Movement Disorders
CLINICAL PRACTICE
BRIEF REPORT

# An Open-Label, Non-randomized, Drug-Repurposing Study to Explore the Clinical Effects of Angiotensin II Type 1 (AT1) Receptor Antagonists on Anxiety and Depression in Parkinson's Disease

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**Abstract:** Background: The cerebral Renin-Angiotensin System might have a role in anxiety and depression development.
Objective: We explored the effects of Angiotensin II Type 1 receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACE-Is) on anxiety and depression in Parkinson's Disease (PD).
Methods: Four hundred and twenty-three newly diagnosed drug-naïve PD patients were evaluated using the State–Trait Anxiety Inventory (STAI) and Geriatric Depression Scale (GDS-15) tests and were monitored at baseline and for up to 3 years.
Results: Twelve patients were treated with ARBs and 42 with ACE-Is. ARB-treated patients had lower anxiety STAI scores than those on ACE-Is or drug-free at baseline (17.2 $\pm$ 1.3 vs. 21.3 $\pm$ 1.3, or 23.8 $\pm$ 0.5, respectively, $P = 0.021$) and during the follow-up ($P < 0.01$). Depression scores were unaffected by any of the drugs throughout the study.
Conclusion: This small sample of ARB-treated PD patients displayed lower levels of anxiety. Randomized clinical trials are warranted.

Parkinson's disease (PD) is the most frequent movement disorder and the second most prevalent neurodegenerative condition.[1] Historically understood as primarily a motor disease[2] characterized by bradykinesia, muscular rigidity, rest tremor, and postural instability,[3] PD also encompasses non-motor symptoms, notably reducing patients' quality of life.[4] Among these, neuropsychiatric symptoms are the most frequent[3,5] and include mood alteration, cognitive impairment, and psychosis. On top of the life quality loss, the caregiver labor burden increases and so the risk of institutionalization.[6,7]

Depression is the prevailing mood disorder[8] affecting up to 50% of patients during disease development,[7] while anxiety, despite its considerable comorbidity, remains relatively under-studied.[7] The pathophysiology of depression and anxiety in PD

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involves the specific loss of limbic dopaminergic and noradrenergic innervation.[9] The most recent evidence-based review from the Movement Disorders Society EBM Committee failed to identify any randomized controlled trial for anxiety and could identify only pramipexole and venlafaxine as clinically useful for the treatment of depression.[10,11] Investigations into the Renin-Angiotensin System (RAS) unveiled its importance on cardiovascular and renal circuits, particularly in hypertension.[12] Recent evidence suggests that local RAS brain circuits affect cardiovascular function, anxiety, depression, and memory consolidation[13–15] and their alterations are linked to Alzheimer's, Parkinson's, and other neurodegenerative diseases.[13,15,16] Studies on clinical PD population have found correlation between plasma RAS levels and depression scores.[17,18] RAS-modulating drugs like Angiotensin II Type 1 receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACE-Is) were reported to benefit life quality because of mental features improvement in hypertensive patients[19] and might improve depression and anxiety in PD. To test this hypothesis, our study examined the effects of RAS-modulating drugs on anxiety and depression levels in PD patients.

# Methods

## Study Participants

This study included 423 untreated, de novo PD patients from the "Parkinson's Progression Marker Study" (PPMI). To be included, patients had to have received a PD diagnosis supported by a dopamine transporter-protein deficit measured by single- photon emission computed tomography (SPECT) within the two preceding years, disease severity at enrollment should have been mild to moderate according to Hoehn and Yahr stage I or II. Patients expected to start on PD medication within the first 6 months after the initial evaluation were excluded.

## Study Design

This was a cohort study of data retrieved from the PPMI database. Anxiety and depression scale total scores were measured during the first visit (baseline) and over the following 3 years. Depression was measured using the Geriatric Depression Scale (GDS-15)[20] and anxiety, using the State–Trait Anxiety Inventory for adults (STAI).[21] The Geriatric Depression Scale is a 15 yes-no items list and evaluates depression in the elderly[20,22] which was developed to circumvent interferences like fatigue and poor concentration of the elderly during the test administration.[20] The State–Trait Anxiety Inventory (STAI),[21] comprises two 20-item scales, one of which evaluates anxiety as regards an emotional state and the other one examines anxiety susceptibility as a personality trait.[21]

