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Are Selective Serotonin Reuptake Inhibitors Associated With Greater Apathy in Parkinson's Disease?

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Abstract

Apathy is a common neuropsychiatric feature of Parkinson's disease (PD), but little is known of relationships between apathy and specific medications in PD. Following a retrospective database and chart review of 181 Parkinson's patients, relationships between Apathy Scale scores and use of psychotropic and antiparkinsonian medications were examined with multiple regression. Controlling for age, sex, education, and depression, the use of selective serotonin reuptake inhibitors (SSRIs), but not other antidepressants, was associated with greater apathy. Use of monoamine oxidase B inhibitors was associated with less apathy. Longitudinal studies are needed to evaluate a potential SSRI-induced apathy syndrome in PD.

Apathy is a multidimensional syndrome that can occur independently of depression in a variety of neurological conditions. Apathy refers to a primary lack of motivation that manifests in cognitive (e.g., lack of interest), behavioral (e.g., reduced productivity), and affective (e.g., blunted affect) domains. Research indicates that up to 60% of patients with Parkinson's disease (PD) experience clinically significant apathy, and approximately 30% of patients with PD report apathy in the absence of depression.[1] Apathy is a negative prognostic indicator, and can disrupt quality of life for both patients and caregivers.[2] Unfortunately, there are currently no empirically-supported treatments for apathy.

Apathy in PD has been linked to underactivity in the ventral striatum and disruption of basal ganglia circuitry due to midbrain neurodegeneration.[3] Improvements in PD apathy symptoms have been noted with the administration of dopaminergic medications, such as dopamine agonists.[4] Although deep brain stimulation (DBS) surgery has been reported to induce apathy in PD, few studies have investigated other iatrogenic contributions to the pathogenesis of PD apathy.[5] Selective serotonin reuptake inhibitors (SSRIs) are the most commonly-prescribed antidepressants in the PD population, in which the prevalence of depression is estimated to be 40%.[6] These findings indicate that a large number of individuals with PD are routinely prescribed SSRIs. Research suggests that SSRIs may worsen apathy in depressed individuals, but no studies have examined this association in PD.[7] Currently, there are no available studies investigating associations among

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antidepressants, PD medications, and apathy in a single cohort. Given the high prevalence of apathy in PD, a better understanding of factors contributing to its occurrence is needed in order to facilitate the development of effective treatment approaches. The present study examines the associations between medications and apathy in a multivariate framework controlling for factors known to be associated with apathy (e.g., age).

METHOD

Participants and Procedures

The present convenience sample included 181 individuals with idiopathic PD, based on the U.K. Brain Bank Criteria,[8] being followed at the University of Florida (UF) Center for Movement Disorders and Neuro-restoration. All participants signed informed consent for inclusion in an IRB-approved database and chart review (UF INFORM database). Participants were identified for an ongoing longitudinal study after having completed at least three apathy questionnaires over 18 months as part of their normal clinical care. Only data from the baseline occasion, which took place between August 2006 and March 2009, were examined in the present study. The sample included 120 men and 61 women, who ranged in age from 31 to 90 years (mean: 66.2; SD: 9.7). Average PD duration in the sample was 103.9 months (SD: 88.0). Average motor severity assessed on medications with the Unified Parkinson's Disease Rating Scale-Motor Portion (UPDRS-III), was 28.3 (SD: 10.6).

Demographic and disease characteristics were obtained from the UF INFORM clinical research database. A chart review was conducted, in which dosages of the following medications were recorded: carbidopa/levodopa, pramipexole, ropinirole, rotigotine, amantadine, selegiline, rasagiline, entacapone, sertraline, fluoxetine, paroxetine, escitalopram, citalopram, duloxetine, mirtazapine, venlaxafine, bupropion, buspirone, modafinil, methyl-phenidate, memantine, galantamine, donepezil, rivastigmine, quetiapine, clozapine, and all benzodiazepines. Medications were current at the time of assessment.

Measures

The primary outcome measure for this study was the Apathy Scale (AS), a well-validated, 14-item self-report measure.[9] Scores on this scale range from 0 to 42, and scores of ≥14 indicate clinically meaningful apathy in PD.[9] Depression severity was quantified with the Beck Depression Inventory (BDI), a widely used, 21-item self-report measure.[10] Scores range from 0 to 63, and scores >14 indicate clinically meaningful depression in PD.[11] Questionnaires were completed during routine clinical visits while patients were on their dopaminergic medications.

Statistical Analyses

Statistical analysis was carried out with PASW Statistics. Because levodopa dosage and total BDI scores were not normally distributed, square-root transformations were performed. Distributions of all other medications were dichotomized for analysis due to skewness. Pearson's correlations, Spearman's rho, and chi-square comparisons were used to examine univariate associations between the variables, and multiple linear regressions were utilized to investigate unique relationships.

