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Aggression Towards Caregivers in Parkinson's Disease and Related Disorders: A Mixed Methods Study

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ABSTRACT: Background: Aggression is one manifestation of behavioral disturbances in neurodegenerative disease with emerging literature suggesting a high prevalence in Parkinson's disease and related disorders (PDRD).

Objectives: Our aim was to describe characteristics, associated factors, and consequences of aggression towards caregivers in PDRD.

Methods: This is a convergent mixed methods study, leveraging data from 296 PDRD patient-caregiver dyads in a clinical trial of palliative care and semi-structured interviews with a subgroup of 14 caregivers who reported aggression. The primary outcome was baseline caregiver-reported aggression. Using multivariate linear regression, baseline dyad characteristics (eg, measures of disease, psychosocial issues, caregiver strain) were examined to identify factors associated with aggression. Thematic analysis of interviews was used to augment these findings.

Results: Associated variables included disease duration ($r = 0.15, P < 0.05$), patient grief ($r = 0.22, P < 0.001$), symptom burden ($r = 0.18, r < 0.01$), resistance to care ($r = 0.40, P < 0.01$), caregivers' depression ($r = 0.16, P < 0.05$), and caregiving burden ($r = 0.34, P < 0.001$). We identified five themes: (1) Aggressive behaviors range from verbal abuse to threats of physical violence; (2) Caregivers believe that aggressive behaviors result from the difficulty patients experience in coping with disease progression and related losses; (3) Caregivers' stress and mental health are worsened by aggressive behaviors; (4) Aggressive behaviors negatively affect patient-caregiver relationships; (5) Caregivers are ill-prepared to manage aggressive behaviors and cope with the consequences on their own.

Conclusions: Aggression in PDRD is driven by diverse factors (eg, grief, fluctuations in cognition) with serious consequences for caregivers. Neurologists and movement specialists should consider screening for aggression while prioritizing caregiver education and wellbeing.

Caregivers of people living with Parkinson's disease and related disorders (PDRD) can experience significant caregiving strain.¹⁻³

Behavioral disturbances in PDRD represent one major driver of caregiver burden, while also increasing the risk of hospitalization,

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institutionalization, and mortality for patients.^{4–6} Behavioral changes in PDRD can occur independently of dementia, with the development of behavioral impairments in Parkinson's disease being a determinant for future risk of dementia.⁷

Aggression, including physical harm, verbal abuse, or unwanted sexual advances towards others, is well-documented in Alzheimer's disease (AD) but less studied in other neurodegenerative illnesses.^{8,9} Emerging research suggests the prevalence of aggression in PDRD is comparable to AD.^{8–11} Of 170 patient–caregiver dyads, physical aggression was reported by 18.2% of caregivers.¹¹ Previous studies utilizing the perspectives of caregivers in AD and non-PDRD dementia have adopted the Antecedent–Behavior–Consequence (ABC) framework for examining problematic behaviors.^{12,13} This framework is based on how individuals experience specific situations and has the benefit of leveraging eyewitness (i.e., caregiver) observations to provide a complete description of these behaviors.^{13,14}

Examining aggression by incorporating the caregiver perspective is directly relevant to movement disorder specialists as they work with caregivers to manage behavioral disturbances and help them cope with the evolving nature of caregiving strain.¹⁵ Existing literature lacks descriptions of aggression towards caregivers in PDRD and there is a dearth of research which examines the impact on caregivers. Quantitative analyses alone do not capture the caregivers' experience nor the relationships between associated factors and their consequences. Incorporating caregivers' perspectives is critical to overcoming these limitations and provides a contextual understanding of real-life experiences and insight into patients' behaviors and environment.¹⁶ A mixed methods approach in a community-based cohort can provide a comprehensive description of aggression in PDRD. This study's aim is to describe the characteristics, associated factors, and consequences of aggression towards caregivers in PDRD using a mixed methods approach.

Methods

We conducted a descriptive mixed methods study utilizing a convergent study design. This approach allows us to examine both data sources for the purposes of providing a comprehensive description of aggression in PDRD.¹⁷ The quantitative component leveraged secondary analyses of data from a recent clinical trial of palliative care for PDRD. The qualitative component comprised semi-structured interviews with a subgroup of caregivers who reported aggression during the trial. Quantitative and qualitative data were collected separately with merging and triangulation occurring at the analysis and reporting stages.¹⁷ Results were triangulated through a team-based review of quantitative correlates categorically linked to the ABC framework and the identification of themes.¹² Final interpretations were reached through a comparison of results, recognizing any corroboration or divergence.

Study Participants

Quantitative Patient–Caregiver Dyad Sample

A total 592 participants (296 patients and 296 caregivers) were enrolled as dyads in the parent clinical trial of integrated, outpatient palliative care for PDRD versus routine neurologic care. Participants were recruited from community-based, outpatient neurology practices in Colorado, California and Wyoming and were referred by the patient's primary neurologist. Eligibility for enrollment included English-speaking fluency, age ≥ 40 years, PDRD diagnosis (idiopathic Parkinson's disease, dementia with Lewy bodies [DLB], progressive supranuclear palsy, multiple systems atrophy, or vascular parkinsonism), and moderate to high palliative care needs identified by the Brief Needs Assessment Tool (BNAT), a modified version of the palliative care needs assessment tool used in studies of palliative care for PD.^{18,19} There are no items relevant to aggression on the BNAT. Caregivers were identified either by either patients' response to the question "Could you please tell us the one person who helps you the most with your PD outside of clinic?" or caregiver self-referral.

