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Hienen, M.M. van; Kuiper, R.; Middelkoop, H.A.M.; Hilten, J.J. van; Contarino, M.F.; Geraedts, V.J.

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Research Report

Patient-Related Factors Influencing Caregiver Burden in Parkinson's Disease Patients: Comparison of Effects Before and After Deep Brain Stimulation

Marle M. Van Hienen[a], Roy Kuiper[a], Huub A.M. Middelkoop[a,c], Jacobus J. Van Hilten[a], Maria Fiorella Contarino[a,b] and Victor J. Geraedts[a,d,*]
[a]*Department of Neurology, LUMC, Leiden, the Netherlands*
[b]*Department of Neurology, Haga Teaching Hospital, Den Haag, the Netherlands*
[c]*Institute of Psychology, Health, Medical and Neuropsychology Unit, Leiden University, Leiden, the Netherlands*
[d]*Department of Clinical Epidemiology, LUMC, Leiden, the Netherlands*

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Abstract.
Background: Caregivers of Parkinson's disease (PD) patients provide important support during the pre- and postoperative phase of deep brain stimulation (DBS). High levels of caregiver burden have been reported after DBS. However, a comparison between preoperative and postoperative burden and associated factors has been insufficiently studied.
Objective: To investigate the influence of DBS on caregiver burden, and to identify the differential impact of patient-related factors on caregiver burden before and after DBS.
Methods: Consecutive patients referred for DBS eligibility screening or during one-year follow-up assessments were included. Caregiver burden was measured with the short Zarit Burden Interview (ZBI-12). Inverse Probability Weighting (IPW) was used to compare caregiver burden between preoperative and postoperative assessments.
Results: We included 47 patients (24 screening, 23 follow-up) (median age 65 years, 29.4% female sex). DBS did not impact caregiver burden (screening: median ZBI-12 9.5 (IQR 3.25, 16.75); follow-up median ZBI-12 6 (IQR 4, 14); IPW-coefficient 0.57 (95% CI –2.75, 3.89)). Worse caregiver burden during DBS screening was associated with worse patient-related scores on depressive symptoms, anxiety, QoL, and impulsiveness. Worse scores on depressive symptoms, anxiety, apathy, postural-instability-gait-disorder, and QoL were associated with worse caregiver burden at one-year follow-up.
Conclusion: DBS appears not associated with changes in caregiver burden. Various symptoms are valued differently between screening and follow-up assessments in terms of caregiver burden. Early recognition of caregivers "at risk" may improve guidance of patient-caregiver dyads throughout the DBS process.

Keywords: Parkinson's disease, caregiver burden, deep brain stimulation, quality of life, epidemiology

INTRODUCTION

Parkinson's disease (PD) is characterized by both motor and non-motor symptoms, resulting in a significant reduction of quality of life (QoL) [1]. Caregivers

*Correspondence to: Victor J. Geraedts, MD, PhD, Department of Neurology, Albinusdreef 2, 2333ZA, Leiden, the Netherlands. E-mail: v.j.geraedts@lumc.nl.

of PD patients are crucial contributors to maintaining patients' QoL despite disease progression, and concomitantly reduce both morbidity and mortality rates [2]. Given the variety and complexity of PD symptoms, a caregiver role may be highly demanding and cause a high burden for themselves. This may have a negative influence on their mental and general health [3], and social life [2–4], which in turn negatively influences the effectiveness and tolerability of caregiving [5].

PD patients with motor complications refractory to oral therapy may be eligible for deep brain stimulation (DBS) [6], which relieves motor complications and significantly improves QoL [7]. However, several PD motor and non-motor symptoms are stimulation-resistant and generally worsen as the disease advances [8]. Notably, non-motor symptoms may exert a larger negative influence on caregivers compared to motor symptoms [5]. The perioperative DBS setting imposes additional stress and raises an additional need of a well-functioning social support system [9, 10]. Early recognition of potentially problematic situations, and knowledge of modifiable factors influencing caregiver burden after DBS, may provide targets for supporting a well-functioning patient-caregiver dyad. In spite of the positive outcomes in PD patients, up to 50% of the caregivers rated their wellbeing as decreased after DBS in an earlier study [11].

