



A narrative review of clinical and non-clinical determinants of health-related quality of life in advanced Parkinson's disease

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by a wide range of motor and non-motor symptoms that lead to substantial disability over time, particularly in advanced stages, with a significant impact on patients' quality of life (QoL). Given the chronic and currently incurable nature of the disease, symptom management and the preservation of health-related QoL (HRQoL) are central therapeutic priorities from a patient-centered perspective. In this context, there has been a growing emphasis on the use of patient-reported outcome measures (PROMs) to capture the subjective burden of disease and to better reflect the real-world benefits of therapeutic interventions beyond traditional clinical endpoints. In parallel, increasing attention has been paid to the consequences of PD on caregivers, whose HRQoL is often substantially affected, especially as the disease progresses and care demands intensify in advanced PD. This narrative review synthesizes current evidence on HRQoL in advanced PD, with particular focus on the contribution of motor symptoms, non-motor symptoms, and other disease-related factors to HRQoL impairment in patients and caregivers. Additionally, the available data on the impact of advanced therapies on HRQoL outcomes in patients are critically discussed, highlighting their role in comprehensive, patient-centered care.

Keywords Parkinson's disease · Advanced PD · Quality of life · Health-related quality of life · Caregiver

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (Han et al. 2025). Recent epidemiological studies indicate a significant upward trend in both its incidence and prevalence, even after accounting for demographic shifts (Han et al. 2025).

Consequently, PD has become one of the neurological conditions showing the greatest increase in disability-adjusted life years (DALYs) since the 1990s (Ney et al. 2025). As a chronic disease with no curative therapies, improving quality of life (QoL) ultimately becomes the primary goal of any intervention for this condition.

QoL is a global concept that is defined by the World Health Organization Quality Of Life (WHOQOL) assessment as *an individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns* (1995). Although numerous definitions of QoL have been proposed over recent decades, there is broad consensus regarding its core characteristics: it is subjective and context-dependent, grounded in individual perceptions and expectations; it is multidimensional, encompassing physical, psychological, and social domains; and it requires the evaluation of both positive and negative aspects of life (1995). Although the terms QoL and health-related QoL (HRQoL) are often used interchangeably, they represent distinct concepts (Den Oudsten et al. 2007; Martínez-Martin 2017). HRQoL is a narrower construct that specifically

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refers to the impact of disease on an individual's life, in line with the WHO definition of health as *not only the absence of disease or infirmity, but the presence of physical, mental, and social well-being* (Testa and Simonson 1996; Martinez-Martin 2017). Importantly, HRQoL does not refer to health status per se, understood as the ability to perform physical, emotional, and social activities, but rather to the patient's subjective perception of their health status (Den Oudsten et al. 2007).

Recognizing the multidimensional burden and the progressive nature of PD is essential for effectively improving HRQoL in affected individuals (Bloem et al. 2021). PD is characterized by a wide range of motor, non-motor and treatment-related symptoms, that lead not only to motor disability, but also to impaired psychosocial well-being and overall HRQoL (Bloem et al. 2021). Non-motor symptoms (NMS) are increasingly recognized as the most disabling features, even in the early stages of the disease (Tosin et al. 2024). Furthermore, because PD is not a static disease, patients' needs evolve over time and require continuous adaptation of care strategies.

Equally important is the recognition of the pivotal role caregivers play, particularly in late disease, when functional independence is commonly lost and patient care becomes their primary occupation (Martinez-Martin 2017; Perepezko et al. 2023). Caregiving responsibilities are associated with early retirement, social isolation, emotional stress, and reduced well-being among caregivers, which in turn negatively affects patients (Rashid et al. 2023; Merritt et al. 2023). Therefore, a comprehensive evaluation of QoL in PD must also encompass the impact of the disease on caregivers.

This review provides a narrative synthesis of the evidence on the impact of both motor and NMS on HRQoL in individuals with PD and their caregivers, with a particular focus on advanced disease stages and related therapies.

Literature search strategy

For this narrative review, we conducted a non-systematic search of peer-reviewed articles published in English up to December 2025. The search was performed using the PubMed database. The following search terms were used in various combinations: ("Parkinson*" AND ("health-related quality of life" OR "HRQoL" OR "quality of life" OR "QoL")). Additional relevant studies were identified through manual screening of the reference lists of selected articles. Given the narrative nature of this review, studies were selected based on their relevance to the scope of the manuscript.

HRQoL in PD and how to measure it

The assessment of HRQoL provides direct insight into patients' perceptions of PD and its impact on daily life, complementing clinical evaluation and revealing potential discrepancies between patient and clinician perspectives (Martinez-Martin 2017). Over recent decades, increasing emphasis has been placed on patient-reported outcomes measures (PROMs) to evaluate both the impact of the disease and the effectiveness of therapeutic interventions. These standardized and validated instruments assess health status from the patients' perspective (Churruca et al. 2021; De La Cuadra-Grande et al. 2025).

PROMs can be broadly categorized as generic or disease-specific, with PD-specific instruments generally demonstrating greater sensitivity to disease-related change (Cummins et al. 2004; Churruca et al. 2021) (Table 1). In 2011, the Movement Disorder Society (MDS) published recommendations on the most appropriate instruments for assessing HRQoL in PD (Martinez-Martin et al. 2011a, b). These recommendations encompassed both generic measures, such as the Nottingham Health Profile (NHP), Sickness Impact Profile (SIP), Short Form 36-item Health Survey (SF-36), and EuroQol Five-Dimension questionnaire (EQ-5D), and disease-specific instruments, including the 39-item Parkinson's Disease Questionnaire (PDQ-39), 8-item Parkinson's Disease Questionnaire (PDQ-8), Parkinson's Disease Quality of Life Questionnaire (PDQL), Parkinson's Impact Scale (PIMS), and Scales for Outcomes in Parkinson's Disease–Psychosocial (SCOPA-PS). More recently, a systematic review applying the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) framework identified six instruments with the strongest psychometric evidence for HRQoL assessment in PD, all receiving a COSMIN recommendation A: PDQ-39, PDQ-8, PDQL, Parkinson's Disease Quality of Life Instrument (PDQUALIF), PIMS, and the Neuro Quality of Life measurement system (Neuro-QOL) (De La Cuadra-Grande et al. 2025). Given the multidimensional nature of HRQoL in PD, current evidence supports the combined use of disease specific and generic instruments, most robustly PDQ-39 or PDQ-8 together with a generic instrument such as Neuro-QOL, SF-36, or EuroQol Five-Dimension questionnaire (EQ-5D), to maximize clinical sensitivity while enabling cross-disease comparisons and health-economic analyses (Martinez-Martin et al. 2011a, b; De La Cuadra-Grande et al. 2025) (Table 2). Although many PD studies using these instruments claim to assess QoL, the PROMs employed predominantly capture HRQoL.

The impact of PD on caregivers' HRQoL has been comparatively understudied, and the available assessment instruments are limited and heterogeneous across studies

Table 1 Generic and disease-specific HRQoL instruments in PD (Martinez-Martin et al. 2011a, b; De La Cuadra-Grande et al. 2025)

Instrument	Domains assessed	Strengths	Limitations	COSMIN / MDS recommendation
<i>Generic instruments</i>				
Neuro-QOL	Physical, emotional, cognitive, social	Feasible, valid, and reliable in PD	Lack of PD-specific items	A / –
SF-36	Physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health	Captures broad aspects of health and global well-being; good comparability across populations	Floor/ceiling effects; limited sensitivity to change	B / Recommended
EQ-5D	Mobility, self-care, usual ADL, pain/discomfort, anxiety/depression	Widely used in PD; may differentiate disease stages; responsiveness to treatment	Floor/ceiling effects	B / Recommended
SIP	Physical, psychosocial	Convergent validity	Lengthy; less used in PD	– / Recommended
NHP	Mobility, pain, sleep, energy, emotional reactions, and social isolation	Convergent validity	Lengthy; floor effect	– / Recommended
<i>Disease-specific instruments</i>				
PDQ-39	Mobility, ADL, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort	Gold standard for HRQoL in PD; external validity	Lengthy	A / Recommended
PDQ-8	Same as PDQ-39	Brief; strong correlation with PDQ-39	Less sensitive than PDQ-39	A / Recommended
PDQL	Parkinsonian symptoms, systemic symptoms, emotional function, and social function	Widely used in PD; comprehensive assessment; internal consistency	Limited external validation	A / Recommended
PIMS	Emotional, social, and economic	Strong focus on psychosocial, occupational and socioeconomic aspects	Limited external validation; no motor or mental items	A / Recommended
SCOPA-PS	Emotional, psychological, social	Brief; no floor/ ceiling effects; external validity	No motor or mental items	– / Recommended
PDQUALIF	Mobility, ADL, emotional, psychological, social, facing PD	Reliably used in clinical trials	Limited external validation; not useful for cognitive impairment in PD	A / Suggested

ADL: activities of daily living; COSMIN: consensus-based standards for the selection of health measurement instruments; EQ-5D: EuroQol 5-Dimension questionnaire; HRQoL: health-related quality of life; Neuro-QOL: Quality of Life in Neurological Disorders; NHP: Nottingham Health Profile; PD: Parkinson’s disease; PDQ-8: 8-item Parkinson’s Disease Questionnaire; PDQ-39: 39-item Parkinson’s Disease Questionnaire; PDQL: Parkinson’s Disease Quality of Life Questionnaire; PDQUALIF: Parkinson’s Disease Quality of Life Scale; PIMS: Parkinson’s Impact Measure Scale; SCOPA-PS: Scales for Outcomes in Parkinson’s Disease–Psychosocial; SF-36: Short Form 36-item Health Survey; SIP: Sickness Impact Profile

Table 2 Choosing the right HRQoL instrument (Martinez-Martin et al. 2008, 2011a, b; Schrag et al. 2009; De La Cuadra-Grande et al. 2025)

Clinical goal	Recommended PROMs
Assessing treatment effects	PDQ-39, PDQ-8, SF-36, EQ-5D
Frequent assessments, lower respondent burden	PDQ-8, EQ-5D
Assessing caregiver HRQoL	PIMS
Long-term HRQoL tracking	PDQ39, PDQL, SF-36, SCOPA-PS
Health-economic studies	EQ-5D

EQ-5D: EuroQol 5-Dimension questionnaire; HRQoL: health-related quality of life; PD: Parkinson’s disease; PDQ-8: 8-item Parkinson’s Disease Questionnaire; PDQ-39: 39-item Parkinson’s Disease Questionnaire; PDQL: Parkinson’s Disease Quality of Life Questionnaire; PIMS: Parkinson’s Impact Scale; PROMs: patient-reported outcome measures; SCOPA-PS: Scales for Outcomes in Parkinson’s Disease–Psychosocial; SF-36: Short Form 36-item Health Survey

(Page et al. 2017; Perepezko et al. 2023). Among them, the

26-item Parkinsonism Carers’ Quality of Life questionnaire (PQoL Carer) and the Parkinson’s Disease Questionnaire-Carer (PDQ-Carer) have been specifically developed and validated for PD (Jenkinson et al. 2012; Pillas et al. 2016, 2017; Ferrer-Cascales et al. 2016). Although systematic reviews support their use as appropriate, neither instrument is currently included among the scales formally recommended by the MDS.

HRQoL deterioration in PD is influenced by a wide range of factors that extend beyond motor and NMS to include mental, functional, and social domains (Martinez-Martin 2017). Compared with healthy controls, patients with PD exhibit significantly poorer HRQoL across most domains, with meta-analytic evidence identifying motor dysfunction, neuropsychiatric symptoms, cognitive decline, fatigue, sleep disturbances, disease severity and duration, treatment-related side effects, and lack of social support as the strongest contributors (Zhao et al. 2021). In the early stages of

the disease, NMS burden, particularly depression, sleep disturbances, cognitive decline, and apathy, as well as motor impairment, especially gait and balance disturbances, are the most influential determinants of HRQoL (Marras et al. 2008; Barone et al. 2009; Post et al. 2011; Müller et al. 2013; Santos García et al. 2019; Tosin et al. 2024). During these early phases, the psychological and social impact of the disease is particularly pronounced, as patients are more active, and professionally and socially engaged (Mehanna and Jankovic 2019).

As the disease advances, the progressive accumulation of both motor symptoms, NMS, and fluctuations, further compromises HRQoL and increases caregiver burden (Rahman et al. 2008; Gallagher et al. 2010; Soh et al. 2011; Valkovic et al. 2014; Pigott et al. 2024; Ledda et al. 2025). Because PD represents a clinical continuum, defining advanced PD remains challenging, and no universally accepted definition currently exists. The most widely accepted features characterizing advanced PD include: moderate to severe motor fluctuations, ≥ 1 h of troublesome dyskinesia per day, ≥ 2 h of OFF-state, the need for ≥ 5 daily oral levodopa doses, dementia, troublesome hallucinations, recurrent falls despite optimized treatment, and significant difficulties with activities of daily living (ADL) (Antonini et al. 2018; Fasano et al. 2019; Malaty et al. 2022; Aslam et al. 2024).

From a pragmatic perspective, advanced PD is not defined by disease duration or motor severity alone, but rather by the point at which troublesome motor or NMS respond inadequately to oral therapies, resulting in significant functional impairment that cannot be reversed with standard medication (Antonini et al. 2018; Aslam et al. 2024).

In the following sections, we analyze the impact of advanced disease on HRQoL (Fig. 1). It should be noted that most studies assessing HRQoL in PD do not stratify cohorts by disease stage. Nevertheless, the studies reviewed include a substantial proportion of patients with long disease duration, Hoehn and Yahr stage ≥ 3 , and motor fluctuations, allowing reasonably robust conclusions regarding the impact of PD on HRQoL in the advanced population (Tosin et al. 2024).

