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End of life planning in parkinsonian diseases

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ABSTRACT

Introduction: The utilization of advance directives in individuals with Parkinson's disease (PD) and atypical parkinsonian disorders (APD) and their caregivers requires further investigation. This study determined the utilization rates of four forms of advance directives: living will, durable power of attorney, durable power of attorney for healthcare, and medical orders in these individuals. We hypothesized that having a neurodegenerative parkinsonian disorder or exposure to these disorders would increase the likelihood of having advance directives.

Methods: 50 PD participants, 49 APD participants, 50 caregivers and 50 non-caregiver controls were surveyed regarding advance directives.

Results: The median number of advance directives was 1 in controls, 2 in caregivers and PD participants and 3 in APD participants. Patients with PD were 4.08 times more likely to have durable power of attorney ($p < 0.001$) and 2.08 times more likely to have durable power of attorney for healthcare ($p = 0.011$) than controls. Patients with APD were 1.66 times more likely to have a living will ($p = 0.006$), 4.81 times more likely to have a durable power of attorney ($p < 0.001$) and 2.47 times more likely to have a durable power of attorney for healthcare ($p = 0.003$) than controls. Caregivers were1.58 times more likely to have a living will ($p = 0.012$) and 2.21 times more likely to have a durable power of attorney for healthcare than controls.

Conclusion: Having or being exposed to parkinsonian disorders significantly increases the likelihood of utilizing advance directives. Additionally, exposure to a parkinsonian disorder as a caregiver increases advance directive use.

1. Introduction

Advance directives provide individuals with means of expressing wishes for care they want to receive at the end of life. They are especially important when individuals are no longer capable of expressing choices directly. Individuals who request limited care are more likely to be spared invasive end of life procedures [1,2]. Until the 1990s, advance directives were not commonly utilized in the United States [2]. Currently, one in three Americans have some form of advance directive [3]. Major categories of advance directives include: a) the living will, in which the individual writes wishes for end of life care in the event he becomes unable to communicate decisions; b) the durable power of attorney, in which the individual names someone to make decisions on his behalf in regards to private, legal or business affairs in the event that he dies or is otherwise unable; c) the durable power of attorney specifically for healthcare (healthcare proxy) and d) medical orders, standardized forms that addresses major healthcare decisions [1].

Neurodegenerative parkinsonian disorders are associated with progressive disability and reduced quality of life, especially at the end of life [4]. This group includes Parkinson's disease (PD) and the atypical parkinsonian disorders (APD): progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and Corticobasal Syndrome (CBS). The most common co-morbidities in late-stage PD and APD include: dysphagia, falls and dementia, which frequently lead to aspiration pneumonia, fractures, and nursing home placement [5–7]. Aspiration pneumonia and dysphagia may necessitate the use of artificial ventilation and parenteral nutrition. Fractures can increase hospitalizations and time spent in the intensive care unit. Undesired hospitalizations and procedures can be avoided if patients participate in advance planning [6]. Additionally, because many individuals with late stage

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parkinsonism have comorbid dementia [5] or difficulty communicating [8], an advance directive with the patient's medical preferences is even more valuable.

Utilization of advance planning has been studied in rapidly progressing illnesses including amyotrophic lateral sclerosis and for acute onset illnesses like stroke. However, there is a dearth of research about advance medical planning in chronically progressing neurological illnesses such as PD [9]. There is also no research in patients with APD. Additionally, there has not been research that determines how exposure to a chronic illness as a caregiver affects advance planning utilization.

This study aimed to investigate the differences in utilization of advance medical planning for participants with PD, those with APD, caregivers of patients with these disorders and healthy controls. We hypothesized that there would be a difference in rates of different forms of end of life planning. We hypothesized that having a rapidly disabling (i.e., APD) rather than a slowly (i.e., PD) progressive neurodegenerative parkinsonian disorder, would increase the likelihood of having advance directives. We also expected that caregivers would have higher rates of advance medical planning than controls.

