, a marginally larger proportion of prevalent ET cases than controls were on an antihypertensive agent; however, this difference was largely due to the higher proportion of ET cases taking β -blockers (presumably for tremor). Use of other antihypertensive medications (including calcium channel blockers) was similar in ET cases and controls. Baseline use of antihypertensive agents was not associated with reduced risk of incident ET; in fact, it was marginally associated with increased risk of incident ET. Antihypertensive medication use was not associated with either prevalent or incident PD. Calcium channel blocker use was marginally reduced in prevalent dementia cases but was not associated with increased/reduced risk of incident dementia. Hence, there is no evidence from this study that antihypertensives reduced the risk of any of these disorders.

One case-control study demonstrated a reduction in the odds of PD with use (in general) of antihypertensive medications [4]. That study was a case-control study nested within a prospective cohort study of 13,979 residents of Leisure World Laguna Hills, California. They identified 395 PD cases and each was matched to 6 controls. The odds of PD was significantly reduced in users of

blood pressure medication (adjusted OR 0.62, 95% CI 0.48–0.80). One other study showed a reduced odds of prevalent PD with calcium channel blocker use but not with other antihypertensive drugs [3]. That was a case-control analysis within the UK-based General Practice Research Database. They identified 3,637 PD cases and an equal number of matched controls. As compared to nonuse of antihypertensive drugs, the adjusted OR for current use of calcium channel blockers was 0.77 (95% CI 0.63–0.95). A 3rd study showed no change in odds [5]. We also found no association. Hence, cross-sectional studies have reported mixed results. Whether demographic or other population-specific factors could account for these mixed results is an interesting question but one that is difficult to address. Ethnicity is not reported in most of these studies but presumably was predominantly Caucasian. The four studies have been conducted in a variety of settings in different countries (UK, Australia, USA, Spain), which could account for some variance in results. Importantly, no prior studies of PD have used prospective, longitudinal data. In the current study, antihypertensive medication use (in general as well as with regard to specific classes) was not associated with either prevalent PD or a reduction in the risk of incident PD.

There is one caveat with respect to PD and parkinsonism. Although we have been discussing the possible neuroprotective effects of calcium channel blockers, curiously there is also literature on the development of drug-induced parkinsonism in the setting of current calcium channel blocker use [22]. The pathological mechanism responsible for this is still not completely understood; however, the occurrence of drug-induced parkinsonism in this setting would make it more difficult for epidemiological studies to detect a neuroprotective effect of these agents (i.e., lower risk of PD) should such an effect exist.

In terms of dementia, the literature is more limited. One study, which was a prospective longitudinal study, did not find that the use of calcium channel blockers was associated with a reduced risk of developing incident AD [6]. Our results, which look more broadly at dementia, are in concordance with the earlier study. Interestingly, there is a sizable literature about the relationship among hypertension, antihypertensive drug use and dementia. Studies have shown that cerebrovascular risk factors (hypertension included) are related to the development of dementia and AD [23, 24]. In NEDICES, hypertensive participants had a greater risk of developing dementia, and the combination of several cardiovascular risk factors has been related to the incidence of dementia and AD [25]. A Cochrane review of several blood pressure-lowering trials

did not demonstrate that antihypertensive medications decreased dementia incidence [26], but a more recent trial indicates a possible effect [27].

There have been no prior studies, either cross-sectional or longitudinal, of antihypertensive medication use and reduced odds or risk of ET. Our study does not support such an association.

One limitation is that we did not take into account the dose of these medications, so we were not able to evaluate whether higher current dose or cumulative dose of these medications was associated with lower risk of these disorders. One other issue is that orthostatic hypotension may be a feature of PD or PD medications. The presence of hypotension could have resulted in the discontinuation of antihypertensive medications in some PD cases, a scenario that we were not able to assess. However, this would only have been a concern in our cross-sectional analyses; in the prospective analyses, we assessed antihypertensive medication use prior to the onset of PD or PD medication use. Strengths of the study include: its population-based design; division of antihypertensive medications into separate subclasses; the ability to supplement our initial cross-sectional analyses with prospective anal-

yses that examined baseline exposure to medication and risk of incident disease, and the broad examination of 3 neurodegenerative disorders.

In summary, we did not find evidence to support a protective effect of antihypertensive medications (including calcium channel blockers) in these 3 neurodegenerative disorders.

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