Impact of motor symptoms on HRQoL in advanced PD

Motor symptoms contribute to HRQoL impairment not only through limitations in mobility-related domains but also by adversely affecting patients' overall HRQoL (Schrag et al. 2000; Diamond 2005; Rahman et al. 2008). In advanced PD, axial motor symptoms such as gait impairment, postural instability, and falls, show particularly strong associations

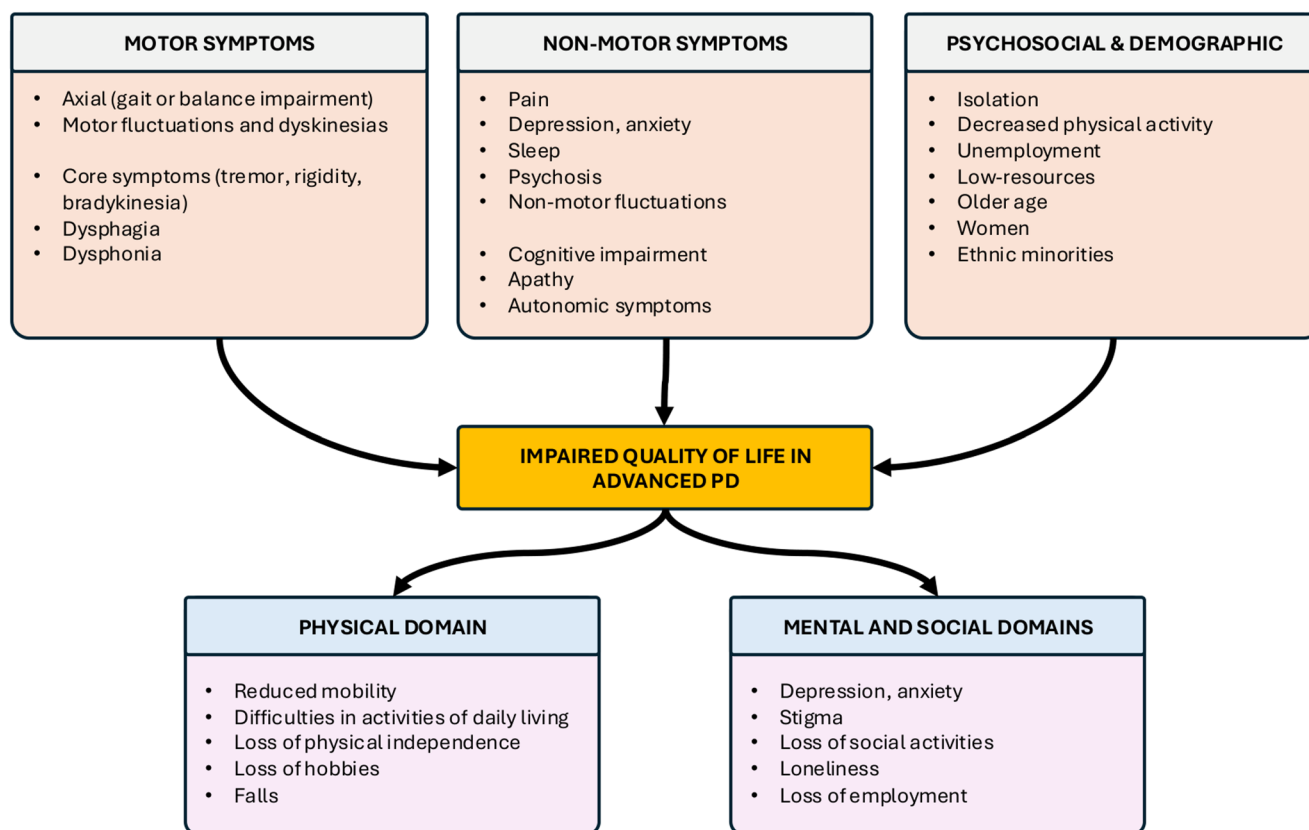


Fig. 1 Factors and consequences of advanced PD on HRQoL. PD: Parkinson's disease

with reduced HRQoL (Rahman et al. 2008; Visser et al. 2008; Tosin et al. 2024). In addition, cardinal motor features such as bradykinesia, rigidity, and tremor impair manual dexterity and fine motor control, further contributing to HRQoL deterioration (Rahman et al. 2008; Martínez-Martín et al. 2014). These motor deficits translate into PD-related functional difficulties, including problems with eating, dressing, walking, and maintaining balance, ultimately leading to loss of independence in ADL (Rahman et al. 2008; Martínez-Martín et al. 2014; Klietz et al. 2018; Pigott et al. 2024). Shuffling gait and difficulty turning are particularly relevant, as they increase the risk of falls and may further compromise HRQoL through injury, hospitalization, social embarrassment, and fear of falling, which often results in activity avoidance and reduced social participation (Wielinski et al. 2005). Other motor manifestations, such as bulbar symptoms including dysphagia and dysphonia, which become more prominent in advanced stages, have also been shown to negatively affect HRQoL due to their substantial psychosocial impact (Plowman-Prine et al. 2009; Van Hoozen et al. 2016).

Motor fluctuations and dyskinesias are well-recognized complications of chronic levodopa therapy in PD, typically emerging after several years of treatment as a result of nigrostriatal degeneration and pulsatile dopaminergic stimulation (Tanner and Ostrem 2024). The prevalence of motor fluctuations increases with disease duration and cumulative levodopa exposure, affecting over half of patients after 5 years of onset and nearly all by 10 years; dyskinesias are less common but still affect a substantial proportion, with risk factors including younger age at onset, higher levodopa dose, and longer treatment duration (Manson et al. 2012; Kelly et al. 2019; Tanner and Ostrem 2024). Large cohort studies consistently identify motor fluctuations and to a lesser extent dyskinesias as major determinants of impaired HRQoL (Chapuis et al. 2005; Hechtner et al. 2014; Perez-Lloret et al. 2017; Wu et al. 2019; Santos-García et al. 2024). Motor fluctuations have a particularly strong influence through their duration and unpredictability rather than their severity, with a clear dose-dependent relationship between average daily OFF-state time and HRQoL (Perez-Lloret et al. 2017; Thach et al. 2021). In a Spanish cohort, the presence of dyskinesias was associated with worse HRQoL at baseline, and the development of disabling dyskinesias during a 5-year follow-up predicted further HRQoL deterioration (Santos-García et al. 2024). The impact of dyskinesias on HRQoL appears to be domain-specific, particularly affecting mobility, ADL, emotional well-being, stigma, and pain or discomfort, with peak dose dyskinesias more strongly associated with impairments in ADL and cognition, and biphasic dyskinesias exerting a greater effect on stigma (Chapuis et al. 2005; Hechtner et al. 2014; Santos-García et

al. 2024). Among all motor complication subtypes, biphasic dyskinesias, nocturnal akinesia, and unpredictable OFF episodes, have demonstrated the most detrimental impact in HRQoL (Chapuis et al. 2005; Hechtner et al. 2014). The cumulative burden of motor fluctuations and dyskinesias, together with their unpredictable and disabling nature, interferes with employment, functional independence, and social interactions, while also increasing caregiver strain (Carter and Nutt 1998; Adler 2002; Regensburger et al. 2025). In a US observational study, patients experiencing OFF episodes were less likely to maintain full-time employment and more likely to live with extended family members or reside in long-term care facilities (Thach et al. 2021). Consequently, early recognition and optimal management of motor complications are critical for preserving HRQoL in patients with PD.

Impact of non-motor symptoms on HRQoL in advanced PD

Both the overall burden of NMS and individual NMS have been consistently associated with poorer HRQoL in PD, showing equal or greater impact than motor symptoms (Chrischilles et al. 2002; Forsaa et al. 2008; Rahman et al. 2008; Gallagher et al. 2010; Li et al. 2010; Martínez-Martín et al. 2014; Maeda et al. 2017; Bock et al. 2022; Tosin et al. 2024; Morimoto et al. 2024; Williamson et al. 2025; Ledda et al. 2025). Unlike motor manifestations, NMS predominantly affect the psychosocial domain rather than the physical domain (Cassidy et al. 2024). The spectrum of individual NMS associated with worse HRQoL includes cognitive impairment, psychosis, depression, anxiety, apathy, irritability, fatigue, pain, dysautonomia, sleep disturbances, and impulse control disorders (Herlofson and Larsen 2003; Martínez-Martín et al. 2006; Schrag 2006; Carod-Artal et al. 2007; Havlikova et al. 2008; Visser et al. 2009; Leroi et al. 2011; Yamanishi et al. 2013; Storch et al. 2013; Phu et al. 2014; Valkovic et al. 2014; Skovranek et al. 2015; Rieu et al. 2016; Berganzo et al. 2016; Sun et al. 2018; Merola et al. 2018; Kurihara et al. 2020; Lubomski et al. 2021; Bugalho et al. 2021; Grall-Bronnec et al. 2024; Caap-Ahlgren and Dehlin 2026). Although most of these studies include mixed PD populations, a substantial proportion of patients represent an advanced disease, making these findings highly informative for these stages, in which many NMS become more prominent (Gallagher et al. 2010; Valkovic et al. 2015; Pigott et al. 2024; Ledda et al. 2025).

Despite variability in the relative impact of individual NMS across studies, pain, anxiety, and depression consistently emerge as key determinants of poor HRQoL (Martínez-Martín 2011; Zhao et al. 2021). Pain has repeatedly been identified as one of the most bothersome symptoms

in patients with advanced PD (Roh et al. 2009; Skorvanek et al. 2015; Choi et al. 2017; Lubomski et al. 2021; Tosin et al. 2024; Williamson et al. 2025). In these stages, musculoskeletal, neuropathic, and dystonic pain become more frequent and have a greater negative impact in HRQoL than in earlier stages (Valkovic et al. 2015; Soumiya et al. 2022). Similarly, depression and anxiety are among the most extensively studied NMS and show a strong and consistent association with impaired HRQoL, in some reports exerting an effect-size up to twice that of motor symptoms (The Global Parkinson's Disease Survey (GPDS) Steering Committee 2002; Sławek et al. 2005; Schrag 2006; Greene and Camicioli 2007; Carod-Artal et al. 2008; Visser et al. 2008; Gallagher et al. 2010; Soh et al. 2011; Gómez-Esteban et al. 2011; Winter et al. 2011; Hanna and Cronin-Golomb 2012; Hinnell et al. 2012; Skorvanek et al. 2015; Rieu et al. 2016; D'Iorio et al. 2017). Mood disorders are particularly disruptive due to their association with disengagement from social and family environments (Soh et al. 2011). Furthermore, the relationship between depression and HRQoL appears to be bidirectional: depressive symptoms contribute to poorer HRQoL, while reduced HRQoL arising from other factors may increase vulnerability to depression (Schrag 2006; Santos-García and De La Fuente-Fernández 2013).

Attentional/executive deficits can negatively affect HRQoL in the early stages, potentially modulated by a preserved insight; however, as the disease advances, dementia appears to have a greater impact (The Global Parkinson's Disease Survey (GPDS) Steering Committee 2002; Klepac et al. 2008; Winter et al. 2010b; Leroi et al. 2012; Lawson et al. 2016; D'Iorio et al. 2017; Bock et al. 2022; Magano et al. 2024). Nevertheless, cognitive impairment has not been consistently associated with poorer HRQoL across studies (Žiropada et al. 2009; Martinez-Martin 2011; Bugalho et al. 2016). This may partly reflect methodological issues, as patients with dementia are often excluded from HRQoL assessments due to concerns regarding the reliability of PROMs.

Within the spectrum of autonomic dysfunction, orthostatic hypotension has been identified as one of the most influential factors negatively affecting HRQoL, even when symptoms are mild or subclinical (Merola et al. 2016, 2018; Longardner et al. 2022). Other autonomic disturbances, including gastrointestinal, thermoregulatory, urinary, and sexual dysfunction, have also been shown to contribute to reduced HRQoL (Merola et al. 2018).

Beyond motor complications, non-motor fluctuations (NMF) are a common feature of advanced PD and represent a major, yet often underrecognized, determinant of HRQoL (Martinez-Fernandez et al. 2016a, b). NMF are typically categorized into three domains: cognitive/neuropsychiatric, dysautonomic, and sensory/pain-related (Riley

and Lang 1993). They occur more frequently during the OFF-state, when patients commonly experience increased anxiety, depressive symptoms, and attention/concentration impairment, whereas during ON-state they may sometimes report an elevated mood (Martinez-Fernandez et al. 2016a, b; Ossig et al. 2017). From a patient-centered perspective, NMF are frequently perceived as equally or even more disabling than motor fluctuations (Witjas et al. 2002). Nevertheless, the specific contribution of NMF to HRQoL has been less studied. Recent evidence suggests that both OFF- and ON-state NMF negatively affect HRQoL, with OFF-state fluctuations exerting the greatest impact, particularly through anxiety, depression, or pain (Storch et al. 2013; Rieu et al. 2016; Kakimoto et al. 2023; Ledda et al. 2024; Williamson et al. 2025).

Collectively, NMS and NMF produce a strong multidimensional impact on HRQoL, affecting ADL, emotional well-being, social functioning, physical capacity, occupational performance, and economic status (Williamson et al. 2025; Ledda et al. 2025).

Demographic, socioeconomic, cultural, and psychological determinants of HRQoL in advanced PD

Beyond disease-specific clinical features, a wide range of demographic, socioeconomic, cultural, and psychological factors substantially shape HRQoL in PD. Although individual studies often identify different predictors reflecting methodological and population heterogeneity, a consistent body of evidence demonstrates that many of these factors play a critical and independent role.

Among demographic variables, older age and lower educational level are consistently associated with poorer HRQoL across multiple cohorts (Hobson 1999; Cubo et al. 2002; Žach et al. 2004; Winter et al. 2010a, b; Santos García et al. 2021; Magano et al. 2024). Sex-related differences have also been reported, with women often experiencing poorer HRQoL, particularly driven by higher levels of depression, fatigue, and perceived stigma (Behari et al. 2005; Moore et al. 2005; Winter et al. 2010a; Yoon et al. 2017; Balash et al. 2019; Crispino et al. 2020; Meng et al. 2022). This likely reflects persistent gender-related social stressors and inequities embedded within patriarchal societal structures, which can exacerbate psychological burden and reduce coping resources.

A broad set of socioeconomic and structural factors further contribute to diminished HRQoL. Belonging to ethnic minorities, low-resource countries, unemployment, low income, malnutrition, or residence in rural areas have all been linked to worse HRQoL (Cubo et al. 2002; Žach et al. 2004; Ray et al. 2006; Klepac et al. 2007; Carod-Artal et al.

Table 3 Advanced therapies and HRQoL in PD

Therapy	Strengths	Limitations	Effect on HRQoL	
			Short-term	Long-term
DBS	Adjustable; robust efficacy; widely studied	Surgical procedure; device-related complications	+++	+
CSAI	Reversible; less invasive	Neuropsychiatric, hypotension and skin adverse effects	++	±
LCIG	Reduced need for oral therapy	Surgical procedure; device-related complications	++	±
MRgFUS	Minimally-invasive	Non-adaptable; non-reversible; limited long-term data	+++	±
CSLCI	Reversible; less invasive	Limited long-term data	++	NA

DBS: deep-brain stimulation; CSAI: continuous subcutaneous apomorphine infusion; CSLCI: continuous subcutaneous (fos)levodopa-(fos)carbidopa infusion; HRQoL: health-related quality of life; LCIG: levodopa-carbidopa intestinal gel; LCSCI: levodopa-carbidopa or foslevodopa/foscarbidopa subcutaneous infusion; MRgFUS: Magnetic resonance-guided focused ultrasound; NA: not available; PD: Parkinson's disease

2007; Sheard et al. 2014; Ongun 2018; Gruber et al. 2020; Trang et al. 2020; Lubomski et al. 2021; Bailey et al. 2022; Bock et al. 2022; Hoseinipalangi et al. 2023; Di Luca et al. 2023; Magano et al. 2024). These findings underscore the role of social vulnerability, reflecting inequalities in access to healthcare resources, increased disease-related stigma, delayed help-seeking behavior due to limited health education, and broader structural barriers to care.

Finally, several psychosocial and lifestyle-related factors negatively influence HRQoL. Lack of psychological support for adequate disease-related adjustment, social isolation, excessive caregiver burden, and sedentary behavior are consistently associated with poorer outcomes (Suzukamo et al. 2006; Winter et al. 2010b; Andreadou et al. 2011; Martinez-Martin et al. 2012; Chen et al. 2020; Trang et al. 2020; Subramanian et al. 2020; Lubomski et al. 2021; Prell et al. 2023; Rashid et al. 2023; Cassidy et al. 2024; Morley et al. 2026).

