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Lack of independent mood-enhancing effect for dopaminergic medications in early Parkinson's disease

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ABSTRACT

Background: A direct antidepressant effect has been reported for certain dopaminergic medications used in the treatment of Parkinson's disease (PD).
Objective: To examine whether dopaminergic medications may exert differential effects on mood in early PD.
Methods: We analyzed prospectively-collected 5-year data on 405 early, drug-naïve (at baseline) PD patients enrolled in the Parkinson's Progression Markers Initiative (PPMI) cohort study, initiated on levodopa, dopamine agonists (DAs), or monoamine-oxidase type B inhibitors (iMAO-B) under naturalistic conditions. The outcome for depressive symptoms was the 15-item Geriatric Depression Scale (GDS-15) score. Potential motor and cognitive confounders were measured using the Unified Parkinson's disease Rating Scale (MDS-UPDRS-III) and the Montreal Cognitive Assessment (MoCA). Three statistical models were used to determine medication effects on GDS-15 scores: unadjusted, adjusted, and a marginal structural model.
Results: One-third of patients in this cohort met GDS-15 threshold for clinically-significant depressive symptoms (GDS-15 ≥ 5). There was a marginal positive effect on GDS-15 scores after iMAO-B treatment initiation (− 0.35 95%; CI: − 0.73, 0.04; $p = 0.08$). There were no significant interactions between any of the three medication groups, but robust interactions between MoCA scores and both DAs ($p = 0.005$) and iMAO-B ($p = 0.03$) use on GDS-15 scores. Specifically, as MoCA scores worsened, DAs yielded a steeper worsening of GDS-15 scores while iMAO-B a moderating effect on GDS-15.
Conclusion: Dopaminergic medications have no direct effect on mood in early, unselected PD patients.

1. Introduction

Depression is a common comorbidity in Parkinson's disease (PD), affecting approximately 30–40% of patients [1]. The tricyclics amitriptyline, nortryptiline, and desipramine; selective serotonin reuptake inhibitors citalopram, escitalopram, and paroxetine; and the serotonin-norepinephrine reuptake inhibitor venlafaxine, may have antidepressant effects in PD [2–6]. Preliminary evidence suggests that there may also be a direct antidepressant effect by dopamine agonists (DAs) [7–13] and monoamine oxidase type B inhibitors (iMAO-B) in PD [14,15]. These observations have been from single-agent retrospective or placebo-controlled studies [13]. which preclude a definitive answer to the question of whether putative antidepressant effects are unique to a specific drug or drug class or typical of dopaminergic medications as a whole. Further, the lack of comparisons across all dopaminergic medications, including levodopa, has made it difficult to determine the extent to which mood enhancement may be explained by the differential improvement in motor function that these drugs are known to exert. The latter is the reason regulatory authorities consider PD-associated depression a "pseudospecific" therapeutic target [16], which has hampered efforts at designing studies to properly examine the putative mood-enhancing effects of DAs compared to other dopaminergic medications.

The primary objective of this study was to examine the effect on mood by different dopaminergic drugs (levodopa, iMAO-B, and DAs) after correcting for their effects on motor function, using the

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naturalistic treatment conditions of the longitudinal Parkinson Progression Markers Initiative (PPMI) study cohort, whereby these drugs were administered to early, treatment-naïve patients to target motor impairment rather than mood impairment.

2. Methods

2.1. Participants

Patients with newly diagnosed, untreated PD were enrolled in the PPMI study, an observational, international, multicenter (16 sites from the US, 5 from Europe, and 1 from Australia) study designed to identify PD progression biomarkers. The aims and methodology of the study have been published elsewhere [17]. The study was approved by the institutional review board at each of the participating sites and written informed consent was obtained from all participants. At completion of study baseline there were data from a total of 423 PD patients.

2.2. Assessments

PPMI participants underwent baseline and periodic assessments of motor and non-motor features. Severity of depressive symptoms was assessed using the 15-item Geriatric Depression Scale (GDS-15), a validated screening tool for depression in PD, with a cut-off score of ≥ 5 recommended to indicate the presence of clinically-significant depressive symptoms [18]. Severity of state and trait anxiety symptoms was assessed with the State-Trait Anxiety Inventory (STAI) [19]. Cognitive function was measured with the Montreal Cognitive Assessment (MoCA) [20] and motor severity with the motor subscale of the Movement Disorders Society-Unified Parkinson's disease Rating Scale (MDS-UPDRS-III) [21].