Caregiver Participant Sample for Semi-Structured Interviews

Caregivers who experienced aggression were identified by their responses to two questions: (1) "Do you feel that your relative is physically aggressive towards you or others?"; (2) "Do you feel that your relative is sexually aggressive towards you or others?" Responses ranged from "never," "rarely," "sometimes," "quite frequently," to "nearly always." Caregivers responded to these questions privately and their responses were not shared with patients. To improve maximum variation in the sample, other than those caregivers who responded "never," all others were considered eligible. A total of 16 potential participants were approached through purposeful sampling and on a rolling basis with a total of 14 consenting to interviews prior to data saturation. All interviewees were remunerated with a \$25 gift card and were associated with the University of Colorado study site.

Data Collection Procedures

Quantitative and qualitative data collection were completed separately. Quantitative data collection for all patients and caregivers occurred after enrollment at baseline and every 3 months over 12 months between March 1, 2017 and December 31, 2020.

Qualitative data collection was completed over a 4-month period (March 1, 2021–July 31, 2021) after the last quantitative data collection timepoint. One-time individual semi-structured telephone interviews with caregiver participants were conducted by author Z.A.M., a behavioral neurologist with experience treating patients with PDRD. Interviews lasted on average 34.3 minutes (range = 15.9–60.5 minutes) and were professionally transcribed and de-identified. Data were managed using ATLAS.

ti qualitative data analysis software, Version 9.1.1, ATLAS.ti Scientific Software Development GmbH, Berlin, Germ.

Measures

Patient and Caregiver Quantitative Variables and Measures

Patient variables included demographics like age, sex, race, ethnicity, education, PDRD primary diagnosis, annual household income, disease duration, the presence of dementia, and medication use. Functional status was measured using the Palliative Performance Scale (PPS).²⁰ Other patient-reported outcomes included quality of life, using the Quality of Life in Alzheimer's Disease scale (QOL-AD) and McGill Quality of Life Questionnaire (McGill QOL),^{21,22} patient mood with the Hospital Anxiety and Depression Scale (HADS),²³ and grief, measured by the Prolonged Grief Questionnaire (PG-12).^{23,24} Additional patient variables relevant to disease included motor symptom severity, measured by the Unified Parkinson's Disease Rating Scale Part III Motor score (UPDRS-III),²⁵ and cognitive impairment, measured by the Montreal Cognitive Assessment (MOCA).²⁶ The Edmonton Symptom Assessment System Revised: Parkinson Disease (ESAS-PD) assessed motor and non-motor symptom burden, including pain, fatigue, gastrointestinal symptoms, depression, anxiety, wellbeing, shortness of breath, stiffness, dysphagia, confusion, apathy, and hallucinations.²⁷

Caregiver variables included age, sex, race, ethnicity, education, duration of caregiving, relationship and living situation relative to the patient. Other caregiver-reported outcomes included caregiver burden, measured by the Zarit Burden Interview (ZBI) and Modified Caregiver Strain Index (MCSI),^{28,29} caregiver-perceived patient quality of life, measured by the Quality of Life in Alzheimer's Disease-Caregiver Reported scale (QOL-AD Caregiver),²¹ and caregiver depression and anxiety, assessed using the HADS.²³ Additional surveys were administered to caregivers relevant to patients' recent healthcare utilization and patient-caregiver dynamic (eg, resistance to care).

Caregiver Interview Guide

The ABC model helped frame the interview guide (Appendix S1), addressing the following domains: (a) antecedents or risk factors which lead to aggression; (b) observations of the characteristics of aggressive behaviors; (c) consequences of aggression; (d) strategies for managing aggression. Development and revision of the guide was accomplished through input from a scientific advisory committee including experts in qualitative and mixed methods research, movement disorders, palliative medicine, geriatric psychiatry, and a caregiver representative. Based on their recommendations, the guide was modified with a focus on rapport building and creating a safe space for caregivers to speak openly.

Analyses

Quantitative Analysis

Descriptive statistics were used for patient and caregiver variables and measures to estimate frequencies, means, and standard deviations. Reported aggression was defined by dichotomizing the aggression questionnaire items into "never" or any other answer aside from "never." Multivariate linear regression models were used to examine associations between baseline aggression and baseline participant characteristics, adjusting for patient age, sex, study site, and primary diagnosis. We used a level of statistical significance set at $\alpha = 0.05$. Statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, North Carolina, US).

Qualitative Analysis

Thematic analysis of data was completed using a team-based, deductive and inductive approach. All aspects of the qualitative analysis were overseen by co-authors and qualitative methodologists S.S. and R.A. The ABC model guided development of a codebook addressing antecedents (defined as symptoms, situations, or events perceived by caregivers to be triggers of precede aggressive behaviors), descriptions of behaviors (defined as actions or words perceived by caregivers to be verbal, physical, or sexual aggression), and consequences (actions, events, described by caregivers to succeed aggression). Study team members (Z.A.M., S.S., R.A., M.B.) individually coded the data and routinely met to discuss any discrepancies to maintain rigor.³⁰ Data collection and analyses of interviews were completed iteratively until thematic saturation was reached.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by institutional review boards at both study sites. The parent clinical trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03076671). All participants provided consent or, if lacking capacity, provided assent with informed consent obtained from a legally authorized representative such as a medical proxy. The University of California San Diego Brief Assessment of Capacity to Consent was used to assess capacity to consent.³¹ Study personnel were available to intervene in situations where there was concern or risk for physical harm or self-harm to participants. Study personnel were available to intervene in situations where there was concern or risk for physical harm or self-harm.