These findings highlight that HRQoL in PD is not solely determined by symptom severity but is strongly modulated by social characteristics, psychological resilience, social connectedness, and lifestyle factors. Although many of these determinants might be expected to exert a greater influence during earlier disease stages, the studies cited also include patients with advanced PD, suggesting that their impact on HRQoL persists across the entire disease course.

Role of device-aided and other advanced therapies in improving HRQoL

Advanced therapies provide continuous dopaminergic stimulation and have demonstrated clinical efficacy in controlling OFF fluctuations, dyskinesias, and NMS, thereby restoring autonomy and stability (Table 3). Earlier initiation of these therapies may facilitate earlier achievement of optimal functioning and help avoid missing a potential therapeutic window. Numerous studies have evaluated the impact of these therapies on HRQoL in advanced PD.

Deep brain stimulation (DBS)

DBS of the subthalamic nucleus (STN-DBS) is a well-established and effective treatment for improving motor and NMS in patients with advanced PD (Deuschl et al. 2006). Large clinical trials and cohort studies have also demonstrated that STN-DBS is superior to best medical treatment in improving HRQoL in patients whose symptoms are insufficiently controlled with oral medication (Martínez-Martín et al. 2002; Just and Ostergaard 2002; Lagrange et al. 2002; Erola et al. 2005; Deuschl et al. 2006; Weaver 2009; Moro et al. 2010; Williams et al. 2010; Okun et al. 2012; Gorecka-Mazur et al. 2019; Lachenmayer et al. 2021; Kähkölä et al. 2024). These improvements are attributable not only to motor benefits, such as reduced dyskinesia, decreased OFF time, and improved mobility, but also to improvements in NMS or NMF, facilitating more active participation in daily and social life (Dafsari et al. 2018; Krack et al. 2019; Ledda et al. 2024). Although predictors of improvement in HRQoL remain controversial, associations have been reported with preoperative ON/OFF differences, dyskinesia burden, age, cognitive performance, and NMS burden (Witt et al. 2011; Floden et al. 2014; Geraedts et al. 2020; Gronostay et al. 2024). In addition, changes in depression and anxiety, development of apathy following medication reduction, comorbidities, and psychosocial factors have a substantial influence on these improvements (Daniels et al. 2011; Tykocki et al. 2012; Martinez-Fernandez et al. 2016).

Long-term follow-up studies have consistently demonstrated sustained motor benefits of STN-DBS; however, the durability of HRQoL improvements remains less clear (Bove et al. 2021). While recent data suggest that HRQoL may remain stable even beyond 5 years after surgery, available studies are heterogeneous (Lyons and Pahwa 2005; Siderowf et al. 2006; Bove et al. 2021; Castrioto et al. 2022; Jost et al. 2024; Starr et al. 2025). Several studies have reported a gradual decline in benefits over time, with scores returning to preoperative levels (Aviles-Olmos et al. 2014; Lezcano et al. 2016; Büttner et al. 2019; Bjerknæs et al. 2022). Overall, the available evidence suggests that

while HRQoL gains may attenuate over time, STN-DBS appears to stabilize trajectories compared with the progressive decline observed under oral therapies.

Globus pallidus internus (GPi) DBS represents the second most commonly used surgical target in PD. Several clinical trials have consistently demonstrated that GPi-DBS leads to significant improvements in HRQoL in advanced PD (Rodrigues et al. 2007; Volkmann et al. 2009; Moro et al. 2010). However, long-term outcomes remain less clear due to the limited available literature. As with STN-DBS, a gradual attenuation of HRQoL benefits over extended follow-up has been attributed to disease progression, increasing NMS burden, and/or adaptive changes in patients' subjective perception of health status over time (Volkmann et al. 2009; Weaver et al. 2012).

While the STN is frequently selected as the preferred target for DBS, the choice of the optimal target remains a matter of ongoing debate. Comparative studies conducted to date have yielded conflicting results, with most failing to demonstrate significant differences in HRQoL outcomes between targets, either in the short- or long-term (Volkmann et al. 2009; Zahodne et al. 2009; Follett et al. 2010; Weaver et al. 2012; Odekerken et al. 2013; Cerner et al. 2020; Murcia Carretero et al. 2024). Consequently, there is currently no clear recommendation favoring one target over the other, and further well-designed comparative studies are needed to clarify potential differences in HRQoL improvements between DBS targets (Rughani et al. 2018; Zhang et al. 2021; Lachenmayer et al. 2021).

Continuous infusion therapies

Multiple randomized trials and *real-world* studies have shown that initiation of continuous subcutaneous apomorphine infusion (CSAI) in patients previously treated with oral dopaminergic therapy is associated with significant improvements in HRQoL across both physical and mental domains, which correlate closely with improvements in motor and NMS (Martinez-Martin et al. 2015; Drapier et al. 2016; Kimber et al. 2017; Houvenaghel et al. 2018; Dafsari et al. 2019; Fernández-Pajarín et al. 2021; Fernández-Pajarín et al. 2022; Isaacson et al. 2025). However, not all studies have demonstrated sustained benefits, with some reporting absent short-term effects or a loss of gains over longer follow-up despite persistent motor improvement (Auffret et al. 2017; Katzenschlager et al. 2018, 2021; Meira et al. 2021; De Cock et al. 2022).

Similarly, levodopa-carbidopa intestinal gel infusion (LCIG) has consistently demonstrated improvements in motor symptoms, OFF-state time, dyskinesias, NMS, and HRQoL, with effects maintained over time in numerous clinical trials and observational studies (Antonini et al.

2008, 2017, 2020; Honig et al. 2009; Foltynie et al. 2013; Olanow et al. 2014; Fernandez et al. 2015; Martinez-Martin et al. 2015; Chang et al. 2016; Pålhagen et al. 2016; Murata et al. 2016; Krüger et al. 2017; De Fabregues et al. 2017; Vijjaratnam et al. 2018; Ehlers et al. 2020; Standaert et al. 2021; Simu et al. 2021; Valldeoriola et al. 2021; Fasano et al. 2023; Ramirez-Zamora et al. 2025). Nonetheless, some studies have also failed to demonstrate clear advantages over optimized oral therapy or sustained benefits over time in terms of HRQoL (Slevin et al. 2015; Fernandez et al. 2018). One proposed explanation is that HRQoL in LCIG correlates more strongly with improvements in NMS, particularly sleep disturbances, than with motor improvement (Kovács et al. 2022). Another potential explanation is that patients selected for infusion therapies typically represent a more advanced and vulnerable clinical profile, being older and exhibiting a higher NMS burden, more severe motor impairment, and reduced autonomy (Santos-García et al. 2025). This raises the possibility that introducing infusion therapies earlier in patients with a less advanced disease as for DBS, may lead to greater improvements in HRQoL. Additional contributing factors may include disease progression and suboptimal LCIG dosing in routine clinical practice (Szatmári et al. 2024).

Levodopa-entacapone-carbidopa intestinal gel (LECI) infusion represents a more recent therapeutic option, achieving higher and more stable plasma levodopa concentrations compared with LCIG (Senek et al. 2017). *Real-world* evidence suggests that LECIG is associated with clinically meaningful improvements in motor symptoms and HRQoL (Öthman et al. 2021; Santos-García et al. 2025; Lungu et al. 2025).

Comparative studies between classical advanced therapies

Comparative studies among classical device-aided therapies remain scarce and heterogeneous. Overall, available evidence indicates that improvements in HRQoL are evident across all of them. While some studies report no significant differences between treatment modalities, others suggest a greater HRQoL benefit with LCIG or CSAI (Dafsari et al. 2019; Antonini et al. 2022; Santos-García et al. 2025).

Other advanced therapies

Recent advances in medical and surgical therapies have substantially expanded the therapeutic armamentarium for improving HRQoL in patients with advanced PD.

Magnetic resonance-guided focused ultrasound (MRg-FUS), a less invasive alternative to DBS, enables targeted ablation of deep brain structures without craniotomy and has been most extensively studied in thalamic and STN targets,

demonstrating robust short- and long-term motor improvement (Bond et al. 2017; Martínez-Fernández et al. 2020). For thalamotomy, these symptomatic benefits consistently translate into meaningful gains in HRQoL, whereas unilateral and bilateral subthalamotomy show clear short-term HRQoL improvements, with long-term effects that are less consistent in some studies (Schlesinger et al. 2015; Bond et al. 2017; Martínez-Fernández et al. 2018, 2020, 2023, 2024; Zaaroor et al. 2018; Sperling et al. 2018; Maragkos et al. 2023; Monteiro et al. 2024; Armengou-Garcia et al. 2024; Katunina et al. 2025). In a recent comparative study, STN-MRgFUS was classified as an effective therapy for improving HRQoL, although its magnitude of benefit was lower than that observed with GPi-DBS and STN-DBS (Liang et al. 2025). Evidence for less frequently targeted regions (e.g., GPi, pallidothalamic tract, or dual targets) remains comparatively sparse but similarly suggests that symptomatic improvement can yield parallel benefits in HRQoL (Jung et al. 2018; Gallay et al. 2020, 2021; Krishna et al. 2023; Chen et al. 2023; Ikezawa et al. 2025).

In parallel, continuous subcutaneous infusion of levodopa-carbidopa or foslevodopa-foscarbidopa have emerged as alternatives to CSAI, LCIG and LCEIG, providing improved control of motor fluctuations and sleep disturbances in patients inadequately managed with oral therapy, and consistently translating into meaningful improvements in HRQoL (Soileau et al. 2022, 2025; Aldred et al. 2023, 2025; Espay et al. 2024; Chaudhuri et al. 2024; Baille et al. 2025; Desjardins et al. 2025; Antonini et al. 2025).

HRQoL in caregivers

Caregivers play a central role in the management of a progressive and disabling condition such as PD. Their involvement has been associated with better patient HRQoL, delayed institutionalization, and reduced healthcare costs (Rashid et al. 2023; Bhanupriya et al. 2024). However, as the disease progresses, increasing dependency, fluctuating symptoms, and neuropsychiatric manifestations place substantial demands on caregivers, with negative consequences for both caregivers and patients (Rashid et al. 2023). Traditionally, caregiver-centered research has focused primarily on burden, understood as the objective tasks associated with caregiving. More recently, attention has shifted toward caregiver HRQoL, a distinct construct that captures the broader impact of caregiving responsibilities on caregivers' physical, psychological, and social well-being (Martinez-Martin et al. 2012). In this sense, HRQoL may remain relatively preserved despite high levels of burden, underscoring that HRQoL, rather than burden alone, should be considered the primary outcome when evaluating caregiver well-being (Schrage et al. 2006; Martinez-Martin et al. 2012).

Overall, caregivers of PD patients report significantly lower HRQoL than the general population, with a progressive decline as the disease advances and caregiving becomes increasingly time-consuming, physically, and psychologically demanding (Carter et al. 1998; Aarsland et al. 1999; Martínez-Martín et al. 2005; Schrage et al. 2006; Martinez-Martin et al. 2008a; Goldsworthy and Knowles 2008; Kelly et al. 2012; Genç et al. 2019; Lee et al. 2019; Henry et al. 2020; Lubomski et al. 2021; Nagaki et al. 2023; Merritt et al. 2023). This progressive increase in caregiving responsibilities often leads to social isolation and loneliness, particularly in advanced PD (Balash et al. 2017; Rosqvist et al. 2021; Merritt et al. 2023). Nevertheless, cultural context may modulate this experience, as caregiving may be perceived as less burdensome in cultures where caring for a family member is regarded as a valued responsibility and a source of pride (Smith et al. 2020).

Similar to patient HRQoL, NMS have a greater negative impact on caregiver HRQoL than motor symptoms (Rosqvist et al. 2022; Nagaki et al. 2023; Tosin et al. 2024). Among these, depression and anxiety show the most consistent and robust associations (Miller et al. 1996; Schrage et al. 2006; Martínez-Martín et al. 2007; Ozdilek and Gunal 2012; Martinez-Martin et al. 2012; Tanji et al. 2013; Carod-Artal et al. 2013). Other relevant NMS include sleep disturbances, apathy, impulsivity, cognitive impairment, psychosis, and NMF (Happe 2002; Pal et al. 2004; Aarsland et al. 2007; Morley et al. 2012; Martinez-Martin et al. 2012; Lee et al. 2019; Rosqvist et al. 2022; Nagaki et al. 2023; Gencer et al. 2023; Ledda et al. 2025). In advanced PD, dementia and psychosis, are particularly prevalent and have been linked to social isolation, depressive symptoms, and suicidal ideation among caregivers (Mantri et al. 2021). Beyond cognitive/neuropsychiatric symptoms, sleep disturbances and axial motor symptoms emerge as key determinants of caregiver HRQoL at these stages (Tosin et al. 2024).

Demographic and social factors further influence caregiver HRQoL. Most caregivers are partners or direct descendants, typically women (Martinez-Martin et al. 2008b). Female sex has been associated with poorer caregiver HRQoL, potentially reflecting socially constructed gender roles in which caregiving is perceived as an expected duty (Henry et al. 2020; Rosqvist et al. 2022; Nagaki et al. 2023). Greater social support, a positive patient-caregiver relationship, and not being the patient's partner or close family member are also associated with better HRQoL (Lee et al. 2019; Rosqvist et al. 2022).

Given the substantial time, physical, and emotional demands of caregiving in PD, supportive interventions should be systematically considered. These include cognitive-behavioral therapy, psychoeducational interventions, support groups, rehabilitation programs, communication

skills training, and respite care, all of which may help mitigate caregiver distress and improve HRQoL (Martinez-Martin et al. 2012).

Conclusions

The assessment of HRQoL has become an essential dimension of clinical research in PD and other neurodegenerative disorders. This growing relevance is driven by several converging factors. On the one hand, in the postmaterialist era, where economic and material security has largely stabilized, societal priorities have shifted toward values such as self-expression, HRQoL, personal fulfillment, and subjective well-being. Patients are increasingly aware not only of what treatments can achieve, but also of what they hope to maintain or regain in their daily lives. On the other hand, given the chronic nature of the disease the emergence of increasingly complex and costly therapeutic strategies has intensified the need to distinguish interventions that truly improve patients' lived experience from those that provide measurable clinical benefits without a tangible impact on well-being. This distinction is particularly relevant in advanced PD, where therapeutic interventions often entail substantial economic costs. Patients with advanced PD generate significantly higher direct and indirect healthcare costs, not only due to advanced therapies themselves but also because of increased healthcare utilization, caregiver needs, and social support requirements (García-Agua Soler et al. 2025). In public healthcare systems, where resources are inherently finite, cost-effectiveness analyses have become central to decision-making, often framed around willingness-to-pay thresholds per DALY gained. Notably, some pharmacoeconomic evaluations have shown that certain advanced therapies, such as LCIG, may exceed commonly accepted DALY thresholds in specific contexts (García-Agua Soler et al. 2025). These considerations further reinforce the importance of pharmacoeconomic research and of incorporating HRQoL outcomes into therapeutic evaluations.