2. Methods

2.1. Study design

This cross-sectional prospective study included four groups: (1) participants with PD who met the probable UK PD Brain Bank criteria [10], (2) participants with possible or probable APD based on the 2nd consensus MSA criteria [11], possible or probable PSP based on the National Institute of Neurological Disorders and Society for PSP diagnostic criteria [12] and CBS based on Bak and Hodges clinical criteria [13], (3) healthy caregivers of individuals with PD, MSA or PSP and (4) controls: subjects over age 60 without exposure to caregiving. Participants were recruited from the outpatient Movement Disorder Clinic at the University of Louisville between August 21st, 2008 and October 21st, 2010. Inclusion required a Mini-Mental State Examination [14] (MMSE) score ≥ 24. PD participants were included if onset of symptoms occurred more than one year prior to recruitment date, regardless of disease stage. Those who had received deep brain stimulation were excluded. APD participants were included regardless of disease duration or stage. Participants from the caregiver group were caregivers of patients with parkinsonian disorders who presented to the clinic. Controls were individuals who presented to the Internal Medicine Clinic for routine follow up and were not exposed to caregiving. Caregivers or controls had to be independent in their activities of daily living and were excluded if they suffered from chronic disabling disorders, such as end-stage cancer, end-stage chronic renal failure and acquired immunodeficiency syndrome. Well-controlled diabetes and previous ischemic stroke with modified Rankin scale ≤ 3 were not exclusionary. Written informed consent was obtained from all subjects. The project was approved by the Institutional Review Board at the University of Louisville.

2.2. Procedures

Subjects in all four groups self-completed a standardized survey that included demographic information and current advance directives (living will, durable power of attorney, durable power of attorney for healthcare or medical order). Disease duration and measures of severity including the Unified Parkinson's Disease Rating Scale (UPDRS) [15], Hoehn and Yahr (H&Y) [16] and Schwab and England [17] were collected on the day of survey completion.

2.3. Data analysis

Demographic variables were assessed across groups (PD, APD, caregivers and controls) using the chi-squared test for categorical variables and the Kruskal-Wallis test for continuous variables. Fisher's exact test was used as an alternative to the chi-squared test in cases where low expected cell counts violated the assumptions of the chi-squared test. We performed pairwise comparisons between groups with chi-squared tests for categorical variables and the Mann-Whitney *U* test for continuous variables. Bonferroni-Holm adjustment was applied to account for multiple comparisons. We used a univariable log binomial regression to compare utilization rates between the four groups and to analyze the effects of demographics and disease severity on advance directives. A likelihood ratio test was used to assess the significance of each variable. Variables that were significant at the 0.10 level were included in a multivariable log binomial regression for demographics and disease severity. Missing values were not imputed. We consider p-values below 0.05 to indicate statistical significance. All analyses were performed using the latest version of R (3.5.0).

3. Results

The study included 199 participants: 50 with PD, 49 with APD, 50 caregivers and 50 healthy controls who answered at least 90% of the survey questions. The APD group included 25 patients with MSA, 22 with PSP and two with CBS. Eight patients with PD, six patients with APD, three caregivers and one control declined to participate. One participant with APD was excluded for an MMSE ≤ 24. Three participants with PD were excluded: two did not complete the survey and one had an MMSE ≤ 24. One caregiver was excluded for not completing the survey.

Fifty-six percent of caregivers (28/50) were caregivers for PD participants while 44% (22/50) were caregivers for APD participants. Caregivers were mainly spouses (43/50) of PD (22/28) and APD (21/22) participants. The remaining caregivers were close relatives or friends (four daughters, two siblings, one friend).

Demographics and psychosocial characteristics are shown in detail in Table 1. There were significant between group differences in age, sex, religiousness, income and MMSE score. Controls were younger than individuals with PD, APD and their caregivers ($p = 0.007$, $p < 0.001$, $p = 0.043$, respectively). Participants with PD and APD were more likely to be male than the caregiver group ($p = 0.004$, $p = 0.015$). Caregivers reported a lower income than PD participants ($p = 0.002$). Participants with APD had lower MMSE scores than participants in the control, PD and caregiver groups ($p < 0.001$, $p = 0.003$, $p < 0.001$, respectively).

Table 2 shows the disease specific variables for PD and APD participants. PD participants had a longer disease duration, higher Schwab and England scores, and lower H&Y, UPDRS part I, II, II and total UPDRS scores. Notably, within the APD group there were missing roughly ten percent of H&Y, and Schwab & England scores and roughly 30% of UPDRS scores. Missing values were due to difficulties completing severity assessments during the time allotted for the clinic appointment.