Data Sharing

Any and all data that support the findings of this study are available from the corresponding author, Z.A.M., upon request.

TABLE 1 Baseline participant characteristics

Variables	Patients (N = 296) No. (%)	Caregivers (N = 296) No. (%)
Age, mean (SD)	74.5 (8.5)	67.6 (11.4)
Sex, male	198 (66.9)	69 (23.4)
Race		
Caucasian	283 (95.6)	278 (94.9)
African American	2 (0.7)	0 (0.0)
Asian	6 (2.0)	8 (2.7)
Native American	2 (0.7)	3 (1.0)
Other	2 (0.7)	4 (1.4)
Ethnicity, Hispanic/Latino (yes)	12 (4.1)	15 (5.0)
Education		
Less than high school diploma	12 (4.1)	6 (2.0)
High school diploma	51 (17.3)	41 (13.9)
Some college	52 (17.7)	69 (23.5)
Associate's or Bachelor's degree	101 (34.4)	103 (35.0)
Post-graduate degree	78 (26.5)	75 (25.5)
Primary diagnosis		
Idiopathic Parkinson's disease	197 (66.6)	—
Dementia with Lewy bodies	35 (11.8)	—
Progressive supranuclear palsy	21 (7.1)	—
Multiple systems atrophy	14 (4.7)	—
Corticobasal degeneration, probable	13 (4.4)	—
Vascular Parkinsonism	3 (1.0)	—
Other parkinsonism	13 (4.4)	—
Annual household income		
≤\$29,999	45 (16.9)	31 (11.9)
\$30,000–59,999	72 (27.0)	67 (25.7)
\$60,000–99,999	76 (28.5)	80 (30.7)
\$100,000+	74 (27.7)	83 (31.8)
Disease duration, mean years (SD)	9.0 (7.6)	—
Duration of caregiving, mean (SD)	—	5.0 (5.1)
Dementia present, yes	149 (50.3)	—

*(Continues)***TABLE 1** Continued

Variables	Patients (N = 296) No. (%)	Caregivers (N = 296) No. (%)
UPDRS-3 score, mean (SD)	26.7 (11.3)	—
MOCA score, mean (SD)	21.2 (6.1)	—
QOL-AD score, mean (SD)	35.1 (6.4)	—
ZBI, mean (SD)	—	16.4 (8.6)
HADS-Anxiety score, mean (SD)	7.5 (4.0)	6.7 (3.9)
HADS-Depression, score mean (SD)	7.8 (3.9)	4.5 (3.5)
Patient-caregiver relationship		
Wife	—	172 (58.3)
Husband	—	55 (18.6)
Son	—	12 (4.1)
Daughter	—	34 (11.5)
Daughter-in-law	—	2 (0.7)
Paid caregiver	—	3 (1.0)
Other	—	17 (5.8)
Patient-caregiver share a household, yes	—	244 (82.4)

Abbreviations: SD, standard deviation; MOCA, Montreal Cognitive Assessment; UPDRS-3, Unified Parkinson's Disease Rating Scale-Motor section; HADS, Hospital Anxiety and Depression Scale; QOL-AD, Quality of Life in Alzheimer's Disease scale; PDQ-39, Parkinson's Disease Questionnaire 39; PDRD, Parkinson's disease and related disorders; ZBI, Zarit Burden Interview.

Result

Clinical Trial Participant Characteristics

Caregivers were disproportionately women (76.6%), highly educated (50% college educated), married to the patient (76.9%), and shared a household (82.4%). Average disease duration was 9.0 (SD = 7.6) years, and average duration of caregiving was 5.0 (SD = 5.1) years. At baseline, 50.3% of patients had dementia, and 33.4% had an atypical parkinsonian diagnosis. In total, 22.3% of caregivers (N = 66) reported experiencing either type of aggression at baseline. Physical aggression was reported in 17.6% of caregivers (N = 52) and sexual aggression in 8.8% (N = 26). Table 1 outlines the characteristics of patient-caregiver dyads enrolled in the study.

Characteristics of Qualitative Interview Caregiver Participants

Fourteen caregivers (21.2% of caregivers reporting aggression) participated in semi-structured interviews. Participants were

TABLE 2 Baseline dyad characteristics for interviewed caregivers

Variables	Patients (N = 14) No. (%)	Caregivers (N = 14) No. (%)
Age, mean (SD)	72.9 (9.5)	67.3 (4.1)
Sex, male	10 (71.4)	4 (28.6)
Race/ethnicity		
Caucasian	13 (92.9)	13 (92.9)
American Native/Indian	1 (7.1)	0 (0)
Unknown	0 (0.0)	1 (7.1)
Ethnicity, Hispanic/Latino (yes)	1 (7.7)	2 (15.4)
Education		
Less than high school diploma	0 (0.0)	0 (0.0)
High school diploma	1 (7.1)	2 (14.3)
Some college	2 (14.3)	4 (28.8)
Associate's or Bachelor's degree	7 (50.0)	4 (28.8)
Post-graduate degree	4 (28.6)	4 (28.8)
Primary diagnosis		
Idiopathic Parkinson's disease	11 (78.6)	–
Atypical parkinsonian condition	3 (21.4)	–
Annual household income		
\$0–29,999	2 (14.3)	2 (16.7)
\$30,000–59,999	5 (35.7)	4 (33.3)
\$60,000–99,999	4 (28.6)	4 (33.3)
\$100,000+	2 (21.4)	2 (16.7)
Disease duration, mean years (SD)	11.4 (6.3)	–
Duration of caregiving, mean (SD)	–	6.6 (5.7)
Dementia present, yes	10 (71.4)	–
UPDRS-III score, mean (SD)	29.8 (12.0)	–
MOCA score, mean (SD)	19.8 (5.8)	–
QOL-AD score, mean (SD)	34.2 (6.2)	–
ZBI, mean (SD)	–	17.4 (8.3)
HADS-Anxiety score, mean (SD)	6.2 (3.8)	7.3 (3.8)
HADS-Depression, score mean (SD)	7.6 (4.3)	5.0 (4.1)
Patient–caregiver relationship		
Wife	–	8 (57.1)