While motor impairment, particularly axial symptoms, undoubtedly exert a substantial impact on HRQoL in advanced PD, the evidence consistently demonstrates that NMS have an even greater influence. This impact arises not only from more static symptoms but also from NMF. Unlike motor symptoms, NMS frequently remain unrecognized, especially in healthcare settings with high clinical workload. Limited patient awareness regarding the non-motor features attributable to PD further contributes to this under-detection (Chaudhuri et al. 2010). Consequently, NMS are often undertreated, despite becoming increasingly burdensome in advanced stages and, in many cases, being amenable to relatively straightforward therapeutic

interventions (Rodríguez-Antigüedad et al. 2025). This highlights the need to move away from a traditionally paternalistic model of care toward a more participatory approach, in which patients are empowered to actively engage in disease management. The systematic use of PROMs, diaries, and questionnaires can facilitate the identification of clinically relevant symptoms that are difficult to capture within the constraints of brief outpatient visits. Such strategies will substantially enhance HRQoL by enabling more targeted and timely interventions. In addition, avoiding delays in the assessment of advanced therapies is essential to optimize HRQoL, given the well-established efficacy of these treatments.

In advanced PD, the role of caregivers deserves particular attention, as their well-being is intrinsically linked to patient outcomes (Santos-García and De La Fuente-Fernández 2015). Eventually, every patient will require caregiver support to varying degrees. Although caregivers have been underrepresented in clinical research, there is increasing recognition that caregiver burden and HRQoL should be systematically assessed and integrated into study outcomes (Tosin et al. 2024).

Finally, two gaps emerge from the current literature. First, relatively few studies analyze early and advanced stages of PD separately, despite the highly dynamic nature of the disease and the differences in symptom profiles. Pooling heterogeneous populations may obscure stage-specific determinants of HRQoL and limit the interpretability of results. Second, several studies report clear symptomatic improvements that fail to translate into HRQoL gains, either in the short- or long-term. This discrepancy may reflect disease progression, the disproportionate influence of NMS on HRQoL that respond less to certain interventions, or limitations inherent to the instruments used to measure HRQoL. Potential floor effects or insufficient sensitivity of some scales underscore the importance of selecting appropriate, disease-specific PROMs.

In conclusion, improving HRQoL represents the ultimate goal of any intervention in PD. Achieving this requires a comprehensive understanding of the multidimensional nature of the disease and the use of PD-specific instruments to accurately capture HRQoL. NMS warrant particular consideration, as they exert the greatest impact on patients' well-being while frequently remaining overlooked. Demonstrating meaningful improvements in HRQoL for patients and caregivers should be considered an essential criterion for the approval of symptomatic or disease-modifying therapies in public healthcare systems.

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Declarations

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References

Aarsland D, Larsen JP, Karlsen K et al (1999) Mental symptoms in Parkinson's disease are important contributors to caregiver distress. *Int J Geriatr Psychiatry* 14:866–874

Aarsland D, Bronnick K, Ehrt U et al (2007) Neuropsychiatric symptoms in patients with Parkinson's disease and dementia: frequency, profile and associated care giver stress. *J Neurol Neurosurg Psychiatry* 78:36–42. <https://doi.org/10.1136/jnnp.2005.083113>

Adler CH (2002) Relevance of motor complications in Parkinson's disease. *Neurology* 58:S51–S56. https://doi.org/10.1212/wnl.58.suppl_1.s51

Aldred J, Freire-Alvarez E, Amelin AV et al (2023) Continuous subcutaneous Foslevodopa/Foscarbidopa in Parkinson's disease: safety and efficacy results from a 12-month, single-arm, open-label, phase 3 study. *Neurol Ther* 12:1937–1958. <https://doi.org/10.1007/s40120-023-00533-1>

Aldred J, Bouchard M, Martínez-Castrillo JC et al (2025) Efficacy and safety of Foslevodopa/Foscarbidopa monotherapy in patients with Parkinson's Disease. *Movement Disord Clin Pract*. <https://doi.org/10.1002/mdc3.70245>

Andreadou E, Anagnostouli M, Vasdekis V et al (2011) The impact of comorbidity and other clinical and sociodemographic factors on health-related quality of life in Greek patients with Parkinson's disease. *Aging Ment Health* 15:913–921. <https://doi.org/10.1080/13607863.2011.569477>

Antonini A, Mancini F, Canesi M et al (2008) Duodenal Levodopa infusion improves quality of life in advanced Parkinson's disease. *Neurodegener Dis* 5:244–246. <https://doi.org/10.1159/000113714>

Antonini A, Poewe W, Chaudhuri KR et al (2017) Levodopa-carbidopa intestinal gel in advanced Parkinson's: final results of the GLORIA registry. *Parkinsonism Relat Disord* 45:13–20. <https://doi.org/10.1016/j.parkreldis.2017.09.018>

Antonini A, Stoessl AJ, Kleinman LS et al (2018) Developing consensus among movement disorder specialists on clinical indicators for identification and management of advanced Parkinson's disease: a multi-country Delphi-panel approach. *Curr Med Res Opin* 34:2063–2073. <https://doi.org/10.1080/03007995.2018.1502165>

Antonini A, Abbruzzese G, Berardelli A et al (2020) The TANDEM investigation: efficacy and tolerability of levodopa-carbidopa intestinal gel in (LCIG) advanced Parkinson's disease patients. *J Neural Transm* 127:881–891. <https://doi.org/10.1007/s00702-020-02175-1>

Antonini A, Pahwa R, Odin P et al (2022) Comparative effectiveness of device-aided therapies on quality of life and off-time in advanced Parkinson's disease: a systematic review and Bayesian network meta-analysis. *CNS Drugs* 36:1269–1283. <https://doi.org/10.1007/s40263-022-00963-9>

Antonini A, Bergmans B, Kern DS et al (2025) Foslevodopa/Foscarbidopa in younger patients earlier within advanced Parkinson's disease: post hoc analysis of a randomized trial. *Neurol Ther*. <https://doi.org/10.1007/s40120-025-00856-1>

Armengou-Garcia L, Sanchez-Catasus CA, Aviles-Olmos I et al (2024) Unilateral magnetic resonance-guided focused ultrasound lesion of the subthalamic nucleus in Parkinson's disease: a prospective study. *Mov Disord* 39:2230–2241. <https://doi.org/10.1002/mds.30020>

Aslam S, Manfredsson F, Stokes A, Shill H (2024) "Advanced" Parkinson's disease: a review. *Parkinsonism Relat Disord* 123:106065. <https://doi.org/10.1016/j.parkreldis.2024.106065>

Auffret M, Le Jeune F, Maurus A et al (2017) Apomorphine pump in advanced Parkinson's disease: effects on motor and nonmotor symptoms with brain metabolism correlations. *J Neurol Sci* 372:279–287. <https://doi.org/10.1016/j.jns.2016.11.080>

Aviles-Olmos I, Kefalopoulou Z, Tripoliti E et al (2014) Long-term outcome of subthalamic nucleus deep brain stimulation for Parkinson's disease using an MRI-guided and MRI-verified approach. *J Neurol Neurosurg Psychiatry* 85:1419–1425. <https://doi.org/10.1136/jnnp-2013-306907>

Bailey M, Anderson S, Stebbins G et al (2022) Comparison of motor, non-motor, and quality of life phenotype in Black and White patients with Parkinson's disease. *Parkinsonism Relat Disord* 96:18–21. <https://doi.org/10.1016/j.parkreldis.2022.01.018>

Baille G, Patte-Karsenti N, Salardaine Q et al (2025) Switching from Levodopa/Carbidopa intestinal gel to continuous subcutaneous Foslevodopa/Carbidopa infusion in advanced Parkinson's Disease: a case series. *Movement Disord Clin Pract*. <https://doi.org/10.1002/mdc3.70317>

Balash Y, Korczyn AD, Knaani J et al (2017) Quality-of-life perception by Parkinson's disease patients and caregivers. *Acta Neurol Scand* 136:151–154. <https://doi.org/10.1111/ane.12726>

Balash Y, Korczyn AD, Migirov AA, Gurevich T (2019) Quality of life in Parkinson's disease: a gender-specific perspective. *Acta Neurol Scand* 140:17–22. <https://doi.org/10.1111/ane.13095>

Barone P, Antonini A, Colosimo C et al (2009) The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord* 24:1641–1649. <https://doi.org/10.1002/mds.22643>

Behari M, Srivastava AK, Pandey RM (2005) Quality of life in patients with Parkinson's disease. *Parkinsonism Relat Disord* 11:221–226. <https://doi.org/10.1016/j.parkreldis.2004.12.005>

Berganzo K, Tijero B, González-Eizaguirre A et al (2016) Motor and non-motor symptoms of Parkinson's disease and their impact on quality of life and on different clinical subgroups. *Neurología*

- (Engl Ed) 31:585–591. <https://doi.org/10.1016/j.nrleng.2014.10.016>
- Bhanupriya R, Haridoss M, Lakshmi GS, Bagepally BS (2024) Health-related quality of life in Parkinson's disease: systematic review and meta-analysis of EuroQol (EQ-5D) utility scores. *Qual Life Res* 33:1781–1793. <https://doi.org/10.1007/s11136-024-03646-8>
- Bjerknes S, Toft M, Brandt R et al (2022) Subthalamic nucleus stimulation in Parkinson's disease: 5-year extension study of a randomized trial. *Movement Disord Clin Pract* 9:48–59. <https://doi.org/10.1002/mdc3.13348>
- Bloem BR, Okun MS, Klein C (2021) Parkinson's disease. *Lancet* 397:2284–2303. [https://doi.org/10.1016/S0140-6736\(21\)00218-X](https://doi.org/10.1016/S0140-6736(21)00218-X)
- Bock MA, Brown EG, Zhang L, Tanner C (2022) Association of motor and nonmotor symptoms with health-related quality of life in a large online cohort of people with Parkinson disease. *Neurology*. <https://doi.org/10.1212/WNL.0000000000200113>
- Bond AE, Shah BB, Huss DS et al (2017) Safety and efficacy of focused ultrasound thalamotomy for patients with medication-refractory, tremor-dominant Parkinson disease: a randomized clinical trial. *JAMA Neurol* 74:1412. <https://doi.org/10.1001/jamaneurol.2017.3098>
- Bove F, Mulas D, Cavallieri F et al (2021) Long-term outcomes (15 years) after subthalamic nucleus deep brain stimulation in patients with Parkinson disease. *Neurology* 97:e254–e262. <https://doi.org/10.1212/WNL.0000000000012246>
- Bugalho P, Lampreia T, Miguel R et al (2016) Non-motor symptoms in Portuguese Parkinson's disease patients: correlation and impact on quality of life and activities of daily living. *Sci Rep* 6:32267. <https://doi.org/10.1038/srep32267>
- Bugalho P, Ladeira F, Barbosa R et al (2021) Progression in Parkinson's disease: variation in motor and non-motor symptoms severity and predictors of decline in cognition, motor function, disability, and health-related quality of life as assessed by two different methods. *Mov Disord Clin Pract* 8:885–895. <https://doi.org/10.1002/mdc3.13262>
- Büttner C, Maack M, Janitzky K, Witt K (2019) The evolution of quality of life after subthalamic stimulation for Parkinson's disease: a meta-analysis. *Mov Disord Clin Pract* 6:521–530. <https://doi.org/10.1002/mdc3.12819>
- Caap-Ahlgren M, Dehlin O (2026) Insomnia and depressive symptoms in patients with Parkinson's disease Relationship to health-related quality of life. an interview study of patients living at home
- Carod-Artal FJ, Vargas AP, Martinez-Martin P (2007) Determinants of quality of life in Brazilian patients with Parkinson's disease. *Mov Disord* 22:1408–1415. <https://doi.org/10.1002/mds.21408>
- Carod-Artal FJ, Ziolkowski S, Mourão Mesquita H, Martínez-Martin P (2008) Anxiety and depression: main determinants of health-related quality of life in Brazilian patients with Parkinson's disease. *Parkinsonism Relat Disord* 14:102–108. <https://doi.org/10.1016/j.parkreldis.2007.06.011>
- Carod-Artal FJ, Mesquita HM, Ziolkowski S, Martinez-Martin P (2013) Burden and health-related quality of life among caregivers of Brazilian Parkinson's disease patients. *Parkinsonism Relat Disord* 19:943–948. <https://doi.org/10.1016/j.parkreldis.2013.06.005>
- Carter JH, Nutt JG (1998) Family caregiving: a neglected and hidden part of health care delivery. *Neurology* 51:1245–1246. <https://doi.org/10.1212/wnl.51.5.1245>
- Carter JH, Stewart BJ, Archbold PG et al (1998) Living with a person who has Parkinson's disease: the spouse's perspective by stage of disease. *Mov Disord* 13:20–28. <https://doi.org/10.1002/mds.70130108>
- Cassidy I, Doody O, Richardson M, Meskell P (2024) Quality of life and living with Parkinson's disease: a qualitative exploration within an Irish context. *BMC Neurol* 24:275. <https://doi.org/10.1186/s12883-024-03769-y>
- Castrioto A, Debù B, Cousin E et al (2022) Long-term independence and quality of life after subthalamic stimulation in Parkinson disease. *Euro J Neurol* 29:2645–2653. <https://doi.org/10.1111/ene.15436>
- Certera S, Eisinger RS, Wong JK et al (2020) Long-term Parkinson's disease quality of life after staged DBS: STN vs GPi and first vs second lead. *NPJ Parkinsons Dis* 6:13. <https://doi.org/10.1038/s41531-020-0115-3>
- Chang FCF, Kwan V, Van Der Poorten D et al (2016) Intraduodenal levodopa-carbidopa intestinal gel infusion improves both motor performance and quality of life in advanced Parkinson's disease. *J Clin Neurosci* 25:41–45. <https://doi.org/10.1016/j.jocn.2015.05.059>
- Chapuis S, Ouchchane L, Metz O et al (2005) Impact of the motor complications of Parkinson's disease on the quality of life. *Mov Disord* 20:224–230. <https://doi.org/10.1002/mds.20279>
- Chaudhuri KR, Prieto-Jurcynska C, Naidu Y et al (2010) The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: an international study using the nonmotor symptoms questionnaire. *Mov Disord* 25:704–709. <https://doi.org/10.1002/mds.22868>
- Chaudhuri KR, Facheris MF, Bergmans B et al (2024) Improved sleep correlates with improved quality of life and motor symptoms with Foslevodopa/Foscarbidopa. *Movement Disord Clin Pract* 11:861–866. <https://doi.org/10.1002/mdc3.14018>
- Chen K, Tan Y, Lu Y et al (2020) Effect of exercise on quality of life in Parkinson's disease: a systematic review and meta-analysis. *Parkinson's Dis* 2020:1–10. <https://doi.org/10.1155/2020/3257623>
- Chen J-C, Lu M-K, Chen C-M, Tsai C-H (2023) Stepwise dual-target magnetic resonance-guided focused ultrasound in tremor-dominant Parkinson disease: a feasibility study. *World Neurosurg* 171:e464–e470. <https://doi.org/10.1016/j.wneu.2022.12.049>
- Choi S-M, Kim BC, Jung H-J et al (2017) Impact of pain and pain subtypes on the quality of life of patients with Parkinson's disease. *J Clin Neurosci* 45:105–109. <https://doi.org/10.1016/j.jocn.2017.08.002>
- Chrischilles EA, Rubenstein LM, Voelker MD et al (2002) Linking clinical variables to health-related quality of life in Parkinson's disease. *Parkinsonism Relat Disord* 8:199–209. [https://doi.org/10.1016/S1353-8020\(01\)00044-X](https://doi.org/10.1016/S1353-8020(01)00044-X)
- Churrua K, Pomare C, Ellis LA et al (2021) Patient-reported outcome measures (PROMs): a review of generic and condition-specific measures and a discussion of trends and issues. *Health Expect* 24:1015–1024. <https://doi.org/10.1111/hex.13254>
- Crispino P, Gino M, Barbagelata E et al (2020) Gender differences and quality of life in Parkinson's disease. *IJERPH* 18:198. <https://doi.org/10.3390/ijerph18010198>
- Cubo E, Rojo A, Ramos S et al (2002) The importance of educational and psychological factors in Parkinson's disease quality of life. *Euro J Neurol* 9:589–593. <https://doi.org/10.1046/j.1468-1331.2002.00484.x>
- Cummins RA, Lau AL, Stokes M (2004) HRQOL and subjective well-being: noncomplementary forms of outcome measurement. *Expert Rev Pharmacoecon Outcomes Res* 4:413–420. <https://doi.org/10.1586/14737167.4.4.413>
- D'Iorio A, Vitale C, Piscopo F et al (2017) Impact of anxiety, apathy and reduced functional autonomy on perceived quality of life in Parkinson's disease. *Parkinsonism Relat Disord* 43:114–117. <https://doi.org/10.1016/j.parkreldis.2017.08.003>
- Dafsari HS, Silverdale M, Strack M et al (2018) Nonmotor symptoms evolution during 24 months of bilateral subthalamic stimulation in Parkinson's disease. *Mov Disord* 33:421–430. <https://doi.org/10.1002/mds.27283>