Unfortunately, in previous observational studies the independent association between DBS and caregiver burden was not evaluated [5]. Therefore, the aim of this study was to investigate whether caregiver burden differs before DBS and one year after DBS, and determine which patient-related factors may influence caregiver burden both before and after DBS.

METHODS

Study participants

Consecutive patients referred to the Haga Teaching Hospital/Leiden University Medical Center (Haga/LUMC centre) for either screening for DBS eligibility, or consecutive patients seen during one year follow-up assessments, were prospectively included in this study. Subjects were therefore analyzed only once, no pre-post analysis was possible, and were divided in two separate groups. Patient selection began June 2019 and ended November 2020. All patients gave written informed consent. As this study used only data collected during routine clinical care, a formal ethical evaluation was waived by the local medical ethics committee.

Outcome measures

Motor function was assessed with the Movement Disorder Society Unified Parkinson's Disease Rating Scale part III (MDS UPDRS-III) and part IV (MDS UPDRS-IV) [12]. MDS-UPDRS III scores were assessed during the screening in the Med-ON and Med-OFF conditions, and in the Med-OFF/Stim-ON, Med-OFF/Stim-OFF, and Med-ON/Stim-ON conditions during follow-up assessments. The Med-OFF condition was achieved after an overnight withdrawal from anti-PD medication; the Med-ON condition was achieved through a suprathreshold dosage of 120% of the early morning Levodopa Equivalent Dose (LED) [13].

Anxiety symptoms were measured with the Parkinson Anxiety Scale (PAS) [14], severity of apathy with the Apathy Scale (AS) [15], autonomic symptoms with the Scales for Outcomes in Parkinson's Disease – Autonomic Dysfunction (SCOPA-AUT) [16], cognitive impairment with the Montreal Cognitive Assessment (MoCA) [17], depression with the Beck Depression Inventory-II (BDI-II) [18], the presence of impulsive behavior with the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) [19], Postural Instability and Gait Disorder (PIGD) symptoms with the Freezing of Gait questionnaire (FOG) [20], and QoL with both the 39-item Parkinson's Disease Questionnaire (PDQ-39) [21], and the 5 dimension EuroQoL (EQ-5D) [22]. Sleep disturbances were assessed with the Scales for Outcomes in Parkinson's Disease – Sleep (SCOPA-Sleep) [23], including Night-time Sleep Problems (NSP) and Excessive Daytime Sleepiness (EDS).

The abbreviated version of the Zarit Burden Interview (ZBI-12) was used to quantify caregiver burden. High caregiver burden was defined as a ZBI-12 score above 17 [24].

Statistical analysis

Demographics and clinical variables were compared between screening and one-year follow-up with independent Student's *T*-test, Mann-Whitney U test, and Chi-square test.

Two hypothetical causal frameworks surround caregiver burden related to DBS surgery: 1) Patient-related covariates, such as neuropsychiatric symptoms or motor functioning, impact both DBS

eligibility and caregiver burden after DBS and are therefore best considered confounding factors requiring additional correction, and 2) DBS has an effect on these covariates, which renders them mediators instead of confounders (i.e., the effect of DBS on caregiver burden is mediated through these variables, rather than a distorting effect). In this hypothetical framework, a correction of these mediators could lead to an underestimation of the actual effect of DBS on caregiver burden [25]. Directed Acyclic Graphs (DAGs) were used to reflect both scenarios (see Supplementary Figure 1A and B) [25]. Propensity scores based on the appropriate confounder-structures (different for each of the DAGs) were calculated and used to emulate randomization using Inverse Probability Weighting (IPW) [26, 27]. In the first situation, the propensity score was composed of the following confounders: patients' age, disease duration, motor symptoms, neuropsychiatric and cognitive symptoms, and PIGD. In the second situation, the propensity score was composed only of patients' age, and disease duration. This method allows comparability between groups in the absence of randomization.