2.3. Treatment decisions by PPMI investigators

Study participants could start dopaminergic treatment at any point after baseline at the judgment of the investigators to address motor deficits. The cohort was not selected based on presence or absence of depression. Information about medication dosages was not readily ascertained in the database and is therefore not included. Search terms were used to identify each of the commercially available antidepressant medications in the concomitant medications form.

2.4. Statistical analysis

Traditional methods to estimate the effect of PD medications on GDS scores must control for the presence of multiple confounders (e.g., MDS-UPDRS-III scores, MoCA scores, anti-depressant use, STAI scores, and levodopa-equivalent daily doses) by including them as covariates in a longitudinal model. However, these methods may not properly address the potential role of confounding variables, particularly on a cohort not randomized according to the medications examined, many of which may plausibly impact the use of other medications and affect GDS scores as well as MDS-UPDRS-III and MoCA scores, which in turn may influence the decision-making process by clinicians in choosing one medication over another.

We accessed the baseline and post-treatment Years 1 to 5 for GDS-15 and MDS-UPDRS-III data divided by the three treatment-initiation groups of interest: levodopa, DAs (pramipexole, ropinirole, and rotigotine), and iMAO-B (selegiline and rasagiline) as well as all possible combination therapies involving the three groups. All groups may change each year; some individuals can move from one group to another within a year. Between-group comparisons for baseline age, gender, MoCA, GDS-15, STAI, and MDS-UPDRS-III variables were performed using ANOVA for continuous variables and Chi-square tests for categorical variables. We formulated three questions from the data: (1) is there a significant effect of either of the three treatment groups on GDS scores? (2) are there any significant interactions among the treatments on GDS scores? and (3) are there any significant interactions among the treatments and MDS-UPDRS-III and MoCA scores on GDS scores? For each of these three questions, we used three statistical models:

1. Unadjusted model. This model included baseline characteristics, PD medication use, MDS-UPDRS-III scores, and MoCA scores.
2. Adjusted model. This model includes model 1, but also additional adjustments for antidepressant use, STAI score, and levodopa equivalent daily dose (LEDD).
3. Marginal structural model (MSM). To robustly examine the effect of PD medications on GDS scores given a complex web of relationships between the variables involved, we used MSM, a causal model for the estimation of time-dependent exposure in the presence of time-dependent confounders from observational data [22]. MSM account for the time-dependent confounding through a re-balancing of the study population, as opposed to the traditional approach of including these confounders directly in the statistical model. Implementing MSM requires developing a weight for each participant in the dataset. If a weight is < 1 (but > 0), that particular participant is down-weighted (given less influence than one person-unit). If a weight is > 1, that particular participant is up-weighted (given more influence than one person-unit). In this manner, the entire study population is rebalanced across important time-varying confounders among medications, MDS-UPDRS-III scores, MoCA scores, antidepressant use, STAI score, and LEDD, and direct inference of the medications on GDS scores can be made (see further details in Supplementary Methods, online).

3. Results

Of the 423 PPMI PD subjects, 368 provided at least one complete baseline record and one complete follow-up record. Of the 329 subjects with Year 1 data, 169 (51.4%) were not on medication by the end of Year 1; 63 of 279 (22.6%) remained untreated by the end of Year 2; only 30 of 250 (12.0%) by the end of Year 3; and only 15 of 209 (7.2%) by the end of Year 5 (Fig. 1). As expected, over the course of the study period, monotherapy for DAs and MAO-B inhibitors became less common, in favor of levodopa monotherapy and combination therapy.

3.1. Demographics and assessments at baseline

Because all PPMI subjects were untreated at baseline, we group subjects' baseline characteristics by their treatments recorded at Year 1. Patients on levodopa were older (mean age, 64.7 ± 10.3 years) and had greater motor severity (MDS-UPDRS-III, 25.5 ± 9.2) compared to those on DAs or iMAO-B (Table 1), consistent with recommendations to initiate levodopa in elderly and more impaired patients.