- Dafsari HS, Martinez-Martin P, Rizos A et al (2019) EuroInf 2: Subthalamic stimulation, apomorphine, and levodopa infusion in Parkinson's disease. *Mov Disord* 34:353–365. <https://doi.org/10.1002/mds.27626>
- Daniels C, Krack P, Volkman J et al (2011) Is improvement in the quality of life after subthalamic nucleus stimulation in Parkinson's disease predictable? *Mov Disord* 26:2516–2521. <https://doi.org/10.1002/mds.23907>
- De Cock VC, Dodet P, Leu-Semenescu S et al (2022) Safety and efficacy of subcutaneous night-time only apomorphine infusion to treat insomnia in patients with Parkinson's disease (APOMOR-PHEE): a multicentre, randomised, controlled, double-blind crossover study. *Lancet Neurol* 21:428–437. [https://doi.org/10.1016/S1474-4222\(22\)00085-0](https://doi.org/10.1016/S1474-4222(22)00085-0)
- De Fabregues O, Dot J, Abu-Suboh M et al (2017) Long-term safety and effectiveness of levodopa-carbidopa intestinal gel infusion. *Brain Behav* 7:e00758. <https://doi.org/10.1002/brb3.758>
- De La Cuadra-Grande A, Rejas J, Casado MÁ et al (2025) Quality of life measures in Parkinson's disease: a systematic literature review of patient-reported outcomes measures (PROMs) and their psychometric properties. *J Neurol* 272:598. <https://doi.org/10.1007/s00415-025-13348-x>
- Den Oudsten BL, Van Heck GL, De Vries J (2007) Quality of life and related concepts in Parkinson's disease: a systematic review. *Mov Disord* 22:1528–1537. <https://doi.org/10.1002/mds.21567>
- Desjardins C, Salardaine Q, Brandel J, Baille G (2025) Clinical impact of switching from subcutaneous apomorphine to Foslevodopa/Foscarbidopa in advanced Parkinson's disease: a real-world observational study (FOSAPO). *Mov Disord Clin Pract* 12:2330–2336. <https://doi.org/10.1002/mdc3.70254>
- Deuschl G, Schade-Brittinger C, Krack P et al (2006) A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 355:896–908. <https://doi.org/10.1056/NEJMoa060281>
- Diamond A (2005) The effect of deep brain stimulation on quality of life in movement disorders. *J Neurol Neurosurg Psychiatry* 76:1188–1193. <https://doi.org/10.1136/jnnp.2005.065334>
- Drapier S, Eusebio A, Degos B et al (2016) Quality of life in Parkinson's disease improved by apomorphine pump: the OPTIPUMP cohort study. *J Neurol* 263:1111–1119. <https://doi.org/10.1007/s00415-016-8106-3>
- Ehlers C, Timpka J, Odin P, Honig H (2020) Levodopa infusion in Parkinson's disease: individual quality of life. *Acta Neurol Scand* 142:248–254. <https://doi.org/10.1111/ane.13260>
- Erola T, Karinen P, Heikkinen E et al (2005) Bilateral subthalamic nucleus stimulation improves health-related quality of life in Parkinsonian patients. *Parkinsonism Relat Disord* 11:89–94. <https://doi.org/10.1016/j.parkreldis.2004.08.006>
- Espay AJ, Stocchi F, Pahwa R et al (2024) Safety and efficacy of continuous subcutaneous levodopa-carbidopa infusion (ND0612) for Parkinson's disease with motor fluctuations (BouNDless): a phase 3, randomised, double-blind, double-dummy, multicentre trial. *Lancet Neurol* 23:465–476. [https://doi.org/10.1016/S1474-4222\(24\)00052-8](https://doi.org/10.1016/S1474-4222(24)00052-8)
- Fasano A, Fung VSC, Lopiano L et al (2019) Characterizing advanced Parkinson's disease: OBSERVE-PD observational study results of 2615 patients. *BMC Neurol* 19:50. <https://doi.org/10.1186/s12883-019-1276-8>
- Fasano A, García-Ramos R, Gurevich T et al (2023) Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: long-term results from COSMOS. *J Neurol* 270:2765–2775. <https://doi.org/10.1007/s00415-023-11615-3>
- Fernandez HH, Standaert DG, Hauser RA et al (2015) Levodopa-carbidopa intestinal gel in advanced Parkinson's disease: final 12-month, open-label results. *Mov Disord* 30:500–509. <https://doi.org/10.1002/mds.26123>
- Fernandez HH, Boyd JT, Fung VSC et al (2018) Long-term safety and efficacy of levodopa-carbidopa intestinal gel in advanced Parkinson's disease. *Mov Disord* 33:928–936. <https://doi.org/10.1002/mds.27338>
- Fernández-Pajarín G, Sesar Á, Ares B et al (2021) Continuous subcutaneous apomorphine infusion before subthalamic deep brain stimulation: a prospective, comparative study in 20 patients. *Movement Disord Clin Pract* 8:1216–1224. <https://doi.org/10.1002/mdc3.13338>
- Fernández-Pajarín G, Sesar Á, Jiménez Martín I et al (2022) Continuous subcutaneous apomorphine infusion in the early phase of advanced Parkinson's disease: a prospective study of 22 patients. *Clin Parkinsonism Relat Disord* 6:100129. <https://doi.org/10.1016/j.prdoa.2021.100129>
- Ferrer-Cascales R, Cabañero-Martínez MJ, Sánchez-SanSegundo M et al (2016) Spanish version of the Parkinson's disease questionnaire-carer (PDQ-Carer). *Health Qual Life Outcomes* 14:154. <https://doi.org/10.1186/s12955-016-0546-z>
- Floden D, Cooper SE, Griffith SD, Machado AG (2014) Predicting quality of life outcomes after subthalamic nucleus deep brain stimulation. *Neurology* 83:1627–1633. <https://doi.org/10.1212/WNL.0000000000000943>
- Follett KA, Weaver FM, Stern M et al (2010) Pallidal versus subthalamic deep-brain stimulation for Parkinson's Disease. *N Engl J Med* 362:2077–2091. <https://doi.org/10.1056/NEJMoa0907083>
- Foltynic T, Magee C, James C et al (2013) Impact of duodopa on quality of life in advanced Parkinson's Disease: a UK case series. *Parkinsons Dis* 2013:1–5. <https://doi.org/10.1155/2013/362908>
- Forsaa EB, Larsen JP, Wentzel-Larsen T et al (2008) Predictors and course of health-related quality of life in Parkinson's disease. *Mov Disord* 23:1420–1427. <https://doi.org/10.1002/mds.22121>
- Gallagher DA, Lees AJ, Schrag A (2010) What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? *Mov Disord* 25:2493–2500. <https://doi.org/10.1002/mds.23394>
- Gallay MN, Moser D, Rossi F et al (2020) MRgFUS pallidothalamic tractotomy for chronic therapy-resistant Parkinson's Disease in 51 consecutive patients: single center experience. *Front Surg* 6:76. <https://doi.org/10.3389/fsurg.2019.00076>
- Gallay MN, Moser D, Magara AE et al (2021) Bilateral MR-guided focused ultrasound pallidothalamic tractotomy for Parkinson's disease With 1-year follow-up. *Front Neurol* 12:601153. <https://doi.org/10.3389/fneur.2021.601153>
- García-Agua Soler N, García Trujillo L, García-Ruiz AJ (2025) Cost of quality of life in advanced Parkinson's Disease: efficient strategies for disease assessment. *Rev Neurol* 80:33482. <https://doi.org/10.31083/RN33482>
- Genç F, Yuksel B, Tokuc FEU (2019) Caregiver burden and quality of life in early and late stages of idiopathic Parkinson's Disease. *Psychiatry Investig* 16:285–291. <https://doi.org/10.30773/pi.2019.02.20>
- Gencer GYG, Erdem NŞ, Ipek L et al (2023) Caregiver burden and quality of life of caregivers for patients with Parkinson's disease treated with deep brain stimulation. *Ann Indian Acad Neurol* 26:530–536. https://doi.org/10.4103/aian.aian_210_23
- Geraedts VJ, Feleus S, Marinus J et al (2020) What predicts quality of life after subthalamic deep brain stimulation in Parkinson's disease? A systematic review. *Eur J Neurol* 27:419–428. <https://doi.org/10.1111/ene.14147>
- Goldsworthy B, Knowles S (2008) Caregiving for Parkinson's disease patients: an exploration of a stress-appraisal model for quality of life and burden. *J Gerontol B Psychol Sci Soc Sci* 63:P372–P376. <https://doi.org/10.1093/geronb/63.6.P372>
- Gómez-Esteban JC, Tijero B, Somme J et al (2011) Impact of psychiatric symptoms and sleep disorders on the quality of life of patients

- with Parkinson's disease. *J Neurol* 258:494–499. <https://doi.org/10.1007/s00415-010-5786-y>
- Gorecka-Mazur A, Furgala A, Krygowska-Wajs A et al (2019) Activities of daily living and their relationship to health-related quality of life in patients with Parkinson disease after subthalamic nucleus deep brain stimulation. *World Neurosurg* 125:e552–e562. <https://doi.org/10.1016/j.wneu.2019.01.132>
- Grall-Bronnec M, Verholleman A, Victorri-Vigneau C et al (2024) Parkinson's Disease, impulsive-compulsive behaviors, and health-related quality of life. *J Mov Disord* 17:82–88. <https://doi.org/10.14802/jmd.23042>
- Greene T, Camicioli R (2007) Depressive symptoms and cognitive status affect health-related quality of life in older patients with Parkinson's disease. *J Am Geriatr Soc* 55:1888–1890. <https://doi.org/10.1111/j.1532-5415.2007.01384.x>
- Gronostay A, Jost ST, Silverdale M et al (2024) Stratifying quality of life outcome in subthalamic stimulation for Parkinson's disease. *J Neurol Neurosurg Psychiatry* 95:630–638. <https://doi.org/10.1136/jnnp-2023-332272>
- Gruber MT, Witte OW, Grosskreutz J, Prell T (2020) Association between malnutrition, clinical parameters and health-related quality of life in elderly hospitalized patients with Parkinson's disease: a cross-sectional study. *PLoS ONE* 15:e0232764. <https://doi.org/10.1371/journal.pone.0232764>
- Han S, Chu M, Ren Y et al (2025) Global, regional, and national epidemiology of neurological disorders and subcategories: incidence and disability-adjusted life years, 1990–2021. *Eur J Med Res* 30:711. <https://doi.org/10.1186/s40001-025-02958-w>
- Hanna KK, Cronin-Golomb A (2012) Impact of anxiety on quality of life in Parkinson's disease. *Parkinsons Dis* 2012:1–8. <https://doi.org/10.1155/2012/640707>
- Happe S (2002) The association between caregiver burden and sleep disturbances in partners of patients with Parkinson's disease. *Age Ageing* 31:349–354. <https://doi.org/10.1093/ageing/31.5.349>
- Havlikova E, Rosenberger J, Nagyova I et al (2008) Impact of fatigue on quality of life in patients with Parkinson's disease. *Euro J Neurol* 15:475–480. <https://doi.org/10.1111/j.1468-1331.2008.02103.x>
- Hechtner MC, Vogt T, Zöllner Y et al (2014) Quality of life in Parkinson's disease patients with motor fluctuations and dyskinesias in five European countries. *Parkinsonism Relat Disord* 20:969–974. <https://doi.org/10.1016/j.parkreldis.2014.06.001>
- Henry RS, Lageman SK, Perrin PB (2020) The relationship between Parkinson's disease symptoms and caregiver quality of life. *Rehabil Psychol* 65:137–144. <https://doi.org/10.1037/rep0000313>
- Herlofson K, Larsen JP (2003) The influence of fatigue on health-related quality of life in patients with Parkinson's disease: fatigue and health-related quality of life in PD. *Acta Neurol Scand* 107:1–6. <https://doi.org/10.1034/j.1600-0404.2003.02033.x>
- Hinnell C, Hurt CS, Landau S et al (2012) Nonmotor versus motor symptoms: how much do they matter to health status in Parkinson's disease? *Mov Disord* 27:236–241. <https://doi.org/10.1002/mds.23961>
- Hobson P (1999) Measuring the impact of Parkinson's disease with the Parkinson's Disease Quality of Life questionnaire. *Age Ageing* 28:341–346. <https://doi.org/10.1093/ageing/28.4.341>
- Honig H, Antonini A, Martinez-Martin P et al (2009) Intrajejunal levodopa infusion in Parkinson's disease: a pilot multicenter study of effects on nonmotor symptoms and quality of life. *Mov Disord* 24:1468–1474. <https://doi.org/10.1002/mds.22596>
- Hoseinipalangi Z, Kan FP, Hosseinifard H et al (2023) Systematic review and meta-analysis of the quality-of-life of patients with Parkinson's disease. *East Mediterr Health J* 29:63–70. <https://doi.org/10.26719/emhj.23.013>
- Houvenaghel J-F, Drapier S, Duprez J et al (2018) Effects of continuous subcutaneous apomorphine infusion in Parkinson's disease without cognitive impairment on motor, cognitive, psychiatric symptoms and quality of life. *J Neurol Sci* 395:113–118. <https://doi.org/10.1016/j.jns.2018.10.010>
- Ikezawa J, Yokochi F, Yamaguchi T et al (2025) Bilateral effects of unilateral pallidothalamic tractotomy using focused ultrasound in Parkinson's Disease. *Mov Disord* 40:1983–1989. <https://doi.org/10.1002/mds.30281>
- Isaacson SH, Espay AJ, Pahwa R et al (2025) Continuous, subcutaneous apomorphine infusion for Parkinson disease motor fluctuations: results from the phase 3, long-term, open-label United States InfusON study. *J Parkinsons Dis* 15:361–373. <https://doi.org/10.1177/1877718X241310727>
- Jenkinson C, Dummett S, Kelly L et al (2012) The development and validation of a quality of life measure for the carers of people with Parkinson's disease (the PDQ-Carer). *Parkinsonism Relat Disord* 18:483–487. <https://doi.org/10.1016/j.parkreldis.2012.01.007>
- Jost ST, Aloui S, Evans J et al (2024) Neurostimulation for advanced Parkinson disease and quality of life at 5 years: a nonrandomized controlled trial. *JAMA Netw Open* 7:e2352177. <https://doi.org/10.1001/jamanetworkopen.2023.52177>
- Jung NY, Park CK, Kim M, et al (2018) The efficacy and limits of magnetic resonance-guided focused ultrasound pallidotomy for Parkinson's disease: a Phase I clinical trial. *J Neurosurg*. <https://doi.org/10.3171/2018.2.JNS172514>
- Just H, Ostergaard K (2002) Health-related quality of life in patients with advanced Parkinson's disease treated with deep brain stimulation of the subthalamic nuclei. *Mov Disord* 17:539–545. <https://doi.org/10.1002/mds.10111>
- Kähkölä J, Katisko J, Lahtinen M (2024) Deep brain stimulation of Subthalamic Nucleus improves quality of life in general and mental health domains in Parkinson's Disease to the level of the general population. *Neuromodulation* 27:520–527. <https://doi.org/10.1016/j.neurom.2023.03.007>
- Kakimoto A, Kawazoe M, Kurihara K et al (2023) Impact of non-motor fluctuations on QOL in patients with Parkinson's disease. *Front Neurol* 14:1149615. <https://doi.org/10.3389/fneur.2023.1149615>
- Katunina EA, Martynov MY, Belousov VV et al (2025) The results of a 12-month open-label follow-up study with MRI monitoring of patients with Parkinson's disease after MRI-guided FUS. *JCM* 14:8329. <https://doi.org/10.3390/jcm14238329>
- Katzenschlager R, Poewe W, Rascol O et al (2018) Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Neurol* 17:749–759. [https://doi.org/10.1016/S1474-4422\(18\)30239-4](https://doi.org/10.1016/S1474-4422(18)30239-4)
- Katzenschlager R, Poewe W, Rascol O et al (2021) Long-term safety and efficacy of apomorphine infusion in Parkinson's disease patients with persistent motor fluctuations: results of the open-label phase of the TOLEDO study. *Parkinsonism Relat Disord* 83:79–85. <https://doi.org/10.1016/j.parkreldis.2020.12.024>
- Kelly DH, McGinley JL, Huxham FE et al (2012) Health-related quality of life and strain in caregivers of Australians with Parkinson's disease: an observational study. *BMC Neurol* 12:57. <https://doi.org/10.1186/1471-2377-12-57>
- Kelly MJ, Lawton MA, Baig F et al (2019) Predictors of motor complications in early Parkinson's disease: a prospective cohort study. *Mov Disord* 34:1174–1183. <https://doi.org/10.1002/mds.27783>
- Kimber TE, Fang J, Huddy LJ, Thompson PD (2017) Long-term adherence to apomorphine infusion in patients with Parkinson disease: a 10-year observational study. *Intern Med J* 47:570–573. <https://doi.org/10.1111/imj.13378>
- Klepac N, Pikija S, Kraljić T et al (2007) Association of rural life setting and poorer quality of life in Parkinson's disease patients: a cross-sectional study in Croatia. *Eur J Neurol* 14:194–198. <https://doi.org/10.1111/j.1468-1331.2006.01604.x>