## Exposure to RAS-Modulating Drugs

We assessed exposure to AT1 receptor blockers (ARBs: valsartan, telmisartan, losartan, candesartan, irbesartan, olmesartan, eprosartan, azilsartan, filmasartan, tasosartan) or angiotensin-converting enzyme inhibitors (ACE-Is) both hydrophilic (captopril, enalapril, imidapril, lisinopril) and lipophilic (benazepril, cilazapril, fosinopril, delapril, moexipril, perindopril, quinapril, ramipril, spirapril, temocapril, trandolapril, zofenopril). A patient was exposed to one of these drugs if he/she had been taking the drug for at least 2 years at the moment of the baseline visit. During the follow-up, a patient was regarded as exposed to one of these drugs when treated with these drugs at one and all preceding visits and for 2 years before the baseline visit. Exposure at Year 1 visit meant that a patient had been on these drugs for at least 2 years at baseline and over the entire year thereafter. Similarly, exposure at Year 2 visit meant that the patient had been on these drugs for at least 2 years at baseline and over the 2 years thereafter, and so forth for exposure in Year 3. Then, a patient's status could change from "exposed" to "non-exposed" during the follow-up, but not the other way.

## Statistical Analysis

Between-group differences were analyzed using t-tests (numerical variables) or chi-sq tests (categorical variables). When assumptions for these tests were not met, appropriate replacements were used.

General Estimation Equations (GEE) allowed us to evaluate drug-treatment effects over the 3 year-follow-up. GEE is a general statistical approach to fit models for longitudinal/clustered data, which cannot be accommodated by other statistical techniques.[23] GEE can be reliably applied to clinical trials and observational studies. Sex, age, presence of cardiometabolic comorbidities, cognitive status, as assessed by the Montreal Cognitive Assessment (MoCA), parkinsonian motor symptoms severity, as assessed by the MDS-UPDRS Part III score in the practically defined OFF-condition, non-motor symptom burden, as assessed by the MDS-UPDRS Part I (Non-motor Experiences of Daily Living) score, and exposure to antiparkinsonian drugs were treated as confounding factors. We used an autoregressive correlation structure and the gamma linking function for fitting the model. We used the Quasi-likelihood under the Independence model Criterion (QIC) for model comparison, with higher values indicating a worse fit. The significance level was conventionally set at 0.05 (SPSS v.23, IBM Corp., Armonk, NY, USA).

# Results

Of all the 423 participants, at baseline, 42 (males = 35) were exposed to ACE-Is, 12 (males = 9) were exposed to ARBs, and the remaining 369 received none of these drugs. Table 1 shows that, compared with non-exposed patients, those exposed to

**TABLE 1** *Baseline characteristics of patients on ACEIs or ARBs*

| | Non-exposed (N = 369) | ACE-Is (N = 42) | ARBs (N = 12) | *P*-value |
|---|---|---|---|---|
| Male | 233 (63%) | 35 (83%) | 9 (75%) | 0.026 |
| Age (years) | 60.9 ± 9.8 | 67.0 ± 7.0 | 67.6 ± 7.9 | <0.001 |
| Age at PD diagnosis (years) | 60.4 ± 9.8 | 66.4 ± 7.1 | 66.7 ± 7.4 | <0.001 |
| Family history of PD | 92 (25%) | 7 (17%) | 4 (33%) | 0.377 |
| Elixhauser comorbidity score | 6.2 ± 3.4 | 7.3 ± 3.4 | 6.7 ± 1.5 | 0.112 |
| Hypertension | 90 (24%) | 35 (83%) | 11 (92%) | <0.001 |
| Diabetes | 14 (4%) | 5 (12%) | 2 (17%) | 0.012 |
| Hypercholesterolemia | 69 (19%) | 14 (33%) | 5 (42%) | 0.017 |
| MDS-UPDRS I + II + III IN OFF + IV score | 32.4 ± 13.1 | 32.6 ± 14.3 | 31.3 ± 10.7 | 0.949 |
| MDS-UPDRS I | 1.2 ± 1.5 | 1.3 ± 1.6 | 1.5 ± 2.0 | 0.789 |
| MDS-UPDRS II | 5.9 ± 4.2 | 6.1 ± 4.8 | 5.1 ± 2.9 | 0.761 |
| MDS-UPDRS III (in OFF-state) | 20.9 ± 8.9 | 20.7 ± 8.5 | 21.3 ± 9.4 | 0.984 |
| Hohen and Yahr score | 1.6 ± 0.5 | 1.5 ± 0.5 | 1.7 ± 0.5 | 0.541 |
| Geriatric Depression Scale score | 2.4 ± 2.5 | 2.2 ± 2.1 | 1.8 ± 1.5 | 0.707 |
| State–Trait Anxiety Inventory score | 23.8 ± 9.6 | 21.3 ± 8.7 | 17.2 ± 4.4 | 0.021 |
| Concomitant medications for mood disorders | | | | |
| Benzodiazepines | 67 (12%) | 9 (21%) | 2 (17%) | 0.180 |
| Any antidepressants | 102 (18%) | 11 (26%) | 2 (17%) | 0.419 |
| Tricyclic antidepressants | 10 (2%) | 0 (0%) | 0 (0%) | 0.615 |
| Selective 5HT-reuptake inhibitors | 65 (12%) | 9 (21%) | 1 (8%) | 0.151 |
| Other antidepressants | 41 (7%) | 2 (5%) | 1 (8%) | 0.820 |