Table 3 shows the response rates for the four forms of advance directives surveyed. The median number of advance directives was 1 in controls, 2 in caregivers and participants with PD and 3 in the APD group ($p < 0.001$). Fifty-three percent of controls, 68% of the PD group, 86% of the APD group and 76% of caregivers reported having at least one advance directive. Only 6.1% of controls had all four forms of advance directives surveyed in this study, while 18.0% of caregivers, 14.0% of patients with PD and 20.4% of patients with APD had all four forms of advance directives. There were significant between group differences for all forms of advance directives assessed.

Table 4 shows the relative risk (RR) for use of different forms of advance directives compared to controls. Participants with APD were 1.66 times more likely and caregivers were 1.33 times more likely to have a living will. Participants with PD and APD were 4.08 and 4.81 times more likely to report durable power of attorney. Participants with PD were 2.08 times more likely and participants with APD were 2.47

Table 1
Demographic, social and clinical features of participants.

	Controls n = 50	PD n = 50	APD n = 49	Caregivers n = 50	Overall n = 199	p-value
Age (mean ± SD)[e]	61.3 ± 8.4[b,c,d]	67.3 ± 8.6[a]	71.0 ± 9.9[a]	66.7 ± 10.4[a]	66.6 ± 9.9	< **0.001**
Sex N (%)						
Female	26 (57.8)	19 (38.8)[d]	17 (37.0)[d]	34 (69.4)[b,c]	96 (50.8)	**0.003**
Male	19 (42.4)	30 (61.2)	29 (63.0)	15 (30.6)	93 (49.2)	
Education (years) (mean ± SD)[f]	15.42 ± 2.23	13.87 ± 3.08	15.00 ± 3.00	14.41 ± 3.19	14.67 ± 2.96	0.064
Marital N (%)[g]						
Single	3 (6.7)	2 (4.1)	2 (4.3)	0 (0.0)	7 (3.7)	0.106
Separate/divorced	2 (4.4)	6 (12.2)	1 (2.2)	1 (2.0)	10 (5.3)	
Married	35 (77.8)	37 (75.5)	41 (89.1)	47 (95.0)	160 (84.7)	
Widowed	5 (11.1)	4 (8.2)	2 (4.3)	1 (2.0)	12 (6.3)	
Children (mean ± SD)[h]	0.24 ± 0.88	0.52 ± 1.25	0.28 ± 0.81	0.45 ± 1.34	0.37 ± 1.09	0.582
Religiousness N (%)[g]						
Religious N	35 (77.8)	46 (95.8)	43 (93.5)	47 (95.9)	171 (91.0)	**0.005**
Non-religious	10 (22.2)	2 (4.2)	3 (6.5)	2 (4.1)	17 (9.0)	
Income N (%)[i]						
≤ 75,000k	36 (81.8)	33 (70.2)[d]	31 (91.2)	44 (97.8)[b]	144 (84.7)	**0.002**
≥ 75,000k	8 (18.2)	14 (29.8)	3 (8.8)	1 (2.2)	26 (15.3)	
MMSE (mean ± SD)[j]	29.27 ± 1.23[c]	28.51 ± 1.87[c]	27.07 ± 2.08[a,b,d]	29.07 ± 1.40[c]	28.48 ± 1.88	< **0.001**

PD = Parkinson disease; APD = Atypical Parkinsonian Disorders; MMSE = Mini Mental Status Exam, **bold** = significant difference; Significance is determined by Fisher's Exact test for categorical variables and ANOVA for continuous variables.
[a] = Significant differences from the control group.
[b] Significant differences from the PD group.
[c] Significant differences from the APD group.
[d] Significant differences from caregiver group.
[e] = 3 missing values.
[f] = 4 missing values.
[g] = 2 missing values.
[h] = 7 missing values.
[i] = 15 missing values.
[j] = 9 missing values.

Table 2
Comparison of disease duration and severity in PD and APD.