- Klepac N, Trkulja V, Relja M, Babić T (2008) Is quality of life in non-demented Parkinson's disease patients related to cognitive performance? A clinic-based cross-sectional study. *Eur J Neurol* 15:128–133. <https://doi.org/10.1111/j.1468-1331.2007.02011.x>
- Klietz M, Tulke A, Müschen LH et al (2018) Impaired quality of life and need for palliative care in a German cohort of advanced Parkinson's disease patients. *Front Neurol* 9:120. <https://doi.org/10.3389/fneur.2018.00120>
- Kovács N, Bergmann L, Anca-Herschkovitsch M et al (2022) Outcomes impacting quality of life in advanced Parkinson's disease patients treated with Levodopa–Carbidopa intestinal gel. *J Parkinsons Dis* 12:917–926. <https://doi.org/10.3233/JPD-212979>
- Krack P, Volkmann J, Tinkhauser G, Deuschl G (2019) Deep brain stimulation in movement disorders: from experimental surgery to evidence-based therapy. *Mov Disord* 34:1795–1810. <https://doi.org/10.1002/mds.27860>
- Krishna V, Fishman PS, Eisenberg HM et al (2023) Trial of globus pallidus focused ultrasound ablation in Parkinson's disease. *N Engl J Med* 388:683–693. <https://doi.org/10.1056/NEJMoa2202721>
- Krüger R, Lingor P, Doskas T et al (2017) An observational study of the effect of Levodopa–Carbidopa intestinal gel on activities of daily living and quality of life in advanced Parkinson's disease patients. *Adv Ther* 34:1741–1752. <https://doi.org/10.1007/s12325-017-0571-2>
- Kurihara K, Nakagawa R, Ishido M et al (2020) Impact of motor and nonmotor symptoms in Parkinson disease for the quality of life: The Japanese Quality-of-Life Survey of Parkinson Disease (JAQ-PAD) study. *J Neurol Sci* 419:117172. <https://doi.org/10.1016/j.jns.2020.117172>
- Lachenmayer ML, Mürset M, Antih N et al (2021) Subthalamic and pallidal deep brain stimulation for Parkinson's disease—meta-analysis of outcomes. *NPJ Parkinsons Dis* 7:77. <https://doi.org/10.1038/s41531-021-00223-5>
- Lagrange E, Krack P, Moro E et al (2002) Bilateral subthalamic nucleus stimulation improves health-related quality of life in PD. *Neurology* 59:1976–1978. <https://doi.org/10.1212/01.wnl.0000037486.82390.1c>
- Lawson RA, Yarnall AJ, Duncan GW et al (2016) Cognitive decline and quality of life in incident Parkinson's disease: the role of attention. *Parkinsonism Relat Disord* 27:47–53. <https://doi.org/10.1016/j.parkreldis.2016.04.009>
- Ledda C, Imbalzano G, Tangari MM et al (2024) NoMoFa as a new tool to evaluate the impact of deep brain stimulation on non-motor fluctuations: a new perspective. *Parkinsonism Relat Disord* 126:107073. <https://doi.org/10.1016/j.parkreldis.2024.107073>
- Ledda C, Imbalzano G, Scaglia E et al (2025) Nonmotor fluctuations in Parkinson's disease: impact on caregiving and quality of life. *J Neurol* 272:639. <https://doi.org/10.1007/s00415-025-13390-9>
- Lee J, Kim SH, Kim Y et al (2019) Quality of life of caregivers of individuals with Parkinson's disease. *Rehabil Nurs* 44:338–348. <https://doi.org/10.1097/rnj.0000000000000158>
- Leroi I, Ahearn DJ, Andrews M et al (2011) Behavioural disorders, disability and quality of life in Parkinson's disease. *Age Ageing* 40:614–621. <https://doi.org/10.1093/ageing/af078>
- Leroi I, McDonald K, Pantula H, Harbisetar V (2012) Cognitive impairment in Parkinson disease: impact on quality of life, disability, and caregiver burden. *J Geriatr Psychiatry Neurol* 25:208–214. <https://doi.org/10.1177/0891988712464823>
- Lezcano E, Gómez-Esteban JC, Tijero B et al (2016) Long-term impact on quality of life of subthalamic nucleus stimulation in Parkinson's disease. *J Neurol* 263:895–905. <https://doi.org/10.1007/s00415-016-8077-4>
- Li H, Zhang M, Chen L et al (2010) Nonmotor symptoms are independently associated with impaired health-related quality of life in Chinese patients with Parkinson's disease. *Mov Disord* 25:2740–2746. <https://doi.org/10.1002/mds.23368>
- Liang M, Hou L, Liang J, Bao S (2025) Ameliorating motor performance and quality of life in Parkinson's disease: a comparison of deep brain stimulation and focused ultrasound surgery. *Front Neurol* 16:1449973. <https://doi.org/10.3389/fneur.2025.1449973>
- Longardner K, Merola A, Litvan I et al (2022) Differential impact of individual autonomic domains on clinical outcomes in Parkinson's disease. *J Neurol* 269:5510–5520. <https://doi.org/10.1007/s00415-022-11221-9>
- Lubomski M, Davis RL, Sue CM (2021) Health-related quality of life for Parkinson's disease patients and their caregivers. *JMD* 14:42–52. <https://doi.org/10.14802/jmd.20079>
- Di Luca DG, Luo S, Liu H, et al (2023) Racial and ethnic differences in health-related quality of life for individuals with Parkinson disease across centers of excellence. *Neurology*. <https://doi.org/10.1212/WNL.00000000000207247>
- Lungu M, Oprea VD, Apostol LL et al (2025) Levodopa–carbidopa–entacapone intestinal gel for advanced Parkinson's disease—results from a monocentric study evaluating both motor and non-motor manifestations. *Biomedicines* 13:2191. <https://doi.org/10.3390/biomedicines13092191>
- Lyons KE, Pahwa R (2005) Long-term benefits in quality of life provided by bilateral subthalamic stimulation in patients with Parkinson disease. *J Neurosurg* 103:252–255. <https://doi.org/10.3171/jns.2005.103.2.0252>
- Maeda T, Shimo Y, Chiu S-W et al (2017) Clinical manifestations of nonmotor symptoms in 1021 Japanese Parkinson's disease patients from 35 medical centers. *Parkinsonism Relat Disord* 38:54–60. <https://doi.org/10.1016/j.parkreldis.2017.02.024>
- Magano D, Taveira-Gomes T, Massano J, Barros AS (2024) Predicting quality of life in Parkinson's disease: a machine learning approach employing common clinical variables. *J Clin Med* 13:5081. <https://doi.org/10.3390/jcm13175081>
- Malaty IA, Martinez-Martin P, Chaudhuri KR et al (2022) Does the 5–2–1 criteria identify patients with advanced Parkinson's disease? Real-world screening accuracy and burden of 5–2–1-positive patients in 7 countries. *BMC Neurol* 22:35. <https://doi.org/10.1186/s12883-022-02560-1>
- Manson A, Stirpe P, Schrag A (2012) Levodopa-induced-dyskinesias clinical features, incidence, risk factors, management and impact on quality of life. *J Parkinsons Dis* 2:189–198. <https://doi.org/10.3233/JPD-2012-120103>
- Mantri S, Klawson E, Albert S et al (2021) The experience of care partners of patients with Parkinson's disease psychosis. *PLoS One* 16:e0248968. <https://doi.org/10.1371/journal.pone.0248968>
- Maragkos GA, Kosyakovsky J, Zhao P et al (2023) Patient-reported outcomes after focused ultrasound thalamotomy for tremor-predominant Parkinson's disease. *Neurosurgery* 93:884–891. <https://doi.org/10.1227/neu.00000000000002518>
- Marras C, McDermott MP, Rochon PA et al (2008) Predictors of deterioration in health-related quality of life in Parkinson's disease: results from the DATATOP trial. *Mov Disord* 23:653–659. <https://doi.org/10.1002/mds.21853>
- Martinez-Martin P (2011) The importance of non-motor disturbances to quality of life in Parkinson's disease. *J Neurol Sci* 310:12–16. <https://doi.org/10.1016/j.jns.2011.05.006>
- Martinez-Martin P (2017) What is quality of life and how do we measure it? Relevance to Parkinson's disease and movement disorders. *Mov Disord* 32:382–392. <https://doi.org/10.1002/mds.26885>
- Martínez-Martín P, Benito-León J, Alonso F et al (2005) Quality of life of caregivers in Parkinson's disease. *Qual Life Res* 14:463–472. <https://doi.org/10.1007/s11136-004-6253-y>
- Martinez-Martin P, Catalan MJ, Benito-Leon J et al (2006) Impact of fatigue in Parkinson's disease: the fatigue impact scale for daily use (D-FIS). *Qual Life Res* 15:597–606. <https://doi.org/10.1007/s11136-005-4181-0>