An univariate linear regression analysis including demographic and clinical covariates was performed to determine the influence of patient-related factors on ZBI-12 scores. All assumptions for linear regression were checked prior to analysis. To evaluate whether the effect of the patient-related covariates differed between caregivers prior to surgery and during the one-year follow-up, univariate linear regression analyses were performed in three different strata: 1) Screening, 2) Follow-up, and 3) Combined. To model the combined effect of those covariates with the highest single impact (i.e., highest univariate R^2) on caregiver burden, a multivariable regression model was built. The total number of covariates in the multivariable regression model was based on the one covariate per ten patients rule [28].

The statistical analyses were performed with R Foundation for Statistical Computing version 4.0.3., and IBM Statistical Package for the Social Sciences 25 Software (SPSS).

RESULTS

Population characteristics

Between June 2019 and November 2020, 55 patients received either DBS screening or follow-up assessment. Six patients did not have a caregiver, and two patients returned incomplete questionnaires (and were thus excluded). Forty-seven patients were ultimately included, of whom 24 were referred for DBS screening, and 23 patients had their follow-up assessment. Median patient age was 65 years, median caregiver age was 62 years. Forty-two caregivers were partners, two children, one parent, and two were sibling. The median ZBI-12 was 7, no statistical difference was found between screening and one-year follow-up. Nine caregivers in total experienced caregiver overload (ZBI-12 $\geq$ 17) [24]. Further demographic variables are shown in Table 1. Patients referred for DBS eligibility screening had significantly better MDS-UPDRS III OFF scores than patients during the follow-up assessments (Med-OFF/Stim-OFF), but significantly worse scores in terms of motor fluctuations, autonomic symptoms, depression, impulsiveness, QoL, and NSP.

Impact of DBS on caregiver burden

Multivariable linear regression modelling of the first hypothetical scenario, i.e., with additional correction for PD symptoms, yielded a non-significant adjusted regression coefficient of 1.63 (95% CI –3.46, 6.73). Multivariable linear regression modelling of the second hypothetical scenario, i.e., only corrected for patients' age and disease duration, yielded a non-significant adjusted regression coefficient of –0.59 (95% CI –5.30, 4.13). The IPW regression coefficient was non-significant, i.e., 0.57 (95% CI –2.75, 3.89). All three results indicate no significant causal effect of DBS on caregiver burden.

Determinants of caregiver burden

Depression, anxiety, and patients' QoL were significantly associated with caregiver burden in all strata (screening, follow-up, and combined). Apathy and PIGD were found to be significant one year after DBS and in the combined stratum. Sleep disturbances were only significant when analyzing both screening- and follow-up patients simultaneously, and attentional impulsiveness was only significant in the screening stratum (see Table 2). Worse symptom severity was associated with higher caregiver burden.

The four following covariates were used in the multivariable regression model encompassing both screening and follow-up patients: patients' QoL (measured with the PDQ-39), depression, apathy, and PIGD. Only higher apathy scores were significantly associated with more caregiver burden in a multivariable model (see Table 3). A scatterplot