RESULTS

Prevalence of Apathy and Depression

Of 181 patients, 76 (42%) were apathetic (AS ≥14), whereas only 30/176 patients (17%) were depressed (BDI ≥15). Note that BDI scores were unavailable for 5 patients, who were not included in the final regression analyses. Because 26 of 176 patients (15%) exceeded the

cut-offs for both apathy and depression, only 4 patients (2%) met psychometric criteria for depression in the absence of apathy. Higher apathy scores were associated with less education ($r = -0.28$; $p < 0.001$), advanced age ($r = 0.16$; $p < 0.05$), longer disease duration ($r = 0.17$; $p < 0.05$), and higher BDI scores ($r = 0.60$; $p < 0.001$).

Apathy and Antidepressants

The 35 individuals taking an SSRI were more likely to be apathetic ($\chi^2 = 8.916$; $p = 0.005$). This comparison was not significant for the 22 individuals taking a non-SSRI (SNRI, mirtazapene, or bupropion) antidepressant. In univariate analyses, total apathy score was correlated with use of SSRIs (rho=0.19; p=0.01), but not with use of SNRIs (rho=0.08; NS). There were no differences in BDI scores between patients taking an SSRI versus other antidepressants ($t[51] = -0.26$; $p = 0.80$).

Table 1 presents results from a multiple linear regression that examined relationships among total AS score, control variables (i.e., age, sex, education, disease duration, BDI), and psychotropic medications. The data revealed that advanced age ($\beta = 0.19$; $p < 0.05$), male sex ($\beta = 0.17$; $p < 0.05$), less education ($\beta = -0.14$; $p < 0.05$), and greater depressive symptomatology ($\beta = 0.56$; $p < 0.001$) were each independently associated with higher apathy scores in this multivariate analysis. Controlling for these variables and for other psychotropic prescriptions, use of SSRIs remained independently associated with higher apathy scores ($\beta = 0.14$; $p < 0.05$).

Apathy and PD Medications

The majority of patients were taking carbidopa/levodopa (mean dose: 713.01 mg; SD: 488.67). The 80 individuals taking a dopamine agonist ($\chi^2 = 10.316$; $p = 0.001$) and the 29 individuals taking selegiline/rasagiline ($\chi^2 = 6.432$; $p = 0.011$) were less likely to be apathetic. This comparison was not significant for individuals taking carbidopa/levodopa, amantadine, or entacapone. In univariate analyses, total apathy score was negatively correlated with use of dopamine agonists (rho = −0.22; p=0.003) and use of selegiline/rasagiline (rho = −0.17; p=0.025), but not with use of carbidopa/levodopa or amantadine. Higher levodopa-equivalent dose (LED) of dopamine agonists were associated with less apathy (rho = −0.18; p=0.02). However, total LED did not correlate with apathy (rho=0.11; p=0.32).

Table 2 presents results from a multiple linear regression that examined relationships among total AS score, control variables (i.e., age, sex, education, disease duration, BDI), and PD medications. As shown, advanced age ($\beta = 0.14$; $p < 0.05$), male sex ($\beta = 0.16$; $p < 0.05$), and greater depressive symptoms ($\beta = 0.57$; $p < 0.001$) were each independently associated with higher apathy scores in the multivariate analysis. Controlling for these variables and other dopaminergic medications, use of selegiline/rasagiline remained independently associated with lower apathy scores ($\beta = -0.15$; $p < 0.05$), but use of dopamine agonists did not ($\beta = 0.08$; $p = 0.22$). Controlling for age in the multivariate analysis eliminated the negative association between apathy and dopamine-agonist use: individuals taking a dopamine-agonist were approximately 4.3 years younger than those not taking a dopamine-agonist ($t[178] = 3.031$; $p = 0.003$).

DISCUSSION

The present study provides evidence for an association between SSRI use and apathy in this cohort of PD patients. Importantly, this association was independent of age, sex, education, depressive symptoms, and use of other psychotropic medications. SSRI use explained a significant, but small, proportion of the variance in apathy. Non-SSRI antidepressants were not associated with increased apathy. Because of the cross-sectional design, it cannot be

solidly concluded that SSRIs *caused* apathy. However, other studies have linked SSRIs to the development of behavioral apathy and emotional blunting in non-PD samples.[7,12] Few empirical studies have explicitly investigated the phenomena of SSRI-induced apathy, which occurs in 20%–40% of adults taking an SSRI.[7] Although its etiology is not well understood, the apathy may stem from frontal-lobe dysfunction, with altered serotonergic activity or disruption of serotonergic modulation of midbrain dopaminergic systems projecting to the frontal lobes.[7] A recent experimental study used fMRI to document reduced activation in the ventral striatum and ventral medial/orbitofrontal cortex to rewarding stimuli, as well as reduced activation in the lateral orbitfrontal cortex to aversive stimuli after administration of citalopram. This study, which included 45 healthy subjects, suggests a potential causal role for SSRIs in the development of apathy.[13]