RAS- modulating drugs were more frequently male, older, and had more comorbidities, including diabetes, hypercholesterolemia, and hypertension. ARBs-exposed patients had lower anxiety scores than those non-exposed ($P = 0.021$), while depression scores were comparable (Table 1).

Of the 423 subjects included in the study, 364 (86%) were available in Year 1, 359 (85%) in Year 2, and 359 (85%) in Year 3. From the 61 patients missing at Year 3, 31 patients were discontinued from the study (50%) while the rest of the patients had not attained the three-year visit by the time of the analysis. Reasons for discontinuation were medical events in 19 cases (61%), inability to consent in 5 cases (16%), death in 2 cases (7%), and other reasons in the 5 remaining cases (16%). The distribution of missing cases per group was: 50 cases in the non-exposed group (14% of the baseline sample size), 8 cases in the group exposed to ACE-Is (21% of the group at baseline), and 3 in the ARB group (25%). The difference between groups was not statistically significant (chi-sq = 2.12, $P = 0.34$). The GEE revealed that age at baseline, and MDS-UPDRS Part I and III scores influenced STAI anxiety scores during the follow-up (Supplemental Table S1). Significant differences were also found in STAI anxiety scores between participants on ARBs vs. the non-exposed ($P < 0.001$, Fig. 1). Treatment with ACE-Is did not affect STAI scores. The model, including the interaction term between time and ARB exposure, had a higher QIC value (216.40) as compared to the model including only the main effect of these factors (205.04), and thus the latter was retained. We included the full parameter data of the retained models in Supplemental Table S1.

Regarding GDS depression scores, they were only connected to MDS-UPDRS Part III scores. As shown in Figure 1, exposure to RAS-modulating drugs had no effects.

# Discussion

Mood disorders are frequent in Parkinson's disease (PD) patients and pose challenges due to inadequate treatment options.[7,10] Drug-repurposing is an invaluable tool that may expedite the identification of potential efficacious treatment in PD.[24–26] Experimental evidence suggests the involvement of local RAS brain circuits in regulating mood.[13] Our study is one of the first to confirm the involvement of RAS alterations in anxiety in