(Continues)

TABLE 2 Continued

Variables	Patients (N = 14) No. (%)	Caregivers (N = 14) No. (%)
Husband	–	2 (14.3)
Son	–	1 (7.1)
Daughter	–	1 (7.1)
Paid caregiver	–	0 (0.0)
Other	–	2 (14.3)
Patient–caregiver share a household, yes	–	12 (85.7)

Abbreviations: SD, standard deviation; MOCA, Montreal Cognitive Assessment; UPDRS-III, Unified Parkinson's Disease Rating Scale-Motor section; HADS, Hospital Anxiety and Depression Scale; QOL-AD, Quality of Life in Alzheimer's Disease scale; ZBI, Zarit Burden Interview.

predominantly spouses (69.2%; N = 9) and shared a residence with patients (85.7%; N = 12). Table 2 provides characteristics of interviewed caregiver participants and the patients they cared for.

Quantitative Results

Several patient variables were associated with baseline aggression (Fig. 1A). Lower annual household income, longer disease duration, greater motor symptom severity (UPDRS-III), grief (PG-12), reduced functional status (PPS), and lower quality of life (QOL-AD; McGill QOL) all correlated with baseline aggression. Higher resistance to care, exhibited by patients and reported by caregivers, was correlated with either type of aggression combined and physical aggression alone. Motor symptom severity (UPDRS-III) was associated with physical aggression only. Overall symptom burden, reflected in the ESAS-PD, was also associated with greater aggression (Fig. 1B). This included motor (stiffness) and non-motor symptoms (nausea, depression, anxiety, wellbeing, stiffness, confusion, hallucinations). Paranoia reflect in the ESAS-PD was associated with sexual aggression alone.

There was no association between baseline aggression and primary diagnosis (unadjusted $r = -0.001 [-0.11-0.11]$, $P = 0.98$), the presence of dementia ($r = 0.08 [-0.04-0.19]$, $P = 0.18$), overall cognitive impairment (MOCA; $r = -0.07 [-0.19-0.05]$, $P = 0.26$), nor total levodopa daily dose ($r = 0.04 [-0.08-0.15]$, $P = 0.52$).

We identified several caregiver variables associated with baseline aggression (Fig. 1C) Overall caregiver burden (ZBI; MCSI), caregiver perceptions of patients' quality of life (QOL-AD Caregiver), and caregiver depression (HADS) were associated with greater baseline aggression. Caregiver anxiety (HADS) was solely associated with baseline sexual aggression.

Qualitative Results

We identified five themes exemplifying aggressive behaviors and their effect on caregivers. Table 3 describes each theme (T) with illustrative quotations (Q).