Table 1
Population characteristics

	Screening ($N = 24$)	Follow-up ($N = 23$)	p
Age caregiver[a]	61.5 (52.25, 69.75)	63 (61, 69)	0.321
Sex caregiver, female[b]	70.8% (17)	73.9% (17)	0.813
Relationship caregiver[b]			0.158
Partner	91.7% (22)	87% (20)	
Child	8.3% (2)	0% (0)	
Parent	0% (0)	4.3% (1)	
Brother/Sister	0% (0)	8.7% (2)	
ZBI-12[a]	9.50 (3.25, 16.75)	6 (4, 14)	0.709
Caregiver overload[b+]	25% (6)	13% (3)	0.298
Age patient[a]	64 (53.5, 68)	66 (57, 68)	0.631
Sex patient[b,] female	37.5% (9)	30.4% (7)	0.609
Disease duration[a]	6.05 (5.25, 8.625)	7.7 (6.7, 11)	0.095
MDS-UPDRS III[c]			
*ON**	18.33 (7.93)	21.29 (12.39)	0.340
*OFF***	39.88 (8.49)	49.41 (15.38)	0.012
Med OFF / stim ON	–	32.52 (12.30)	–
MDS-UPDRS IV[c]	10.05 (3.15)	4.91 (4.93)	> 0.001
PAS[c]	12.33 (7.53)	7.87 (8.01)	0.055
AS[a]	11 (9, 13)	11.50 (9, 14.5)	0.444
SCOPA-AUT[c]	18.58 (9.28)	13.13 (6.25)	0.023
MoCA[a]	26 (25, 28)	26 (25, 28)	0.905
BDI-II[a]	15.5 (10.5, 20.75)	7 (4, 12)	0.001
QUIP-RS[a]	11.50 (2.25, 17.75)	1 (0, 12)	0.032
FOG[c]	5.91 (5.49)	5.14 (4.65)	0.612
QoL patient			
PDQ-39[c]	47.79 (22.32)	31.61 (23.36)	0.019
EQ-5D[c]	10.08 (2.78)	8.57 (2.39)	0.051
SCOPA Sleep			
NSP[c]	7.00 (3.74)	4.30 (3.52)	0.015
EDS[c]	4.96 (3.62)	4.39 (2.94)	0.559
Overall sleep quality[b]			0.144
Very well	0% (0)	26.1% (6)	
Well	8.7% (2)	17.4% (4)	
Rather well	21.7% (5)	17.4% (4)	
Not well but not badly	26.1% (6)	17.4% (4)	
Rather badly	26.1% (6)	17.4% (4)	
Badly	13% (3)	4.3% (1)	
Very badly	4.3% (1)	0% (0)	

[a]Mann-Whitney U test, Median (25% IQR, 75% IQR). [b]Chi-square test, % (N). [c]Unpaired *T*-test, Mean (±SD). *The ON situation was defined as 1.2 times the patients' early morning dose at time of screening. At time of follow-up, the ON situation was defined as both 1.2 times the patients' early morning dose and activate DBS device. **The OFF situation was defined as at least 12 hours absence of anti-parkinsonian medication at time of screening. At time of follow-up, the OFF situation was defined as both 12 hours absence of anti-parkinsonian medication and DBS device was switched off. [+]Caregiver overload ≥ 17. [++]NSP ≥ 7. [+++]EDS ≥ 5. ZBI-12, 12-item Zarit Burden Interview; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; PAS, Parkinson Anxiety Scale; AS, Apathy Scale; SCOPA-AUT, Scales for Outcome in Parkinson's Disease – Autonomic Dysfunction; BDI-II, Beck Depression Inventory II; QUIP-RS, Questionnaire for Impulsive-Compulsive disorders in Parkinson's Disease – Rating Scale; FOG, Freezing of Gait questionnaire; MoCA, Montreal Cognitive Assessment; PDQ-39, 39-item Parkinson's Disease Questionnaire; EQ-5D, five dimension EuroQoL; SCOPA-Sleep, Scales for Outcome in Parkinson's Disease – Sleep; NSP, Nighttime Sleeping Problems; EDS, Excessive Daytime Sleeping.

of the unstandardized predicted values versus the observed values is shown in Supplementary Figure 2A. A second multivariable regression model incorporating anxiety scores instead of depression scores (i.e., due to the collinearity between depression and anxiety), showed relatively similar results (see Supplementary Table 1 and Supplementary Figure 2B).