- Martínez-Martín P, Forjaz MJ, Frades-Payo B et al (2007) Caregiver burden in Parkinson's disease. *Mov Disord* 22:924–931. <https://doi.org/10.1002/mds.21355>
- Martínez-Martín P, Arroyo S, Rojo-Abuin JM et al (2008a) Burden, perceived health status, and mood among caregivers of Parkinson's disease patients. *Mov Disord* 23:1673–1680. <https://doi.org/10.1002/mds.22106>
- Martínez-Martín P, Carod-Artal FJ, Da Silveira Ribeiro L et al (2008b) Longitudinal psychometric attributes, responsiveness, and importance of change: an approach using the SCOPA-Psychosocial questionnaire. *Mov Disord* 23:1516–1523. <https://doi.org/10.1002/mds.22202>
- Martínez-Martín P, Jeukens-Visser M, Lyons KE et al (2011a) Health-related quality-of-life scales in Parkinson's disease: critique and recommendations. *Mov Disord* 26:2371–2380. <https://doi.org/10.1002/mds.23834>
- Martínez-Martín P, Jeukens-Visser M, Lyons KE et al (2011b) Health-related quality-of-life scales in Parkinson's disease: critique and recommendations. *Mov Disord* 26:2371–2380. <https://doi.org/10.1002/mds.23834>
- Martínez-Martín P, Rodríguez-Blázquez C, Forjaz MJ (2012) Quality of life and burden in caregivers for patients with Parkinson's disease: concepts, assessment and related factors. *Expert Rev Pharmacoecon Outcomes Res* 12:221–230. <https://doi.org/10.1586/erp.11.106>
- Martínez-Martín P, Rodríguez-Blázquez C, Forjaz MJ et al (2014) Relationship between the MDS-UPDRS domains and the health-related quality of life of Parkinson's disease patients. *Euro J Neurol* 21:519–524. <https://doi.org/10.1111/ene.12349>
- Martínez-Martín P, Reddy P, Katzenschlager R et al (2015) Euro Inf: A multicenter comparative observational study of Apomorphine and levodopa infusion in Parkinson's disease. *Mov Disord* 30:510–516. <https://doi.org/10.1002/mds.26067>
- Martínez-Fernández R, Pelissier P, Quesada J-L et al (2016a) Postoperative apathy can neutralise benefits in quality of life after subthalamic stimulation for Parkinson's disease. *J Neurol Neurosurg Psychiatry* 87:311–318. <https://doi.org/10.1136/jnnp-2014-310189>
- Martínez-Fernández R, Schmitt E, Martínez-Martín P, Krack P (2016b) The hidden sister of motor fluctuations in Parkinson's disease: a review on nonmotor fluctuations. *Mov Disord* 31:1080–1094. <https://doi.org/10.1002/mds.26731>
- Martínez-Fernández R, Rodríguez-Rojas R, Del Álamo M et al (2018) Focused ultrasound subthalamotomy in patients with asymmetric Parkinson's disease: a pilot study. *Lancet Neurol* 17:54–63. [https://doi.org/10.1016/S1474-4422\(17\)30403-9](https://doi.org/10.1016/S1474-4422(17)30403-9)
- Martínez-Fernández R, Mánuez-Miró JU, Rodríguez-Rojas R et al (2020) Randomized trial of focused ultrasound subthalamotomy for Parkinson's disease. *N Engl J Med* 383:2501–2513. <https://doi.org/10.1056/NEJMoa2016311>
- Martínez-Martín P, Valldeoriola F, Tolosa E et al (2002) Bilateral subthalamic nucleus stimulation and quality of life in advanced Parkinson's disease. *Mov Disord* 17:372–377. <https://doi.org/10.1002/mds.10044>
- Martínez-Fernández R, Natera-Villalba E, Mánuez Miró JU, et al (2023) Prospective long-term follow-up of focused ultrasound unilateral subthalamotomy for Parkinson disease. *Neurology*. <https://doi.org/10.1212/WNL.0000000000206771>
- Martínez-Fernández R, Natera-Villalba E, Rodríguez-Rojas R et al (2024) Staged bilateral MRI-guided focused ultrasound subthalamotomy for Parkinson disease. *JAMA Neurol* 81:638. <https://doi.org/10.1001/jamaneurol.2024.1220>
- Mehanna R, Jankovic J (2019) Young-onset Parkinson's disease: its unique features and their impact on quality of life. *Parkinsonism Relat Disord* 65:39–48. <https://doi.org/10.1016/j.parkreldis.2019.06.001>
- Meira B, Degos B, Corsetti E et al (2021) Long-term effect of apomorphine infusion in advanced Parkinson's Disease: a real-life study. *NPJ Parkinsons Dis* 7:50. <https://doi.org/10.1038/s41531-021-00194-7>
- Meng D, Jin Z, Gao L et al (2022) The quality of life in patients with Parkinson's disease: focus on gender difference. *Brain Behavior* 12:e2517. <https://doi.org/10.1002/brb3.2517>
- Merola A, Romagnolo A, Rosso M et al (2016) Orthostatic hypotension in Parkinson's disease: does it matter if asymptomatic? *Parkinsonism Relat Disord* 33:65–71. <https://doi.org/10.1016/j.parkreldis.2016.09.013>
- Merola A, Romagnolo A, Rosso M et al (2018) Autonomic dysfunction in Parkinson's disease: a prospective cohort study. *Mov Disord* 33:391–397. <https://doi.org/10.1002/mds.27268>
- Merritt RK, Hotham S, Schrag A (2023) Support needs in carers of people with Parkinson's from early to later stages: a qualitative study with 36 carers in 11 European countries. *J Geriatr Psychiatry Neurol* 36:505–510. <https://doi.org/10.1177/08919887231168404>
- Miller E, Berrios GE, Politynska BE (1996) Caring for someone with Parkinson's disease: factors that contribute to distress. *Int J Geriatr Psychiatry* 11:263–268. [https://doi.org/10.1002/\(SICI\)1099-1166\(199603\)11:3<263::AID-GPS316>3.0.CO;2-P](https://doi.org/10.1002/(SICI)1099-1166(199603)11:3<263::AID-GPS316>3.0.CO;2-P)
- Monteiro JDS, Silva EBB, De Oliveira RR et al (2024) Magnetic resonance-guided focused ultrasound ventral intermediate thalamotomy for Tremor-Dominant Parkinson's disease: a systematic review and meta-analysis. *Neurosurg Rev* 47:701. <https://doi.org/10.1007/s10143-024-02948-2>
- Moore O, Kreitler S, Ehrenfeld M, Giladi N (2005) Quality of life and gender identity in Parkinson's disease. *J Neural Transm* 112:1511–1522. <https://doi.org/10.1007/s00702-005-0285-5>
- Morimoto R, Kitagawa K, Iijima M (2024) Importance of focusing on subjective symptoms to maintain quality of life in patients with Parkinson's disease for over 5 years. *J Neurol Sci* 466:123253. <https://doi.org/10.1016/j.jns.2024.123253>
- Morley D, Dummett S, Peters M et al (2012) Factors Influencing quality of life in caregivers of people with Parkinson's disease and implications for clinical guidelines. *Parkinson's Dis* 2012:1–6. <https://doi.org/10.1155/2012/190901>
- Morley JF, Subramanian I, Farahnik J et al (2026) Physical activity, patient-reported outcomes, and quality of life in Parkinson's disease. *J Geriatr Psychiatry Neurol* 39:14–23. <https://doi.org/10.1177/08919887251346495>
- Moro E, Lozano AM, Pollak P et al (2010) Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. *Mov Disord* 25:578–586. <https://doi.org/10.1002/mds.22735>
- Müller B, Assmus J, Herlofson K et al (2013) Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. *Parkinsonism Relat Disord* 19:1027–1032. <https://doi.org/10.1016/j.parkreldis.2013.07.010>
- Murata M, Mihara M, Hasegawa K et al (2016) Efficacy and safety of levodopa-carbidopa intestinal gel from a study in Japanese, Taiwanese, and Korean advanced Parkinson's disease patients. *NPJ Parkinson's Dis* 2:16020. <https://doi.org/10.1038/npjparkd.2016.20>
- Murcia Carretero S, Petermann K, Debove I et al (2024) Quality of life after deep brain stimulation in Parkinson's disease: Does the target matter? *Mov Disord Clin Pract* 11:1379–1387. <https://doi.org/10.1002/mdc3.14199>
- Nagaki K, Nakagawa R, Ishido M et al (2023) Impact of Parkinson's disease on caregiver quality of life in Japan. *Mov Disord Clin Pract* 10:658–663. <https://doi.org/10.1002/mdc3.13700>
- Ney JP, Steinmetz JD, Anderson-benge E et al (2025) US burden of disorders affecting the nervous system: From the Global Burden

- of Disease 2021 Study. *JAMA Neurol.* <https://doi.org/10.1001/jama.neuro.2025.4470>
- Odekerken VJ, Van Laar T, Staal MJ et al (2013) Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. *Lancet Neurol* 12:37–44. [https://doi.org/10.1016/S1474-4422\(12\)70264-8](https://doi.org/10.1016/S1474-4422(12)70264-8)
- Okun MS, Gallo BV, Mandybur G et al (2012) Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *Lancet Neurol* 11:140–149. [https://doi.org/10.1016/S1474-4422\(11\)70308-8](https://doi.org/10.1016/S1474-4422(11)70308-8)
- Olanow CW, Kieburtz K, Odin P et al (2014) Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. *Lancet Neurol* 13:141–149. [https://doi.org/10.1016/S1474-4422\(13\)70293-X](https://doi.org/10.1016/S1474-4422(13)70293-X)
- Ongun N (2018) Does nutritional status affect Parkinson's disease features and quality of life? *PLoS One* 13:e0205100. <https://doi.org/10.1371/journal.pone.0205100>
- Ossig C, Sippel D, Fauser M et al (2017) Timing and kinetics of non-motor fluctuations in advanced Parkinson's disease. *J Parkinsons Dis* 7:325–330. <https://doi.org/10.3233/JPD-160996>
- Öthman M, Widman E, Nygren I, Nyholm D (2021) Initial experience of the Levodopa–Entacapone–Carbidopa intestinal gel in clinical practice. *J Pers Med* 11:254. <https://doi.org/10.3390/jpm11040254>
- Ozdilek B, Gunal DI (2012) Motor and non-motor symptoms in Turkish patients with Parkinson's disease affecting family caregiver burden and quality of life. *J Neuropsychiatry Clin Neurosci* 24:478–483. <https://doi.org/10.1176/appi.neuropsych.11100315>
- Page TE, Farina N, Brown A et al (2017) Instruments measuring the disease-specific quality of life of family carers of people with neurodegenerative diseases: a systematic review. *BMJ Open* 7:e013611. <https://doi.org/10.1136/bmjopen-2016-013611>
- Pal PK, Thennarasu K, Fleming J et al (2004) Nocturnal sleep disturbances and daytime dysfunction in patients with Parkinson's disease and in their caregivers. *Parkinsonism Relat Disord* 10:157–168. <https://doi.org/10.1016/j.parkreldis.2003.11.002>
- Pålhagen SE, Sydow O, Johansson A et al (2016) Levodopa-carbidopa intestinal gel (LCIG) treatment in routine care of patients with advanced Parkinson's disease: an open-label prospective observational study of effectiveness, tolerability and healthcare costs. *Parkinsonism Relat Disord* 29:17–23. <https://doi.org/10.1016/j.parkreldis.2016.06.002>
- Perepezko K, Hinkle JT, Forbes EJ et al (2023) The impact of caregiving on quality of life in Parkinson's disease: a systematic review. *Int J Geriatr Psychiatry* 38:e5870. <https://doi.org/10.1002/gps.5870>
- Perez-Lloret S, Negre-Pages L, Damier P et al (2017) L- DOPA -induced dyskinesias, motor fluctuations and health-related quality of life: the COPARK survey. *Eur J Neurol* 24:1532–1538. <https://doi.org/10.1111/ene.13466>
- Phu AL, Xu Z, Brakoulias V et al (2014) Effect of impulse control disorders on disability and quality of life in Parkinson's disease patients. *J Clin Neurosci* 21:63–66. <https://doi.org/10.1016/j.jocn.2013.02.032>
- Pigott JS, Armstrong M, Davies N et al (2024) Factors associated with self-rated health in people with late-stage Parkinson's and cognitive impairment. *Qual Life Res* 33:2439–2452. <https://doi.org/10.1007/s11136-024-03703-2>
- Pillas M, Selai C, Quinn NP et al (2016) Development and validation of a carers quality-of-life questionnaire for parkinsonism (PQoL Carers). *Qual Life Res* 25:81–88. <https://doi.org/10.1007/s11136-015-1071-y>
- Pillas M, Selai C, Schrag A (2017) Rasch analysis of the carers quality of life questionnaire for parkinsonism. *Mov Disord* 32:463–466. <https://doi.org/10.1002/mds.26877>
- Plowman-Prine EK, Sapienza CM, Okun MS et al (2009) The relationship between quality of life and swallowing in Parkinson's disease. *Mov Disord* 24:1352–1358. <https://doi.org/10.1002/mds.22617>
- Post B, Muslimovic D, Van Geloven N et al (2011) Progression and prognostic factors of motor impairment, disability and quality of life in newly diagnosed Parkinson's disease. *Mov Disord* 26:449–456. <https://doi.org/10.1002/mds.23467>
- Prell T, Schönenberg A, Heimrich KG (2023) The impact of loneliness on quality of life in people with Parkinson's disease: results from the survey of health, ageing and retirement in Europe. *Front Med* 10:1183289. <https://doi.org/10.3389/fmed.2023.1183289>
- Rahman S, Griffin HJ, Quinn NP, Jahanshahi M (2008) Quality of life in Parkinson's disease: the relative importance of the symptoms. *Mov Disord* 23:1428–1434. <https://doi.org/10.1002/mds.21667>
- Ramirez-Zamora A, Okun MS, Kukreja P, Hu W (2025) Parkinson's Disease quality of life at 12 months comparing invasive device-aided therapy with oral treatment. *Npj Parkinsons Dis* 11:235. <https://doi.org/10.1038/s41531-025-01093-x>
- Rashid R, Aamodt WW, Horn S, Dahodwala N (2023) Association of caregiver depression risk with patient outcomes in Parkinson disease. *JAMA Netw Open* 6:e2327485. <https://doi.org/10.1001/jamanetworkopen.2023.27485>
- Ray J, Das SK, Gangopadhyay PK, Roy T (2006) Quality of life in Parkinson's disease—Indian scenario. *J Assoc Physicians India* 54:17–21
- Regensburger M, Csoti I, Jost WH et al (2025) Motor and non-motor fluctuations in Parkinson's disease: the knowns and unknowns of current therapeutic approaches. *J Neural Transm.* <https://doi.org/10.1007/s00702-025-02990-4>
- Rieu I, Houeto JL, Pereira B et al (2016) Impact of mood and behavioral disorders on quality of life in Parkinson's disease. *J Parkinson's Dis* 6:267–277. <https://doi.org/10.3233/JPD-150747>
- Riley DE, Lang AE (1993) The spectrum of levodopa-related fluctuations in Parkinson's disease. *Neurology* 43:1459–1464. <https://doi.org/10.1212/wnl.43.8.1459>
- Rodrigues JP, Walters SE, Watson P et al (2007) Globus pallidus stimulation improves both motor and nonmotor aspects of quality of life in advanced Parkinson's disease. *Mov Disord* 22:1866–1870. <https://doi.org/10.1002/mds.21427>
- Rodríguez-Antigüedad J, Olmedo-Saura G, Pagonabarraga J et al (2025) Approaches for treating neuropsychiatric symptoms in Parkinson's disease: a narrative review. *Ther Adv Neurol Disord* 18:17562864251336904. <https://doi.org/10.1177/17562864251336904>
- Roh JH, Kim B-J, Jang J-H et al (2009) The relationship of pain and health-related quality of life in Korean patients with Parkinson's disease. *Acta Neurol Scand* 119:397–403. <https://doi.org/10.1111/j.1600-0404.2008.01114.x>
- Rosqvist K, Kylberg M, Löfqvist C et al (2021) Perspectives on care for late-stage Parkinson's disease. *Parkinson Dis* 2021:1–11. <https://doi.org/10.1155/2021/9475026>
- Rosqvist K, Schrag A, Odin P, the CLASP Consortium (2022) Caregiver burden and quality of life in late stage Parkinson's disease. *Brain Sci* 12:111. <https://doi.org/10.3390/brainsci12010111>
- Rughani A, Schwalb JM, Sidiropoulos C et al (2018) Congress of Neurological Surgeons systematic review and evidence-based guideline on subthalamic nucleus and globus pallidus internus deep brain stimulation for the treatment of patients with Parkinson's disease: executive summary. *Neurosurgery* 82:753–756. <https://doi.org/10.1093/neuros/nyy037>
- Santos García D, De Deus Fonticoba T, Suárez Castro E et al (2019) Non-motor symptoms burden, mood, and gait problems are the