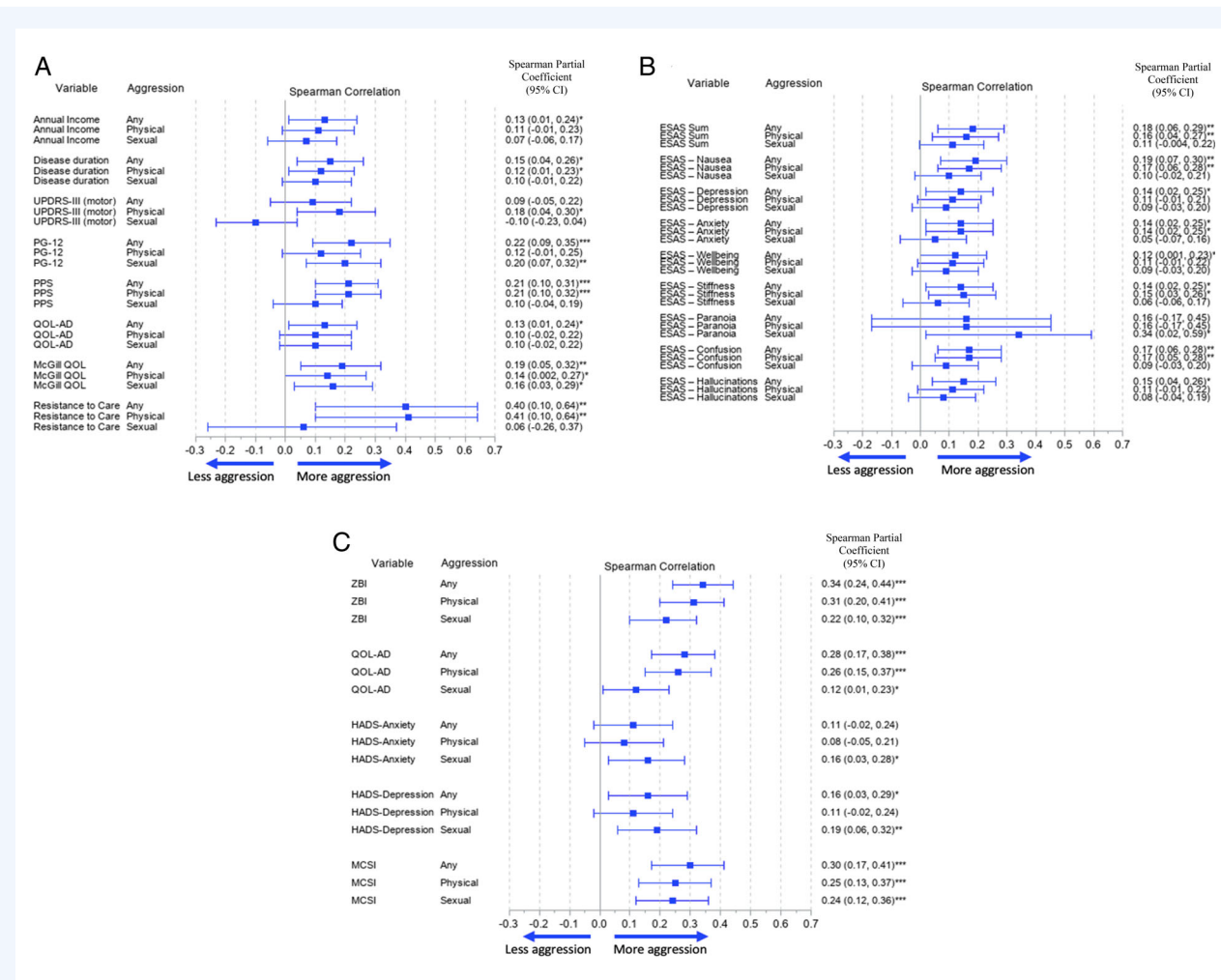


FIG. 1. Patient and caregiver variables associated with baseline caregiver-reported aggression. (A) Patient variables; (B) Edmonton symptom assessment system scale for Parkinson’s disease summary score and subitems. (C) Caregiver variables. Note: Partial coefficients were normalized for annual income, QOL-AD, McGill QOL to illustrate associations with baseline aggression. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Abbreviations: ESAS-PD, Edmonton Symptom Assessment System Scale for PD; ESAS-PD Sum, Edmonton Symptom Assessment System Scale for PD Summary score; HADS, Hospital Anxiety and Depression Scale; PG-12, Prolonged Grief Questionnaire (12-item); UPDRS-3, Unified Parkinson Disease Rating Scale—Motor section; PPS, Palliative Performance Scale; MCSI, Modified Caregiver Strain Index; QOL-AD, Quality of Life in Alzheimer’s Disease scale; McGill QOL, McGill Quality of Life scale; ZBI, Zarit Burden Interview.

Theme 1: Aggressive Behaviors Range from Verbal Abuse to Threats of Physical Violence

Caregivers’ descriptions of aggressive behaviors depicted a range from “passive aggression” to threats of physical aggression. The threat of physical harm towards caregivers was equated with physical aggression and explains why caregivers indicated this as a response in the caregiver assessment questionnaire. While none of the participants described sexually aggressive behaviors, one caregiver reported the patient made sexually inappropriate conversations which were uncharacteristic for him. These were described with embarrassment (eg, laughing uneasily), frustration (eg, stating not knowing what to do) and attempts to be supportive (eg, rationalizing the behaviors). Pre-morbid “passive-aggressive” tendencies among patients reportedly worsened over the disease course to

where one wife noted “he gets angry...or he gets pouty...very hard to handle that one.” Anger manifested by changes in the patients’ demeanor (Table 3, T1-Q1) and also in actions such as “throwing things” (Table 3, T1-Q2). Verbal aggression was most common manifestation and, while direct physical harm was not reported, the threat of injury or violence was apparent (Table 3, T1-Q3, Q4).

Theme 2: Caregivers Believe that Aggressive Behaviors Result from the Difficulty Patients Experience in Coping with Disease Progression and Related Losses

Aggression towards others was perceived as a manifestation of the frustrations from progressive loss of ability and overall

TABLE 3 Themes (T) and illustrative quotes (Q)