There were 121 patients treated with antidepressants throughout the study period, of which 112 (30.4% of the entire cohort) met criteria for clinically-significant depressive symptoms at any time during their follow-up (GDS-15 ≥ 5). Because of the significant differences across groups for age and MDS-UPDRS-III variables, we then investigated all pairwise differences to evaluate the sources of the overall difference. As all pairwise comparisons among the medication groups that were associated with a significant p-value for either the age or MDS-UPDRS-III variables involved the levodopa monotherapy group, we conclude that only levodopa drove the significant differences observed in Table 1. Gender, cognitive function, STAI, and GDS-15 were similar across all groups at baseline.

3.2. Effect of medications on GDS scores

There was a consistent trend in GDS-15 improvement for subjects on iMAO-B versus those not on iMAO-B (per MSM model: -0.35 95%; CI:

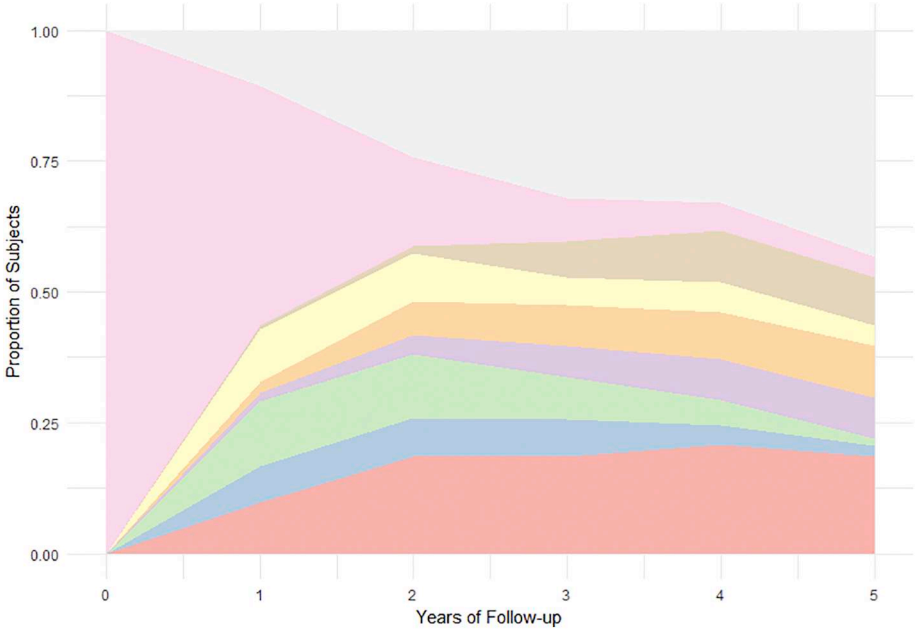

Fig. 1. Proportion of PPMI subjects in each medication group over time. Created from data extracted on May 7, 2018.

−0.73, 0.04; $p = 0.08$). None of the estimates for this or other medication groups were, however, statistically significantly different from zero on any of the statistical models (Table 2).

3.3. Interactions among medications on GDS scores

There were no significant interactions among the medications in any of the statistical models (all $p > 0.05$). There was no evidence that any of the combination therapies were associated with significant changes in GDS scores.

3.4. Interactions among medications and MDS-UPDRS-III and MOCA scores on GDS scores

After removing the non-statistically significant interactions, three interactions were either statistically significant or marginally non-statistically significant in all three statistical models (Table 3). There were strong interactions between MoCA scores and both DAs ($p = 0.005$) and iMAO-B ($p = 0.03$) on GDS-15 scores. Worsening MoCA scores for those on DAs were associated with a larger worsening of GDS-15 scores (total effect of $-0.03 + 0.15 = 0.12$ GDS-15 point increase per MoCA point decrease) while iMAO-B had a moderating effect (total effect of $-0.03 + -0.12 = -0.15 = 0.15$ GDS-15 point decrease per MoCA point decrease). Using the stringent MSM modeling approach, the interaction between MDS-UPDRS-III scores and iMAO-B became marginally non-statistically significant although the effect still pointed in the direction of iMAO-B as a moderator of the effect of changes in MDS-UPDRS-III scores on GDS-15 scores (total effect of $0.04 + -0.03 = 0.01$ GDS-15 point increase per MDS-UPDRS-III point increase).