Table 2
Effect of (univariate) patient-related covariates on caregiver burden

	Screening		Follow-up		Combined	
	β	95% CI	β	95% CI	β	95% CI
Patients' age	–0.071	–0.382, 0.241	–0.107	–0.572, 0.358	–0.085	–0.334, 0.164
Disease duration	–0.143	–0.527, 0.241	0.078	–0.943, 1.098	–0.111	–0.452, 0.231
MDS-UPDRS III 'ON'*	0.246	–0.168, 0.660	0.229	–0.084, 0.542	0.229	–0.001, 0.459
MDS-UPDRS III 'OFF'**	0.298	–0.080, 0.675	0.093	–0.163, 0.349	0.113	–0.070, 0.297
MDS-UPDRS IV	–0.200	–1.440, 1.040	0.158	–0.632, 0.947	0.051	–0.480, 0.581
BDI-II	0.599	0.201, 0.997	0.985	0.521, 1.448	0.603	0.334, 0.873
PAS	0.475	0.076, 0.874	0.546	0.138, 0.955	0.482	0.220, 0.743
SCOPA-AUT	0.308	–0.031, 0.648	0.176	–0.431, 0.783	0.251	–0.027, 0.528
SCOPA-Sleep	0.584	–0.286, 1.453	0.950	–0.047, 1.947	0.684	0.097, 1.271
PDQ-39	0.208	0.087, 0.329	0.242	0.121, 0.363	0.203	0.125, 0.282
EQ-5D	1.256	0.169, 2.343	2.249	1.017, 3.482	1.561	0.802, 2.321
MoCA	–0.014	–1.756, 1.727	0.159	–1.270, 1.587	0.097	–0.941, 1.135
QUIP-RS	0.424	0.118, 0.729	0.013	–0.437, 0.464	0.223	–0.026, 0.472
AS	0.574	–0.425, 1.572	1.097	0.467, 1.727	0.920	0.417, 1.422
FOG	0.249	–0.391, 0.888	1.333	0.736, 1.929	0.689	0.242, 1.136

*The ON situation was defined as 1.2 times the patients' early morning dose at time of screening. At time of follow-up, the ON situation was defined as both 1.2 times the patients' early morning dose and activate DBS device. **The OFF situation was defined as at least 12 hours absence of anti-parkinsonian medication at time of screening. At time of follow-up, the OFF situation was defined as both 12 hours absence of anti-parkinsonian medication and DBS device was switched off. MDS-UPDRS, Movement Disorder Society – Unified Parkinson's Disease Rating Scale; BDI-II, Beck Depression Inventory II; PAS, Parkinson Anxiety Scale; SCOPA-AUT, Scales for Outcome in Parkinson's Disease – Autonomic Dysfunction; SCOPA-Sleep, Scales for Outcome in Parkinson's Disease – Sleep; PDQ-39, 39-item Parkinson's Disease Questionnaire; EQ-5D, five dimension EuroQoL; MoCA, Montreal Cognitive Assessment; QUIP-RS, Questionnaire for Impulsive-Compulsive disorders in Parkinson's Disease – Rating Scale; AS, Apathy Scale; FOG, Freezing of Gait questionnaire.

Table 3
Multivariable regression analysis model

Questionnaire	β	*p*	95% CI	R^2
PDQ-39	0.095	0.210	–0.056, 0.246	0.496
BDI-II	0.268	0.217	–0.166, 0.702	
AS	0.641	0.014	0.139, 1.144	
FOG	0.008	0.974	–0.468, 0.483	

Constant: $B = -5.503$; $p = 0.069$; 95% CI = –11.459 – 0.452. PDQ-39, 39-item Parkinson's Disease Questionnaire; BDI-II, Beck Depression Inventory II; AS, Apathy Scale; FOG, Freezing of Gait Questionnaire.

DISCUSSION

The complexity and variety of PD symptoms can make caring for a PD patient a challenging task [2]. In this study, we investigated the influence of DBS on caregiver burden and determined the differential impact of patient-related factors on caregiver burden before and after DBS.