Themes (T)	Illustrative quotes (Q) (relationship to patient, interview participant #)
T1. Aggressive behaviors range from verbal abuse to threats of physical violence	<ol style="list-style-type: none"> 1. "He does get real shaky and jittery and real flushed, real anxious." (Wife, Participant #13) 2. "I heard him throwing things and went into the bedroom and he was just...he wasn't supposed to be up by himself and he was up throwing things everywhere, like clothes and stuff like that, nothing that would hurt anything, just this, you know, like his shoes and stuff like that which were kind of heavy (laughing)." (Wife, Participant #5) 3. "And he was going to strike me if he could but that wasn't to happen." (Wife, Participant #4) 4. "I mean it hurts for a minute, you know, if he kind of happens to hit you in the glasses or, you know, something like that, but nothing real major." (Wife, Participant #12)
T2. Caregivers believe that aggressive behaviors result from the difficulty patients experience in coping with disease progression and related losses	<ol style="list-style-type: none"> 1. "What really made him mad was the fact that he could not be independent." (Wife, Participant #5) 2. "...like his mind would be okay one minute and the next minute he'd be really frustrated or scared, or I do not know exactly how to even explain that because you'd just have to be there to see how he was, you know?" (Wife, Participant #5) 3. "...you reach a point when there are just some things you just cannot do anymore...I think it just all builds up when he knows he cannot do a lot of stuff." (Wife, Participant #3)
T3. Caregivers' stress and mental health are worsened by aggressive behaviors	<ol style="list-style-type: none"> 1. "...it just crushes me. It makes me sad that that's how she is..." (Daughter, Participant #7) 2. "...he started saying some things that I never heard come out of his mouth before and he said some things to me that were very cruel." (Wife, Participant #5) 3. "He did try towards the end to turn everybody against me. I really have struggled with all that...That was tough...There's still days when I will get depressed." (Wife, Participant #14) 4. "There's no question in my mind that I go through bouts of depression just, you know, because of the situation." (Husband, Participant #8) 5. "[My doctor] put me on an antidepressant...There's still days when I will get depressed and I cannot do that. There's too much that I have to do." (Wife, Participant #1)
T4. Aggressive behaviors negatively affect patient-caregiver relationships	<ol style="list-style-type: none"> 1. "I go like 'why do not you like me all of a sudden' and then I just could not worry about it. I go like, 'are you kidding me? We've been married 57 years.'" (Wife, Participant #14) 2. "I would say for me um...the lack of uh...I guess uh...another...lack of a normal relationship with another adult um...because I mean, you know, she's not the same person that she was prior to the Parkinson's." (Husband, Participant #8) 3. "It's the motor symptoms. And then I think he gets frustrated and so he um...likes to have control somewhere you know? So, like if I'm...I'm political and I like to watch the news and he does not like that. He gets really upset with me for watching the news." (Wife, Participant #1) 4. "[He will] get real aggressive when he wanted something to eat and I did not get it to him quick enough sometimes. And, like I would cook it and it only cooks so fast." (Wife, Participant #5) 5. "Because it almost, this is a horrible thing to say but it's almost like I turned from being his wife to his mother." (Wife, Participant #9) 6. "He would like, he would yell at them [grandchildren] then and he would get red in the face. He'd get right up on top of them and see [the patient] never had a temper ever." (Wife, Participant #9) 7. "We have three children and I try not to share this kind of stuff with them. It's hard for them to see their Dad anyway." (Wife, Participant #1)
T5. Caregivers are ill-prepared to manage aggressive behaviors and cope with the consequences on their own	<ol style="list-style-type: none"> 1. "I think it just all builds up when he knows he cannot do a lot of stuff." (Wife, Participant #3) 2. "...right now, it's more of a, you know, we try to put a little bit of humor with it, you know you say, 'it's time to duck and cover' (laughing)." (Husband, Participant #2) 3. "He was more aggressive the more we reacted." (Wife, Participant #13) 4. "[He] woke me up in the middle of the night screaming and he was saying 'stay away from me,' 'do not touch me,' and he was just so afraid and it was just an awful feeling in the room and he was trying to walk and wasn't walking at that time...and so I had to get behind him and coax him back to bed and at first, he was yelling at me." (Wife, Participant #14)

(Continues)

TABLE 3 Continued

Themes (T)	Illustrative quotes (Q) (relationship to patient, interview participant #)
	5. "One day like he was running out the door...he took off out the front door and...I was thinking 'what am I going to do?' if I go running after him, he's going to run more and there's no way I can catch him." (Wife, Participant #12)
	6. "He did not want me to put him to bed. He was belligerent um...he wanted to strike me." (Wife, Participant #4)
	7. "I just kind of take myself away from the situation and just let him say what he's going to say and do what he's going to do until it passes." (Wife, Participant #13)
	8. "I try to stay away from him then...and so that does not help." (Wife, Participant #1)
	9. "[I] was always worried...I took his car keys away from him. I hid those. I removed all weapons from the home because of course we had guns um...so, I removed all of that." (Wife, Participant #9)

functional status (Table 3, T2-Q1). Complex symptoms and other disease-related issues were identified as culprits such that progressive motor symptoms led to the patient getting "very frustrated when not being able to do things." More specifically fluctuations in cognition and alertness were uniquely identified and were separate from overall cognitive impairment or dementia (Table 3, T2-Q2). Caregivers felt the buildup of these frustrations often led to aggression (Table 3, T2-Q3).

Theme 3: Caregivers' Stress and Mental Health are Worsened by Aggressive Behaviors

Caregivers consequentially experienced worse mental health and increased stress and often expressed sadness and emotional distress (Table 3, T3-Q1). More specifically, the realization that these behaviors were inconsistent with the patients' premorbid personality were especially troubling to caregivers (Table 3, T3-Q2). Paranoia among patients was a source for stress. One caregiver noted her husband was consistently angry and suspicious of her and even removed her from his will. She stated tearfully "change is probably the hardest human thing to me." Sadness and stress sometimes resulted in caregivers getting depressed or needing treatment for clinical depression (Table 3, T3-Q3, Q4, Q5).

Theme 4: Aggressive Behaviors Negatively Affect Patient-Caregiver Relationships

In addition to being the target of aggressive behaviors, caregivers noted the negative impact on the spousal relationship (Table 3, T4-Q1). The patient was perceived as being a "different person" comparatively and directly due to the disease (Table 3, T4-Q2). Prior to disease onset couples may have shared a relationship based on collaboration and mutual respect. However, the disease progression, negatively impacted the relationship as patients exhibited a new desire to dominate and control their spouses (Table 3, T4-Q3). Caregivers were verbally abused by patients when the latter's needs were not fulfilled immediately (Table 3, T4-Q4). With escalations of aggressive behaviors, family relationships changed (Table 3, T4-Q5) and threats of physical

aggression directed at younger family members (eg, grandchildren) negatively also impacted family relationships (Table 3, T4-Q6). Sometimes caregivers limited interactions with their adult children to preserve relationships (Table 3, T4-Q7).