4. Discussion

In this unselected cohort of early PD patients with one-third meeting GDS-15-threshold for depression and followed for 5 years, we found that dopaminergic medications had not effect on mood, as measured by GDS-15. While there was a positive mood trend by iMAO-B, the differences were not statistically significant for any of the medication groups. Thus, these data suggest that changes in the severity of depressive symptoms in PD may be driven by non-dopaminergic mechanisms and any mood stabilization may not be explained by the differential improvement in motor function that dopaminergic

Table 1
Baseline demographics and assessments stratified by medication treatment after one year of follow-up.

		Not on Any	Monotherapy			Combination Therapy				Overall *p*-value
			L-dopa	DAs	iMAO-B	L-dopa + DAs	DA + iMAO-B	L-dopa + iMAO-B	All Three	
Age	Mean (SD)	61.4 (10.2)	64.2 (11.2)	59.8 (7.2)	58.5 (9.4)	66.1 (7.0)	60.1 (9.3)	60.5 (7.3)	60.2 (6.2)	0.226
Sex	N_{Male} ($\%_{Male}$)	106 (63%)	27 (75%)	17 (68%)	33 (72%)	4 (67%)	25 (68%)	4 (50%)	1 (50%)	0.787
MoCA	Mean (SD)	26.3 (2.7)	25.2 (3.4)	27.2 (2.3)	26.5 (2.9)	23.8 (2.7)	26.1 (2.8)	26.8 (3.0)	27.0 (1.4)	0.081
GDS-15	Mean (SD)	2.4 (2.6)	2.7 (2.3)	2.2 (3.1)	2.3 (2.7)	2.0 (1.7)	2.6 (3.1)	1.5 (0.5)	1.5 (2.1)	0.949
STAI	Mean (SD)	63.8 (18.8)	68.4 (18.8)	66.6 (20.6)	64.1 (18.3)	63.3 (12.4)	67.9 (20.8)	59.5 (6.5)	62.5 (20.5)	0.811
MDS-UPDRS-III	Mean (SD)	25.6 (10.4)	29.9 (11.5)	25.8 (12.6)	24.6 (10.8)	24.8 (14.2)	19.9 (10.4)	20.3 (9.3)	10.5 (0.7)	0.004

L-dopa: levodopa; iMAO-B: Monoamine oxidase type B inhibitors; DAs: dopamine agonists. MoCA: Montreal Cognitive Assessment; GDS-15: Geriatric Depression Scale; STAI: State-Trait Anxiety Inventory; MDS-UPDRS-III: motor subscale of the Movement Disorders Society-Unified Parkinson's disease Rating Scale.

Table 2
Effect of medication groups on depression scores (as per Geriatric Depression Scale).

Statistical model	PD Medications								
	Levodopa			Dopamine agonists			MAO-B Inhibitors		
	Estimate (SE)	95% CI	p-value	Estimate (SE)	95% CI	p-value	Estimate (SE)	95% CI	*p*-value
Unadjusted	0.13 (0.16)	(−0.17, 0.44)	0.39	0.02 (0.17)	(−0.31, 0.35)	0.91	−0.29 (0.15)	(−0.59, 0.01)	0.06
Adjusted	0.08 (0.13)	(−0.17, 0.33)	0.54	−0.12 (0.13)	(−0.37, 0.13)	0.33	−0.21 (0.12)	(−0.44, 0.01)	0.07
MSM	0.13 (0.17)	(−0.21, 0.46)	0.46	−0.20 (0.19)	(−0.57, 0.17)	0.29	−0.35 (0.20)	(−0.73, 0.04)	0.08

Positive estimates mean worsening of mood as measured by the GDS-15 (Geriatric Depression Scale); negative estimates mean improvement. MSM: Marginal structural model.

Table 3
Interactions among medications and motor and cognitive scores on depression scores.