Despite results from observational studies, a causal effect of DBS on caregiver burden has not been established. Randomized controlled trials (RCTs) focusing on caregiver burden are not feasible in the setting, and current observational studies carry inherent selection bias and information bias [4]. Although RCTs are widely considered to be the gold standard in determining causal structures, emulation of such trials may model underlying causal structures as well [27]. Our Emulated Target Trial observed no independent association between DBS and caregiver burden; scores for caregiver burden did not differ between patients before and after surgery even after adjustment for other relevant covariates. A previous observational study suggested that this may be due to an increase in caregiver demands after DBS surgery [29]. Moreover, both the current study, as well as previous studies, indicates that neuropsychiatric symptoms of PD such as depression, anxiety, and apathy may have a great influence on caregiver burden, even more so than motor symptoms [5]. Also it has been suggested that newly emerged or progressively worsening of neuropsychiatric symptoms may occur because of malfunctioning of the patient-caregiver dyad [30].

Covariates with a significant influence on worse caregiver burden in both the screening- and follow-up strata were worse depression scores, anxiety scores, and QoL. Additionally, more impulsiveness was significantly associated with worse caregiver burden in caregivers of DBS candidates, but not in caregivers of patients who already received DBS. After DBS-STN surgery, the patients' dopaminergic drug dose is decreased, which most likely reduces impulsiveness (as exemplified in the lower level of QUIP-RS scores in the follow-up population) [30]. We hypothesize

that the reduced variability in impulsiveness scores resulted in the non-significant association of QUIP-RS and caregiver burden in the follow-up stratum. Similarly, worse apathy scores and PIGD scores were significantly associated in caregivers of patients one year after DBS, but not in caregivers of DBS candidates. We hypothesize that these symptoms stand out more after DBS due to the relief of motor fluctuations and perceived improvement of motor function in general [31], causing a relatively higher impact on caregivers than experienced prior to surgery despite similar objective symptom severity scores. Moreover, we hypothesize that the relief of motor symptoms could even lead to an unrealistic desire of caregivers to return to "normal", which was not possible due to a lack of motivation caused by a higher degree apathy. Previous literature has shown some discrepancy in apathy prevalence after DBS, with some studies reporting an increased prevalence with other studies reporting no significant increase [32]. A different study suggested a personal or familial diathesis for mood disturbances, including apathy, regardless of DBS [33]. Even if DBS does not aggravates apathy, the impact of apathy may be larger due to both its under-recognition and its resilience to treatment [32]. Further investigation is required to explore the differential impact of apathy with regard to DBS candidates and patients post-surgery.

The similar symptom severity scores indicate that disease progression or an effect of medication-alterations likely did not contribute to the disparity between the baseline and follow-up groups. Similarly, we observed a relatively larger influence of depression and general QoL in the follow-up stratum than in the screening stratum, although depressive symptoms were considerably lower in the follow-up stratum. Another possibility is that these symptoms persist despite an (unrealistic) desire for improvement [34], causing disappointment of the caregiver and concomitant higher caregiver burden.

Our findings on the influence of depression, anxiety and impulsiveness and lack of influence of motor symptoms on caregiver burden are in line with previous studies [30, 35, 36]. In contrast, previous studies did not find a significant influence of patient QoL on caregiver burden [36]. This may be explained by the fact that whilst baseline scores of the PDQ-39 are relatively similar (i.e., 48.2 vs. 47.8), whereas we observed markedly better QoL scores at follow-up (i.e., 41.6 vs. 31.6). We hypothesize that the better QoL scores in our study may have had a beneficial effect on caregiver burden compared to studies with relatively worse QoL. The significant association between apathy and PIGD and caregiver burden, as well as the non-significant association of sleep disturbances, has not been previously described in previous studies and may have additional utility during patient- and caregiver education during the DBS screening [5]. Strikingly, patients' cognitive function was not associated with caregiver burden in our cohort, despite being associated with caregiver burden in the general population [37]. Previous literature found that the ZBI-12 scale correlated poorly with cognitive dysfunction [24]. Strikingly, the only significant covariate in our multivariable model was apathy, highlighting the importance of neuropsychiatric symptoms on caregiver burden during the DBS process. Finally, we speculate that other instruments to assess caregiver burden may find a significant association with cognition after all. Our model explained close to 50% of the total variance, indicating that there are several other determinants influencing caregiver burden.