Another possible explanation for the positive association between SSRI use and apathy in the current study is that SSRIs were prescribed for the treatment of depression, which is clearly linked to apathy scores, as shown in the analysis. The reduction in depression could have confounded the results. Investigators have reported that SSRIs can address symptoms of general distress and anxiety, but not motivation and hedonic responding.[14] This point is particularly important if apathy is mistaken for depression. In such cases, prescription of an SSRI would be less likely to improve symptoms and may even exacerbate them. Since individuals in the present study who were taking a non-SSRI antidepressant did not report greater apathy than the rest of the sample, it is possible that the non-SSRI antidepressants affected both depression and apathy. Indeed, non-SSRI antidepressants, such as bupropion, a dopamine and norepinephrine reuptake inhibitor, have been linked to improvements in both depression and apathy in non-PD patients.[15] Importantly, apathetic patients are *not* more likely to receive SSRIs, as compared with other antidepressants, at our center; in part, because there is a lack of empirical evidence suggesting that SSRIs treat apathy better than other antidepressants. Thus, it is not likely that the pattern of results can be attributed to differential prescribing practices.

The present results revealed evidence for relationships between PD medications and apathy. Specifically, patients taking the MAO-B-I drugs selegiline or rasagiline reported less apathy than the rest of the sample, and this association remained significant after controlling for demographic factors and for the use of other PD medications. Unlike MAO inhibitors that act on both isoforms of the MAO enzyme (MAO-A and MAO-B), selegiline and rasagiline selectively target MAO-B, the predominant isoform involved in the metabolic breakdown of dopamine in the human brain.[16] Selegiline has been shown to improve apathy in patients with traumatic brain injury, perhaps via the enhancement of dopaminergic activity, but the potential mechanism remains unknown.[17] In PD, dopamine agonists have been reported to improve apathy.[4] In our cross-sectional study, dopamine-agonist use was associated with lower apathy scores, but only in univariate analyses. Lower apathy among patients taking dopamine agonists seemed to relate more to younger age than to the drugs themselves. In the present sample, advanced age was independently associated with apathy, and this has been reported previously in non-PD samples.[18]

In our sample, 42% of patients exceeded a clinical cutoff for apathy. This relatively high prevalence, combined with the negative prognostic value and potential impact on quality of life and family systems, underscores the need for further research on contributors to apathy, and its treatment in PD. One limitation of this study is that patients did not routinely undergo comprehensive psychiatric interviews to diagnose mood disorders. Rather, symptoms of apathy and depression were quantified with well-validated, self-report instruments. Future research should examine relationships between medications and apathy in PD patients with and without formal diagnoses of depression. Future studies should also consider the role of cognitive dysfunction, which may also be associated with apathy. The present study

provides valuable information to clinicians faced with managing the motor and non-motor symptoms of PD, and it suggests avenues for future research. Specifically, longitudinal studies should investigate the prevalence and mechanism of SSRI-induced apathy syndrome in PD, as well as how various PD medications (e.g., MAO-B-Is) may affect the trajectory of apathy.

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TABLE 1

Results of a Multivariate Linear Regression, Including All Control Variables and Psychotropic Medication Use[a]

	Proportion of Patients Taking	B	Standard Error	β	p
Constant	—	0.06	4.39	—	NS
Age, years	—	0.13	0.05	0.19	0.005
Female sex	—	2.43	0.94	−0.17	0.011
Education, years	—	0.32	0.16	−0.14	0.044
Disease duration, months	—	0.00	0.01	0.01	NS
BDI	—	3.09	0.39	0.56	<0.001
SSRIs[b]	19%	2.40	1.18	0.14	0.044
Non-SSRI antidepressant[c]	12%	2.22	1.35	0.11	0.103
Benzodiazepine	11%	0.69	1.41	0.03	0.626
Antipsychotic[d]	9%	1.08	1.65	0.05	0.515

[a] R^2=0.46 (p<0.001); N=144.

[b] Sertraline, fluoxetine, paroxetine, escitalopram, citalopram.

[c] Duloxetine, venlaxafine, mirtazapine, bupropion.

[d] Quetiapine, clozapine.

BDI: Beck Depression Inventory; SSRI: selective serotonin reuptake inhibitor.

TABLE 2

Results of a Multivariate Linear Regression, Including All Control Variables and Parkinson's Disease Medication Use[a]

	Proportion of Patients Taking	B	Standard Error	β	p
Constant	—	1.08	4.86	—	NS
Age, years	—	0.10	0.05	0.14	0.047
Female sex	—	2.30	1.01	−0.16	0.024
Education, years	—	0.23	0.16	−0.10	NS
Disease duration, months	—	0.00	0.01	0.01	NS
Beck Depression Inventory	—	3.279	0.41	0.57	<0.001
Carbidopa/Levodopa	82%	0.05	0.04	0.09	NS
Dopamine agonists[b]	44%	1.14	0.93	−0.08	NS
Amantadine	16%	1.00	1.28	0.05	NS
Selegiline/Rasagiline	21%	2.59	1.19	−0.15	0.032
Memantine	3%	3.06	2.73	−0.07	NS
Entacapone	20%	0.62	1.18	0.04	NS

[a] R^2=0.45 (p<0.001); N=143.

[b] Pramipexole, ropirinole, rotigotine.