Statistical model	PD Medications								
	MDS-UPDRS-III x iMAO-B Use			MoCA x iMAO-B Use			MoCA x DAs Use		
	Estimate (SE)	95% CI	p-value	Estimate (SE)	95% CI	p-value	Estimate (SE)	95% CI	p-value
Unadjusted	−0.03 (0.01)	(−0.05, −0.01)	0.01	−0.09 (0.04)	(0.01, 0.17)	0.03	0.18 (0.06)	(−0.30, −0.06)	0.004
Adjusted	−0.01 (0.01)	(−0.03, 0.004)	0.11	−0.08 (0.03)	(0.01, 0.14)	0.03	0.13 (0.04)	(−0.22, −0.05)	0.002
MSM	−0.03 (0.02)	(−0.07, 0.004)	0.09	−0.12 (0.06)	(0.01, 0.23)	0.03	0.15 (0.05)	(−0.26, −0.05)	0.005

Positive estimates mean worsening of mood as measured by the GDS-15 (Geriatric Depression Scale); negative estimates mean improvement. Coefficients reflect the change in GDS-15 scores per unit of worsening in either the MDS-UPDRS-III or the MoCA scores. MSM: Marginal structural model. iMAO-B: Monoamine oxidase type B inhibitors; DAs: dopamine agonists. MoCA: Montreal Cognitive Assessment; MDS-UPDRS-III: motor subscale of the Movement Disorders Society-Unified Parkinson's disease Rating Scale.

therapies are known to exert. This finding does not exclude the possibility that there may be an antidepressant effect in those with severe depression, a population insufficiently represented in this cohort.

Of interest, we found that cognitive function affected the relationship between medication effect and mood: as MoCA scores worsened, DAs yielded a steeper worsening of GDS-15 scores compared to those not on DAs. Conversely, iMAO-B use led to a moderating or mood stabilizing effect in the setting of worsening MoCA scores.

Our study does not support prior evidence of a mood enhancing effect by iMAO-B in PD [14,15], presumably independent from motor improvement [15], which was shown as not sustained over time in one study [23]. The data argue against the potential for direct antidepressant effects previously suggested for pramipexole [13]. All dopaminergic medications were associated with GDS-15 worsening, in parallel with motor decline.

Some important limitations in our study should be highlighted, largely related to the prospective observational nature of PPMI. The PPMI cohort was treated under naturalistic conditions, creating natural biases in the allocation of medications, such as levodopa initiated more common in older patients with worse motor severity, which required adjusting for age and motor severity in the statistical models. In addition, given that patients were not preselected for presence of depression at baseline, there was a floor effect for GDS-15 scores: the mean baseline score was ≤ 3.0 for all groups, limiting the range of change for any dopaminergic treatment. Also, these scores are sub-threshold for depression (GDS-15 cutoff of 5 is required for optimal sensitivity 71.8% and specificity 78.2% for the diagnosis of depression using the Structured Clinical Interview for DSM-IV [SCID] as gold standard) [24]. Thus, we could not refer to an "antidepressant" effect for any of the drugs examined, but rather as changes in the severity of depression symptoms. Mean changes from baseline in GDS-15 were small (−0.24 (2.28 SD) at Year 1, −0.11 (2.75 SD) at Year 2, −0.14 (2.71 SD) at Year 3, −0.02 (2.87 SD) at Year 4, and 0.14 (3.08 SD) at Year 5). This difference is further diluted given the high variability in the cohorts, the relatively low sample size after dividing the treated PD subjects into seven non-overlapping medication groups, and the reduction in monotherapy-treated patients (as it would be expected in naturalistic conditions) toward Year 5. Finally, there were no motor differences across dopaminergic treatments, which suggest levodopa-treated patients may have been relatively undertreated. The levodopa-treated cohort had a change comparable to DAs and iMAO-B (10.8 MDS-UPDRS-III points in levodopa versus 10.1 and 12.8 in DAs and iMAO-B, respectively). This prevented answering the question of whether a more robust motor improvement, as it may be expected in optimized levodopa-treated patients, might have induced mood-enhancing effects.

In conclusion, these data suggest a correlation between depressive symptoms and severity of motor function but reject an independent effect on mood by any class of dopaminergic medications in a cohort of unselected early PD patients treated under naturalistic conditions. A dedicated prospective study in a large PD population selected for baseline depression but equally optimized for motor function will be required to answer whether any mood-enhancing effect may be revealed by iMAO-B compared with other medications in depressed PD patients, as tentatively suggested in this analysis.

Conflicts of interest

All authors declare that they have no competing interest. Other financial information unrelated to the current research covering the past year is documented at the end of the manuscript.

Ethical standards statement

This research study has been conducted in agreement with international ethical standards for medical research involving human participants, in line with the Declaration of Helsinki.

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Appendix A. Supplementary data

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