	PD n = 50	APD n = 49	Overall	p-value
Disease duration	7.28 ± 4.96	4.14 ± 2.39[a]	5.76 ± 4.22	**0.002**
Hoehn & Yahr	2.35 ± 0.88	3.17 ± 0.72[b]	2.73 ± 0.90	< **0.001**
Schwab & England	81.80 ± 11.73	70.70 ± 16.68[c]	76.67 ± 15.20	< **0.001**
UPDRS part I	1.45 ± 1.48	2.72 ± 1.97[d]	1.98 ± 1.80	**0.002**
UPDRS part II	7.77 ± 5.30	14.69 ± 7.30[e]	10.62 ± 7.04	< **0.001**
UPDRS part III	16.92 ± 10.45	24.25 ± 9.73[f]	19.89 ± 10.73	**0.002**
UPDRS total	26.14 ± 14.98	38.93 ± 19.11[d]	31.49 ± 17.89	< **0.001**

PD = Parkinson disease; APD = Atypical Parkinsonian Disorders, **bold** = significant difference; Significance is determined by Mann-Whitney *U* test.
[a] = 2 missing values.
[b] = 5 missing values.
[c] = 6 missing values.
[d] = 13 missing values.
[e] = 14 missing values.
[f] = 15 missing values.

times more likely to report a durable power of attorney for healthcare. Caregivers were 2.21 times more likely to use this form of advance directive. The APD group was 1.61 times more likely and the caregiver group was 1.43 times more likely to have at least one form of advance directive.

We also compared rates of advance directives between participants with PD and participants with APD. The two groups did not differ in rates of any of the four forms of advance planning. However, participants with APD were 1.28 times more likely to have at least one form of advance directive compared to controls (RR = 1.28, 95%CI: 1.03, 1.65, p = 0.036) (data not shown).

Analysis of variables from Table 1 showed that lower MMSE and male sex were associated with durable power of attorney (RR = 0.923, 95%CI: 0.85–0.99, p = 0.041 and RR = 1.92, 95%CI: 1.3–30, 2.84, p = 0.001, respectively). More years of education was associated medical orders (RR = 1.13, 95%CI: 1.03–1.24, p = 0.008) and older age was associated with the living will (RR = 1.01, 95%CI: 1.01–1.02, p < 0.001). No demographic variables were found to influence the likelihood of a durable power of attorney for healthcare (data not shown).

Disease severity in both PD and APD participants combined was not associated with the living will, durable power of attorney or durable power of attorney for healthcare. Higher H&Y score (RR = 1.52, 95%CI: 1.01–2.29, p = 0.044), lower Schwab & England score (RR = 0.97, 95%CI: 0.96–0.98, p < 0.001) and higher UPDRS part II score (RR = 1.09, 95%CI: 1.03–1.15, p = 0.004) were associated with the medical order.

We also determined the relationship between disease severity and advance directives in participants with PD and APD separately. For participants with PD, higher H&Y score (RR-1.79, 95%CI: 1.09–2.93, p = 0.021) and higher UPDRS part II score (RR = 1.13, 95%CI: 1.08–1.19, p < 0.001) were associated with medical orders. In participants with APD, longer duration of disease was associated with the living will (RR = 1.03, 95%CI: 1.01–1.05, p = 0.003), lower Schwab & England score was associated with medical orders (RR = 0.97, 95%CI: 0.96–0.98, p < 0.001), lower H&Y score was associated with durable power of attorney (RR = 0.68, 95%CI 0.56–0.83, p < 0.001), lower H &Y (RR = 0.61, 95%CI: 0.49–0.78, p < 0.001), lower UPDRS part III score (RR = 0.96, 95%CI 0.94–0.98, p < 0.001) and lower total UPDRS score (RR = 0.98, 95%CI: 0.98–0.99, p < 0.001) were associated with durable power of attorney for health care (data not shown).

4. Discussion

Currently, there is insufficient research about end of life planning in patients with parkinsonism. This is the first study to address end of life planning by patients with typical and atypical parkinsonian disorders

Table 3
Summary of the four groups responses to having different forms of advance medical planning.