Theme 5: Caregivers are Ill-Prepared to Manage Aggressive Behaviors and Cope with the Consequences on Their Own

Caregivers struggled without adequate knowledge or strategies to effectively manage or cope with the unpredictable consequences of aggressive behaviors. One caregiver said she was only told "he had Parkinson's...but I had no idea [about] the personality changes." Left to cope on their own, they were ill-prepared and vacillated from being understanding to reacting in anger or frustration. Sometimes being sympathetic they felt the patients' frustrations were the cause for the aggression (Table 3, T5-Q1), while at other times they tried to find ways to diffuse the aggression (Table 3, T5-Q2). Eventually they reacted knowing that would only "escalate" and "trigger more" aggression (Table 3, T5-Q3). Behaviors were not only hard to manage but the consequences were unpredictable (Table 3, T5-Q4, Q5). Caregiver burden and the growing disconnect between patient expectations of care provided and care actually provided led to more instances of aggression towards the caregiver (Table 3, T5-Q6). Avoidance of interactions with patients though perceived as necessary at times, also had the potential for worsening the situation (Table 3, T5-Q7, Q8). Caregivers had to choose between living with aggression, responding to it and risking escalation of aggression or trying to minimize triggers for aggression while worrying about overall safety (Table 3, T5-Q9).

Discussion

While previous studies have examined behavioral disturbances in PDRD and their impact on caregivers,^{6,32,33} no known study has examined aggression towards caregivers by incorporating caregivers' perceptions on being the target of aggressive behaviors.

TABLE 4 Joint display of corroborating qualitative themes and baseline correlates of caregiver-reported aggression

Triangulated themes (T)	Illustrative quotes (caregiver's relationship to patient)	Corroborating variables [95% CI]
T2. Caregivers believe that aggressive behaviors result from the difficulty patients experience in coping with disease progression and related losses	<ol style="list-style-type: none"> 1. "What really made him mad was the fact that he could not be independent." (Wife) 2. "It's the motor symptoms. And then I think he gets frustrated and so he um...likes to have control somewhere you know?" (Wife) 3. "It wasn't like a sundowning situation where it got progressively worse during the day. Sometimes she would wake up and be great at night, so it was very unpredictable." (Husband) 	<i>Functional status</i> PPS (Any Aggression) Partial $r = -0.21 [-0.31, -0.10]$ *** <i>Grief</i> PG-12 (Any Aggression) Partial $r = 0.22 [0.09, 0.35]$ *** <i>Motor symptoms</i> UPDRS-III (Physical Aggression) Partial $r = 0.18 [0.04, 0.30]$ * ESAS-PD Stiffness (Any Aggression) Partial $r = 0.14 [0.02, 0.25]$ * <i>Confusion</i> ESAS-PD Confusion (Any Aggression) Partial $r = 0.17 [0.06, 0.28]$ **
T3. Caregivers' stress and mental health are worsened by aggressive behaviors	<ol style="list-style-type: none"> 1. "There's no question in my mind that I go through bouts of depression just, you know, because of the situation." (Husband) 2. "There's still days when I will get depressed and I cannot do that. There's too much that I have to do." (Wife) 	<i>Depression</i> HADS [caregiver] (Any Aggression) $r = 0.16 [0.03, 0.29]$ * <i>Caregiver burden</i> ZBI (Any Aggression) $r = 0.34 [0.24, 0.44]$ *** MCSI (Any Aggression) $r = 0.30 [0.17, 0.41]$ ***
T4. Aggressive behaviors negatively affect patient-caregiver relationships	<ol style="list-style-type: none"> 1. "He wanted to do everything by himself. I could not help him in the toilet...which I always had to. He did not want me to put him to bed. He was belligerent um...he wanted to strike me." (Wife) 	<i>Resistance to care</i> Survey item (Any Aggression) $r = 0.40 [0.1, 0.64]$ **

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Abbreviations: PG-12, Prolonged Grief Questionnaire (12-item); UPDRS-3, Unified Parkinson Disease Rating Scale—Motor section; ESAS-PD, Edmonton Symptom Assessment System Scale for PD; HADS, Hospital Anxiety and Depression Scale; ZBI, Zarit Burden Interview; MCSI, Modified Caregiver Strain Index.

The results of this study provide a comprehensive description of the caregiver experience and present informative data for addressing aggression in clinical practice. We noted several points of categorical convergence and corroboration between identified themes and correlating variables related to associated factors and consequences (see Table 4).

Aggression as a Behavioral Disturbance in Parkinsonian Disorders

Research suggests aggression in advanced stages of PDRD is common and associated symptom burden.¹¹ Our study expands on this by pinpointing specific, disease-related factors seen in the context of aggression as a behavioral change in PDRD, such as patients' reactions to functional decline and fluctuations in cognition.

Grief was identified as a contributor to aggression, namely patients' frustrations with progressive decline. Anticipatory grief and bereavement are well-known issues among PD caregivers and it seems patients are experiencing this sense of loss in tandem

as the disease progresses.³⁴ This builds on prior work showing associations between demoralization in patients and inability to cope with motor symptoms.³⁵ Our study is the first to show a relationship between patients' grief and behavioral disturbances in PDRD. Overlapping with patients' sense of loss, patients rejected the care provided despite increasing needs. Caregivers felt aggression was a way for patients to try to gain control of different aspects of their lives affected by the PDRD, but regardless of the cause this led to significant changes in the relationship. Grief counseling may address these issues and is one possible strategy for preemptively mitigating interpersonal issues contributing to escalating behavioral disturbances. This could involve the patient alone or jointly with caregivers.