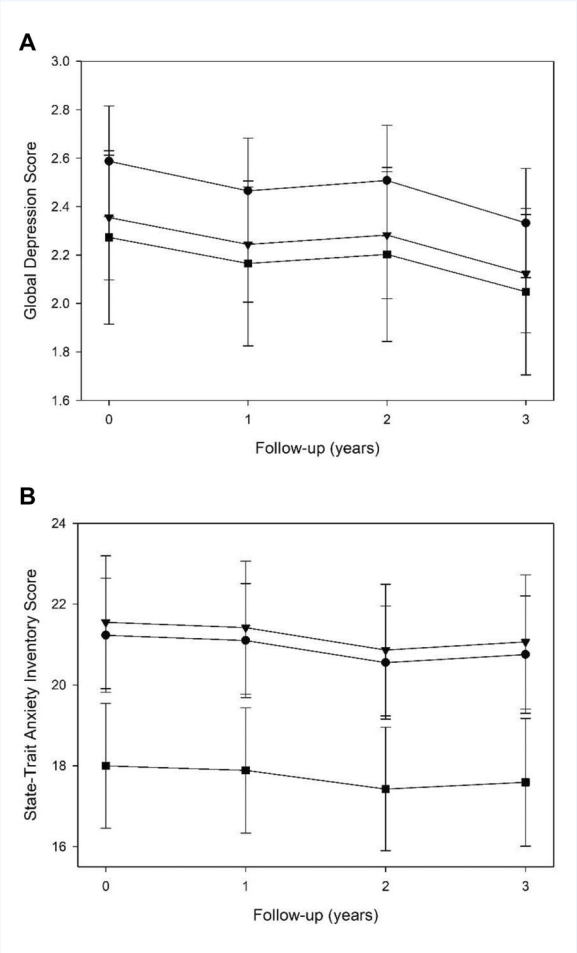


**Figure 1.** Results of anxiety and depression scores. Depression and anxiety scores in patients exposed to ACE-Is (▼) or ARBs (■) compared with those not exposed to these drugs (●), in the **A** and **B** panels, respectively. The Least-Squares means ± standard errors adjusting for sex, age, MDS-UPDRS motor scores in the OFF-state, MDS-UPDRS non-motor experiences of daily living (Part I), use of antiparkinsonian medication, and cardiometabolic comorbidities are shown. Differences were only found in patients exposed to ARBs had lower anxiety scores ($P < 0.01$, GEE).

PD. Our results suggest that AT1 receptors might be a relevant therapeutic target to treat anxiety in PD.

ARBs have shown anxiolytic effects in diverse brain injury and neuroinflammation rodent models being the case for temporal lobe epilepsy,[27] stress,[28] depression,[29] and type 2 diabetes mellitus.[30] Salmani et al[31] used a model of chronic inflammation by systemic endotoxin lipopolysaccharide (LPS) injection in the brain. Their results suggested protective effects from AT1R blockade, also preventing anxiety-like behavior. However, depression-like behavior was refractory to ARBs. A previous study using LPS injection on rodents also reported anxiolytic effects for ARBs.[32]

AT1 receptors are expressed in the prefrontal cortex, amygdala, hippocampus, cingulate cortex, thalamus, hypothalamus, and locus coeruleus. In these regions, AT1 receptors influence noradrenergic activity, whose dysregulation is associated with anxiety.[13,33] Interestingly, anxiety is prominent in the newly described noradrenergic PD phenotype.[34] Other mechanisms potentially underlying the effects of RAS-modulating drugs on anxiety may be the inhibition of oxidative stress, inhibition of inflammation, facilitating GABA-mediated transmission, and modifications in the expression of corticotropin- releasing factor (CRF) receptors.[13,33]

Anxiolytic effect of RAS-modulating drugs in humans have been observed in some studies. A meta-analysis involving hypertensive subjects, which aimed at studying the effects of ARBs and ACE-Is on mental health, found that these drugs improved well- being, and mental and anxiety domains related to the quality of life, but not on depression.[19] An uncontrolled trial that included 16 patients with PD and hypertension showed that the ARB Candesartan decreased anxiety scores after a 6-month follow-up.[35] No effects on depression were found.[35] These findings reinforce the notion that ARBs might be effective drugs to treat anxiety, deserving further clinical trials.

Some limitations must be considered. This study was open-label and not randomized. The sample was small, and many participants withdrew, which prevented us from following up patients beyond the third year. Therefore, our results should be interpreted with caution, as they only highlight a "signal" of potential beneficial effects of ARBs on anxiety, which should be further explored in clinical trials. The findings that the difference in anxiety scores persisted over the 3 years follow up period suggest that the effect is consistent, thus further supporting the potential beneficial effects of these drugs.

In sum, we found reduced anxiety levels in a small sample of patients exposed to ARBs. This "signal" of a potential beneficial effect of AT1 receptor antagonists for PD-associated anxiety should be further explored by means of randomized, double-blind, placebo-controlled trials.

# Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

S.B.: 1A, 1B, 1C, 2C, 3A
L.G.: 1A, 1B, 2C
L.U.: 1C, 2C
G.C.: 1C, 2C
M.O.L.: 2C, 3B
F.C.: 1A, 3B
S.P.L.L.: 1A, 2B, 3A

# Disclosures

**Ethical Compliance Statement:** The PPMI is a deidentified publicly available dataset and thus IRB approval is not needed for exploitation. Similarly, informed patient consent was not

necessary for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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## Data Availability Statement

Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org. ■

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# Supporting Information

Supporting information may be found in the online version of this article.

**TABLE S1.** Results of the GEE analyses on GDS and STAI Beta coefficients ± standard errors are shown. ⋆$P < 0.05$; ⋆⋆$P < 0.01$ (Wald test). REF, Reference category.