	Controls	PD	APD	Caregivers	Overall	χ^2	p-value
The living Will							
No	26 (52.0%)	18 (36.0%)	10 (20.4%)	12 (24.0%)	66 (33.2%)		**0.003**
Yes	24 (48.0%)	35 (64.0%)	39 (79.6%)[a]	38 (76.0%)[a]	133 (66.8%)	13.7	
Durable Power of Attorney							
No	43 (86.0%)	21 (42.9.0%)	16 (32.7%)	38 (76.0%)	118 (59.6%)		**< 0.001**
Yes	7 (14.0%)	28 (57.1%)[a]	33 (67.3%)[a]	12 (24.0%)	80 (40.4%)	40.5	
Durable Power of Attorney for Healthcare[b]							
No	37 (75.5%)	24 (49.0%)	19 (39.6%)	23 (46.0%)	103 (52.6%)		**0.002**
Yes	12 (24.5%)	25 (51.0%)[a]	29 (60.4%)[a]	27 (54.0%)[a]	93 (47.4%)	14.7	
Medical Order[b]							
No	37 (75.5%)	41 (85.4%)	38 (77.6%)	26 (52.0%)	142 (72.4%)		**0.002**
Yes	12 (24.5%)	7 (14.6%)	11 (22.4%)	24 (48.0%)[a]	54 (27.6%)	15.4	
Any AD[c]							
No	23 (46.9%)	16 (33.3%)	7 (14.6%)	12 (24.0%)	58 (29.7%)		**0.004**
Yes	26 (53.1%)	32 (66.7%)	41 (85.4%)	38 (76.0%)[a]	137 (70.3%)	13.3	

PD = Parkinson disease; APD = Atypical Parkinsonian Disorders; **bold** = significant difference.
Count (percentage) is reported for each survey question. A chi-squared test is used to test the association between four groups and responses.
[a] = Rates of utilization of advance directives that significantly differ from controls.
[b] = 3 missing values.
[c] = 4 missing values.

Table 4
Relative risks by group in advance medical planning using controls as a comparison group.

	Relative risk	95% CI	Adjusted p-value
The living will			
PD	1.33	(0.940, 1.945)	0.113
APD	**1.66**	(1.23, 2.36)	**0.006**
Caregivers	**1.58**	(1.16, 2.26)	**0.012**
Durable Power of Attorney			
PD	**4.08**	(2.12, 9.38)	**< 0.001**
APD	**4.81**	(2.56, 10.95)	**< 0.001**
Caregivers	1.71	(0.75, 4.28)	0.212
Durable Power of Attorney for Healthcare			
PD	**2.08**	(1.22, 3.85)	**0.011**
APD	**2.47**	(1.49, 4.49)	**0.003**
Caregivers	**2.21**	(1.31, 4.05)	**0.010**
Medical Order			
PD	0.56	(0.24, 1.35)	0.456
APD	0.92	(0.44, 1.90)	0.812
Caregivers	**1.96**	(1.14, 3.64)	0.062
Any AD			
PD	1.26	(0.91, 1.78)	0.176
APD	**1.61**	(1.23, 2.22)	**0.004**
Caregivers	**1.43**	(1.07, 2.00)	**0.043**

PD = Parkinson disease; APD = Atypical Parkinsonian Disorders; **bold** = significant difference.
Comparison of likelihood of using different forms of advance directives between different groups using healthy controls as the reference group.

and their caregivers. We hypothesized that living with a chronic progressive parkinsonian disorder or being exposed to one as a caregiver, affects how individuals utilize different forms of end of life planning. We found that participants with PD and APD and their caregivers were more likely to have certain forms of advance planning compared to controls. Moreover, participants with APD, a more rapidly progressive disorder that has a typical life expectancy 5–8 years from symptom onset [18–21], were more likely than participants with PD (which does not progress as rapidly as APD) [16,19], to have advance directives and were more likely to have multiple forms.

Participants with PD were approximately four times more likely to have a durable power of attorney and two times more likely to have durable power of attorney for healthcare. Participants with APD, like participants with PD, were almost five times more likely to have a durable power of attorney and two times more likely to have durable power of attorney for healthcare. However, unlike the PD group, they were almost two times more likely to have a living will.

Higher rates among patients with parkinsonian disorders was not seen in all four forms of advanced directives analyzed in this study. Participants with PD had the same rates of the living will and medical order as controls. Decisions about specific end of life issues are less relevant in a disease with longer survival, and longer time until severe symptoms develop, which may explain why PD participants did not have higher rates.

Caregivers were found to have higher rates of living wills and durable power of attorney for healthcare than controls. It is possible that exposure to end of life care may affect how caregivers view end of life planning. By witnessing difficulties that arise during this time, they may be more motivated to use advance care planning.