In PDRD, fluctuations in cognition can manifest as wide shifts in cognitive dysfunction over time, swinging between periods of disorientation and lucidity.³⁶ Our findings suggest this is a specific cognitive symptom contributing to aggression in PDRD. This may be independent of dementia or global cognitive impairment, which were not observed as correlating with nor identified as a contributor. Instead, aggression was associated with fluctuating, episodic confusion and was distinct from dementia. Because of their episodic nature, these behaviors are likely

underrecognized especially for patients who otherwise do not meet criteria for dementia.³⁷ This is especially important for DLB where fluctuations in cognition are a core feature.³⁸ While there are currently no evidence-based treatments for fluctuations in cognition, education of caregivers and families and medications for cognition (eg, acetylcholinesterase inhibitors) or mood (eg, selective serotonin reuptake inhibitors) may help. Movement disorder specialists and neurologists should inquire about the nature of any fluctuations in cognition as a possible entry point for discussion of aggression with caregivers.

Aggression as a Contributor to Caregiver Burden

Caring for an individual living with PDRD can negatively impact the physical, mental, and social aspects of the lives of caregivers.³⁹ Frequently caregivers are faced with increasing concerns related to advancing disease, including their ability to manage the task of caregiving. Broadly thought of as “caregiver burden,” the strain of caregiving can lead to poor psychosocial outcomes for caregivers and reduced quality of life and higher disability for patients.^{40,41} Aggression towards caregivers represents another factor which drives overall caregiver burden and experiences with this type of behavioral disturbance are highly interconnected to other aspects of caregiver burden, namely increased depression and resistance to care. When aggression is suspected or disclosed during routine care, this may prompt discussions surrounding overall caregiver wellbeing and allow clinicians to appreciate the impact of these behaviors on both patients and caregivers. This may allow patients and caregivers to access resources and services which facilitate early intervention, provide guidance and education to families and loved ones, or mobilization of protective services when caregivers’ safety is threatened.

Implications for Clinical Practice and Research

Caregivers feel ill-equipped to manage these behaviors attributing this to a lack of knowledge which forces them adopt ad hoc strategies. One possible strategy for clinicians is to take an active role in screening for aggression or other behaviors projected towards others (eg, delusional disorders), achieved through direct collaboration and ongoing communications with caregiver. This opens opportunities for clinician-caregiver partnership in which clinicians can provide counseling and training on non-pharmacologic ways for managing aggression (eg, modification of home environment, adherence to daily schedules and routines). However, research is needed to produce evidence-based interventions aimed at providing caregivers with education, training, and support in managing aggression. This would involve evaluating and intervention effect on patient and caregiver outcomes (eg, institutionalization, caregiver burden). Potential interventions could involve social workers, psychotherapists, or spiritual counselors who could address grief or

interpersonal problems not easily addressed within the confines of routine care with neurologists.

Strengths and Limitations

This study has several strengths and limitations. Our study utilized data from patient-caregiver dyads enrolled on the basis of having moderate high palliative care needs. While aggression towards caregivers was not a criterion for participation in the parent clinical trial, caregiver burden was included in the assessment of palliative care needs used for determining eligibility for enrollment. Therefore, we cannot generalize these findings to patients with low palliative care needs or for patients in mild stages of disease. Similarly, our cohort was also heterogenous with respect to PDRD diagnosis, with atypical parkinsonian conditions making up 31.4% of our cohort. Future research examining aggression in PDRD should incorporate the patient and clinician perspectives, especially when looking at patient-caregiver interpersonal issues or barriers to effective caregiver-clinician communications. A better understanding of caregiver experiences with specific types of aggression is needed, such as with unwanted sexual advances. Sexual aggression was underrepresented in our sample and may hold diverging factors which influence its onset and impacts. We are also limited in fully explaining fluctuations in cognition as a possible contributor in our quantitative data, owing to the lack of validated measures of fluctuations in cognition both in the parent clinical trial and in PDRD research more broadly. The ESAS-PD confusion item represents the closest surrogate to episodic confusion available in our study. While this is not a validated measure of fluctuations, the association with ESAS-PD confusion, lack of association with cognitive impairment scores (eg, MOCA) or the presence of dementia, and our qualitative findings suggest that episodic confusion rather than static, or slowly progressive cognitive decline may play a role. Prospective studies are needed to look at fluctuations in cognition or variable patterns of cognitive impairment (eg, dysexecutive vs. amnesic) as contributors to aggression across PDRDs.

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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.

Z.A.M.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.

S.S.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.

R.A.: 1A, 1C, 2A, 2C, 3A, 3B.

M.B.: 1A, 1C, 2A, 2C, 3A, 3B.

J.L.: 1B, 1C, 2C, 3B.

H.C.: 1B, 1C, 2C, 3B.

J.M.: 1A, 1C, 2A, 2C, 3B.

S.Z.P.: 1A, 1C, 2A, 2C, 3B.

M.K.: 1A, 1C, 2A, 2C, 3B.

E.J.S.: 1A, 1C, 2A, 2C, 3B.

S.H.S.: 1A, 1B, 1C, 2A, 2B, 2C, 3B.

H.D.L.: 1A, 1B, 1C, 2C, 3B.

B.M.K.: 1A, 1B, 1C, 2A, 2B, 2C, 3B.

Disclosures

Ethical Compliance Statement: This study was approved by the Institutional Review Boards (IRB) at both study sites (Colorado Multiple Institutional Review Board, #16-1400; University of California San Francisco Human Research Protection Program Institutional Review Board, #16-21211). All participants provided consent or, if lacking capacity, provided assent with informed consent obtained from a legally authorized representative such as a medical proxy. 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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Supporting Information

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

Appendix S1 Caregiver qualitative interview guide.