Limitations of this study include a lack of caregiver-related covariates due to the data collection during routine clinical care. Although sex and age of the caregiver were known, these could not be included in the analyses due to collinearity. Second, our cross-sectional study design made it impossible to perform an in-patient analysis. As a result of the COVID-19 pandemic, most follow-up appointments were considered non-essential care and postponed until further notice. Only patients with suboptimal disease control would receive a follow-up appointment, whereas outpatient-appointments of patients with adequate disease control were considered non-essential, which would have resulted in a considerable selection bias. The lack of a control-group could be construed as a limitation but was circumvented by using IPW analyses. Although our sample size is still relatively small, it clearly exceeds previous studies on this topic (i.e., between 12 and 30 patient-caregiver dyads) [5]. Moreover, our study assessed the contribution of patient-related covariates that are typical components of most DBS screening procedures, thus increasing the utility of our findings for clinical practice.

A major limitation is the lack of a control group and/or a longitudinal design including longitudinal within-patient assessments. Ideally, a RCT would validate our findings using a randomized and blinded pre-post assessment of caregiver burden, using either sham-stimulation or actual DBS. A limitation of this design, regardless of ethical considerations to

withhold patients beneficial therapy, is that this disregards non-stimulation-induced effects such as stun-effects or lesion-effects due to lead insertion. Another option would include longitudinal assessments of caregiver burden in DBS-candidates either approved or rejected for the DBS screening. However, this would introduce a major selection bias since patients reject for DBS are inherently different from patients who are found to be suitable DBS candidates, as they may be rejected for a variety of reasons including cognitive deficits or suboptimal oral treatment [34].

Future research should investigate to what degree caregiver-related covariates influence postoperative caregiver burden (i.e., presurgical expectations of caregivers), and whether interventions can be implemented to further relieve caregiver burden after DBS. A previous study described that 27% of caregivers would appreciate professional help after DBS surgery [38]. An intervention-study for caregivers, targeting DBS-related changes, consisted of cognitive-behavioral therapy at weekly intervals and resulted in a substantial reduction of caregiver burden, which was maintained until three months after completing the intervention [39]. It remains to be determined whether these interventions are suitable for all caregivers (even with low scores on caregiver burden instruments), and whether the effects of these interventions are maintained during long-term follow-up.

Further investigation is required to study other potential variables such as sociodemographic variables (i.e., Western vs. non-Western society), surgical timing, mood disturbances other than apathy, fatigue, and sleep disturbances, and their relation to possible dissatisfaction with surgery [40]. In particular, stimulation-induced dysarthria and/or fatigue has to our knowledge not been studied in relation to caregiver burden, however its impact needs to be studied further as these may negatively influence communication with caregivers [41, 42]. This may potentially make them unwilling to participate in life-events, which could further impair the patient-caregiver dyad.

A previous systematic review identified a favorable patient profile for caregiver wellbeing assessed during the DBS screening, which included younger patient age, younger age-at-onset, lower disease duration, lower LED, lower validations on psychiatric rating scales, and higher relationship quality [5]. Additions of this study to this favorable profile for better caregiver outcome after surgery include lower ratings on the QoL scales, lower apathy scores and lower PIGD ratings. Early recognition of this favorable patient profile may benefit both patients and caregivers during the DBS screening and may improve patient- and caregiver education on postoperative expectations [34]. Caregivers "at risk" for high levels of caregiver burden after surgery could be early identified with these influencing factors, both before and after DBS, which makes early interventions and counselling feasible to counteract any negative effects of a non-functional social support system [30].

In conclusion, DBS is not independently associated with caregiver burden, but several patient-related factors were identified to significantly impact caregivers and may be targets for modelling caregiver burden during both the screening phase and follow-up period after DBS, with a particular emphasis on neuropsychiatric covariates. Attention to caregivers "at risk" for high levels of caregiver burden is crucial for maintaining a functional social support system supporting the patient surrounding the time of surgery, which is beneficial for patients, caregivers, and the patient-caregiver dyad.

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CONFLICT OF INTEREST

MM van Hienen reports nothing to disclose.

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SUPPLEMENTARY MATERIAL

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