Disease severity is also a factor associated with likelihood of having certain advance directives. Indicators of increased disease severity for both groups combined (lower Schwab & England and higher H&Y and UPDRS part II scores), were associated with medical orders. In participants with PD, H&Y and UPDRS part II scores were associated with medical orders. In those with APD, medical orders were associated with lower Schwab & England scores. Additionally, in the APD group, longer disease duration was associated with the living will. However, in the APD group lower scores in H&Y, UPDRS part III and UPDRS total, indicating less severe disease, were associated with durable power of attorney for healthcare. Therefore, increased disease severity appears to be associated with medical orders and the living will, while less severe disease was associated with having a durable power of attorney for healthcare.

This study has several limitations. There were significant differences between the participant groups that were related to age, sex, religiousness, income level and MMSE. These differences could potentially be confounding for the use of advance planning. In our multivariable analysis education was associated with increased likelihood of having a medical order, male sex and MMSE score were associated with power of attorney and older age was associated with the likelihood of a living will. Previous studies have shown that older age and higher education level increase the likelihood of having an advance directive [22]. The other demographic variables assessed were not associated with the use of advance directives and there were no between-group differences in education. Although age, religiousness, marital status and income did differ, they were not associated with having an advance directive. The difference in MMSE scores was expected given the early appearance of executive dysfunction in patients with APD [23]. This supports the hypothesis that disease severity is associated with advance

directives, since more severe cognitive impairment was also associated with having a power of attorney.

Another limitation is that the study was conducted in 2008–2010. A previous meta-analysis of advance directives from 2011 to 2016 showed that the proportion of advance directives has been similar throughout this time period [3]. However, it is unclear if these results are applicable to the current population. Another important limitation is that we are missing between 6 and 30% of the values for disease severity metrics in the APD population, which may have biased results. However, this would have likely underestimated the severity of these participants, which may have missed the effects of disease severity on advance directives.

This is the first study to investigate the rates of end of life planning in patients with PD and APD as well as their caregivers. Our results suggest that health status and disease exposure may be predictors of whether or not a person utilizes advance planning. Interestingly, it appears that exposure to a disease is more important than a variety of demographic factors. Disease severity and progression may also be important factors for the use of certain forms of advance planning.

Despite finding higher rates of advance planning than previously reported [3], there is still room to increase the rates of advance planning utilization. End of life planning is a critical discussion that should be addressed frequently, as desires might change as disease progresses.

Although PD and APD participants are using advance directives, it remains to be determined if participants share this information with their physicians or with their family [24]. Data from the National Survey by the Conversation Project in 2013 showed that more than 90% of people thought it was important to discuss their wishes for end of life care with loved ones, but only 30% actually discussed these preferences [25]. Medical technological advances allow for longer survival in end of life settings. However, procedures are often invasive and do not always improve quality of life. Despite physicians' goal to maximize benefit and minimize harm for patients, they must also respect their patients' wishes. Physicians can play a key role in facilitating discussions with patients to make sure these documents are shared with family and other providers.

This study showed that individuals with PD and APD were more likely to utilize advance planning than healthy controls. We found that some demographic variables and measures of disease severity influenced the utilization of certain forms of advance planning. We also found that caregivers of patients with parkinsonian disorders were more likely to use advance planning.

Author contributions

DG- Manuscript: writing of the first draft and manuscript review and critique.

JP- Statistical Analysis: design and execution.

RMS – Research project: conception, organization, execution and manuscript review and critique.

IL- Research project: conception, design, execution, manuscript review and critique.

Conflicts of interest

No conflicts of interest to disclose.

Financial disclosures

DG-none.

JP-none.

RMS- Dr. Simões is currently a consultant for BIAL – PORTELA & C.[a], S.A. and has been a consultant for Merck S.A, Biogen, Novartis, Zambon.

IL- Dr. Litvan was a member of the Biogen Scientific Committee and a consultant for Acorda. Her research is supported by the National Institutes of Health grants: 5P50 AG005131-31, 5T35HL007491, 1U01NS086659 and 1U54NS092089-01; Parkinson Study Group, Michael J. Fox Foundation, International Parkinson and Movement Disorder Society, Parkinson Foundation, AVID Pharmaceuticals, Abbvie and Biogen. She receives salary from the University of California, San Diego and as Chief Editor of Frontiers in Neurology.

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