- most significant factors contributing to a poor quality of life in non-demented Parkinson's disease patients: results from the COPPADIS study cohort. *Parkinsonism Relat Disord* 66:151–157. <https://doi.org/10.1016/j.parkreldis.2019.07.031>
- Santos García D, De Deus Fonticoba T, Cores C et al (2021) Predictors of clinically significant quality of life impairment in Parkinson's Disease. *Npj Parkinsons Dis* 7:118. <https://doi.org/10.1038/s41531-021-00256-w>
- Santos-García D, De Deus T, Cores C et al (2024) Levodopa-induced dyskinesias are frequent and impact quality of life in Parkinson's disease: a 5-year follow-up study. *Mov Disord Clin Pract* 11:830–849. <https://doi.org/10.1002/mdc3.14056>
- Santos-García D, López-Manzanares L, Muro I et al (2025) Effectiveness and safety of levodopa-entacapone-carbidopa infusion in Parkinson disease: a real-world data study. *Eur J Neurol* 32:e16535. <https://doi.org/10.1111/ene.16535>
- Santos-García D, De La Fuente-Fernández R (2013) Impact of non-motor symptoms on health-related and perceived quality of life in Parkinson's disease. *J Neurol Sci* 332:136–140. <https://doi.org/10.1016/j.jns.2013.07.005>
- Santos-García D, De La Fuente-Fernández R (2015) Factors contributing to caregivers' stress and burden in Parkinson's disease. *Acta Neurol Scand* 131:203–210. <https://doi.org/10.1111/ane.12305>
- Santos-García D, Solleiro Á, González-Ortega G, et al (2025) Impact of device-aided therapies on quality of life in patients with Parkinson's disease. A comparative multicenter observational study. *J Neural Transm*. <https://doi.org/10.1007/s00702-025-03066-z>
- Schlesinger I, Eran A, Sinai A et al (2015) MRI guided focused ultrasound thalamotomy for moderate-to-severe tremor in Parkinson's disease. *Parkinson Dis* 2015:1–4. <https://doi.org/10.1155/2015/219149>
- Schrag A (2006) Quality of life and depression in Parkinson's disease. *J Neurol Sci* 248:151–157. <https://doi.org/10.1016/j.jns.2006.05.030>
- Schrag A, Jahanshahi M, Quinn N (2000) How does Parkinson's disease affect quality of life? A comparison with quality of life in the general population. *Mov Disord* 15:1112–1118. [https://doi.org/10.1002/1531-8257\(200011\)15:6%3C1112::AID-MDS1008%3E3.0.CO;2-A](https://doi.org/10.1002/1531-8257(200011)15:6%3C1112::AID-MDS1008%3E3.0.CO;2-A)
- Schrag A, Hovris A, Morley D et al (2006) Caregiver-burden in parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. *Parkinsonism Relat Disord* 12:35–41. <https://doi.org/10.1016/j.parkreldis.2005.06.011>
- Schrag A, Spottke A, Quinn NP, Dodel R (2009) Comparative responsiveness of Parkinson's disease scales to change over time. *Mov Disord* 24:813–818. <https://doi.org/10.1002/mds.22438>
- Senek M, Nielsen EI, Nyholm D (2017) Levodopa-entacapone-carbidopa intestinal gel in Parkinson's disease: a randomized cross-over study. *Mov Disord* 32:283–286. <https://doi.org/10.1002/mds.26855>
- Sheard JM, Ash S, Mellick GD et al (2014) Improved nutritional status is related to improved quality of life in Parkinson's disease. *BMC Neurol* 14:212. <https://doi.org/10.1186/s12883-014-0212-1>
- Siderowf A, Jaggi JL, Xie SX et al (2006) Long-term effects of bilateral subthalamic nucleus stimulation on health-related quality of life in advanced Parkinson's disease. *Mov Disord* 21:746–753. <https://doi.org/10.1002/mds.20786>
- Simu MA, Jianu DC, Dulamea AO et al (2021) Advanced Parkinson's disease treatment simplification and long-term outcomes with Levodopa Carbidopa Intestinal Gel: COSMOS Romanian sub-analysis. *Brain Sci* 11:1566. <https://doi.org/10.3390/brainsci11121566>
- Skorvanek M, Rosenberger J, Minar M et al (2015) Relationship between the non-motor items of the MDS-UPDRS and quality of life in patients with Parkinson's disease. *J Neurol Sci* 353:87–91. <https://doi.org/10.1016/j.jns.2015.04.013>
- Ślawek J, Derejko M, Lass P (2005) Factors affecting the quality of life of patients with idiopathic Parkinson's disease—a cross-sectional study in an outpatient clinic attendees. *Parkinsonism Relat Disord* 11:465–468. <https://doi.org/10.1016/j.parkreldis.2005.04.006>
- Slevin JT, Fernandez HH, Zadikoff C et al (2015) Long-term safety and maintenance of efficacy of levodopa-carbidopa intestinal gel: an open-label extension of the double-blind pivotal study in advanced Parkinson's disease patients. *J Parkinsons Dis* 5:165–174. <https://doi.org/10.3233/JPD-140456>
- Smith ER, Perrin PB, Tyler CM et al (2020) Cross-cultural differences in Parkinson's disease caregiving and burden between the United States and Mexico. *Brain Behav* 10:e01753. <https://doi.org/10.1002/brb3.1753>
- Soh S-E, Morris ME, McGinley JL (2011) Determinants of health-related quality of life in Parkinson's disease: a systematic review. *Parkinsonism Relat Disord* 17:1–9. <https://doi.org/10.1016/j.parkreldis.2010.08.012>
- Soileau MJ, Aldred J, Budur K et al (2022) Safety and efficacy of continuous subcutaneous foslevodopa-foscarbidopa in patients with advanced Parkinson's disease: a randomised, double-blind, active-controlled, phase 3 trial. *Lancet Neurol* 21:1099–1109. [https://doi.org/10.1016/S1474-4422\(22\)00400-8](https://doi.org/10.1016/S1474-4422(22)00400-8)
- Soileau M, Kumar R, Parab A et al (2025) Patients' experience with and perspectives on long-term use of continuous subcutaneous infusion of foslevodopa/foscarbidopa in Parkinson's disease. *J Neurol* 272:416. <https://doi.org/10.1007/s00415-025-13123-y>
- Soumiya R, Paul BS, Aggarwal R, Paul G (2022) Neuropathy in Parkinson's disease: risk determinants and impact on quality of life. *Ann Indian Acad Neurol* 25:428–432. https://doi.org/10.4103/aia.n.aian_902_21
- Sperling SA, Shah BB, Barrett MJ, et al (2018) Focused ultrasound thalamotomy in Parkinson disease: nonmotor outcomes and quality of life. *Neurology*. <https://doi.org/10.1212/WNL.00000000000006279>
- Standaert DG, Aldred J, Anca-Herschkovitsch M et al (2021) DUO-GLOBE: one-year outcomes in a real-world study of levodopa carbidopa intestinal gel for Parkinson's disease. *Mov Disord Clin Pract* 8:1061–1074. <https://doi.org/10.1002/mdc3.13239>
- Starr PA, Shivacharan RS, Goldberg E et al (2025) Five-year outcomes from deep brain stimulation of the subthalamic nucleus for Parkinson disease. *JAMA Neurol* 82:1181. <https://doi.org/10.1001/jamaneurol.2025.3373>
- Storch A, Schneider CB, Wolz M et al (2013) Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. *Neurology* 80:800–809. <https://doi.org/10.1212/WNL.0b013e318285c0ed>
- Subramanian I, Farahnik J, Mischley LK (2020) Synergy of pandemics-social isolation is associated with worsened Parkinson severity and quality of life. *Npj Parkinsons Dis* 6:28. <https://doi.org/10.1038/s41531-020-00128-9>
- Sun Q, Wang T, Jiang T-F et al (2018) Clinical profile of Chinese long-term Parkinson's Disease survivors with 10 years of disease duration and beyond. *Aging Dis* 9:8. <https://doi.org/10.14336/AD.2017.0204>
- Suzukamo Y, Ohbu S, Kondo T et al (2006) Psychological adjustment has a greater effect on health-related quality of life than on severity of disease in Parkinson's disease. *Mov Disord* 21:761–766. <https://doi.org/10.1002/mds.20817>
- Szatmári S, Szász JA, Orbán-Kis K et al (2024) Starting with 24-h levodopa carbidopa intestinal gel at initiation in a large cohort of advanced Parkinson's disease patients. *Sci Rep* 14:3676. <https://doi.org/10.1038/s41598-024-54299-z>
- Tanji H, Koyama S, Wada M et al (2013) Comparison of caregiver strain in Parkinson's disease between Yamagata, Japan, and Maryland, The United States. *Parkinsonism Relat Disord* 19:628–633. <https://doi.org/10.1016/j.parkreldis.2013.02.014>

- Tanner CM, Ostrem JL (2024) Parkinson's disease. *N Engl J Med* 391:442–452. <https://doi.org/10.1056/NEJMra2401857>
- Testa MA, Simonson DC (1996) Assessment of quality-of-life outcomes. *N Engl J Med* 334:835–840. <https://doi.org/10.1056/NEJM199603283341306>
- Thach A, Jones E, Pappert E et al (2021) Real-world assessment of the impact of “OFF” episodes on health-related quality of life among patients with Parkinson's disease in the United States. *BMC Neurol* 21:46. <https://doi.org/10.1186/s12883-021-02074-2>
- The Global Parkinson's Disease Survey (GPDS) Steering Committee (2002) Factors impacting on quality of life in Parkinson's disease: results from an international survey. *Mov Disord* 17:60–67. <https://doi.org/10.1002/mds.10010>
- Tosin MH, Goetz CG, Stebbins GT (2024) Patient with Parkinson disease and care partner perceptions of key domains affecting health-related quality of life: systematic review. *Neurology* 102:e208028. <https://doi.org/10.1212/WNL.0000000000208028>
- Trang I, Katz M, Galifianakis N et al (2020) Predictors of general and health-related quality of life in Parkinson's disease and related disorders including caregiver perspectives. *Parkinsonism Relat Disord* 77:5–10. <https://doi.org/10.1016/j.parkreldis.2020.05.036>
- Tykocki T, Szalecki K, Koziara H, et al (2012) Quality of life and depressive symptoms in parkinson's disease after subthalamic deep brain stimulation: a 2-year follow-up study. *Turk Neurosurg.* <https://doi.org/10.5137/1019-5149.JTN.7184-12.1>
- Valkovic P, Harsany J, Hanakova M et al (2014) Nonmotor symptoms in early- and advanced-stage Parkinson's disease patients on dopaminergic therapy: how do they correlate with quality of life? *ISRN Neurol* 2014:1–4. <https://doi.org/10.1155/2014/587302>
- Valkovic P, Minar M, Singliarova H et al (2015) Pain in Parkinson's disease: a cross-sectional study of its prevalence, types, and relationship to depression and quality of life. *PLoS One* 10:e0136541. <https://doi.org/10.1371/journal.pone.0136541>
- Valldeoriola F, Catalán MJ, Escamilla-Sevilla F et al (2021) Patient and caregiver outcomes with levodopa-carbidopa intestinal gel in advanced Parkinson's disease. *NPJ Parkinsons Dis* 7:108. <https://doi.org/10.1038/s41531-021-00246-y>
- Van Hooren MRA, Bajjens LWJ, Vos R et al (2016) Voice- and swallow-related quality of life in idiopathic Parkinson's disease. *Laryngoscope* 126:408–414. <https://doi.org/10.1002/lary.25481>
- Vijjaratnam N, Hewer S, Varley S et al (2018) Levodopa-carbidopa intestinal gel: is the naso-jejunal phase a redundant convention? *Intern Med J* 48:469–471. <https://doi.org/10.1111/imj.13754>
- Visser M, Van Rooden SM, Verbaan D et al (2008) A comprehensive model of health-related quality of life in Parkinson's disease. *J Neurol* 255:1580–1587. <https://doi.org/10.1007/s00415-008-0994-4>
- Visser M, Verbaan D, Van Rooden S et al (2009) A longitudinal evaluation of health-related quality of life of patients with Parkinson's disease. *Value Health* 12:392–396. <https://doi.org/10.1111/j.1524-4733.2008.00430.x>
- Volkman J, Albanese A, Kulisevsky J et al (2009) Long-term effects of pallidal or subthalamic deep brain stimulation on quality of life in Parkinson's disease. *Mov Disord* 24:1154–1161. <https://doi.org/10.1002/mds.22496>
- Weaver FM (2009) Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: A randomized controlled trial. *JAMA* 301:63. <https://doi.org/10.1001/jama.2008.929>
- Weaver FM, Follett KA, Stern M et al (2012) Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology* 79:55–65. <https://doi.org/10.1212/WNL.0b013e31825dcd1>
- Whoqol Group (1995) The world health organization quality of life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med* 41:1403–1409. [https://doi.org/10.1016/0277-9536\(95\)00112-K](https://doi.org/10.1016/0277-9536(95)00112-K)
- Wielinski CL, Erickson-Davis C, Wichmann R et al (2005) Falls and injuries resulting from falls among patients with Parkinson's disease and other parkinsonian syndromes. *Mov Disord* 20:410–415. <https://doi.org/10.1002/mds.20347>
- Williams A, Gill S, Varma T et al (2010) Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol* 9:581–591. [https://doi.org/10.1016/S1474-4422\(10\)70093-4](https://doi.org/10.1016/S1474-4422(10)70093-4)
- Williamson N, Morel T, Bradley H et al (2025) Understanding the patient experience of advanced Parkinson's disease: qualitative research with patients and expert clinicians to identify symptoms and associated health-related quality of life impacts. *Neurol Ther* 14:1383–1417. <https://doi.org/10.1007/s40120-025-00747-5>
- Winter Y, Campenhausen S, Gasser J et al (2010a) Social and clinical determinants of quality of life in Parkinson's disease in Austria: a cohort study. *J Neurol* 257:638–645. <https://doi.org/10.1007/s00415-009-5389-7>
- Winter Y, Von Campenhausen S, Popov G et al (2010b) Social and clinical determinants of quality of life in Parkinson's disease in a Russian cohort study. *Parkinsonism Relat Disord* 16:243–248. <https://doi.org/10.1016/j.parkreldis.2009.11.012>
- Winter Y, Von Campenhausen S, Arend M et al (2011) Health-related quality of life and its determinants in Parkinson's disease: results of an Italian cohort study. *Parkinsonism Relat Disord* 17:265–269. <https://doi.org/10.1016/j.parkreldis.2011.01.003>
- Witjas T, Kaphan E, Azulay JP et al (2002) Nonmotor fluctuations in Parkinson's disease: frequent and disabling. *Neurology* 59:408–413. <https://doi.org/10.1212/WNL.59.3.408>
- Witt K, Daniels C, Krack P et al (2011) Negative impact of borderline global cognitive scores on quality of life after subthalamic nucleus stimulation in Parkinson's disease. *J Neurol Sci* 310:261–266. <https://doi.org/10.1016/j.jns.2011.06.028>
- Wu J, Lim E-C, Nadkarni NV et al (2019) The impact of levodopa therapy-induced complications on quality of life in Parkinson's disease patients in Singapore. *Sci Rep* 9:9248. <https://doi.org/10.1038/s41598-019-45110-5>
- Yamanishi T, Tachibana H, Oguru M et al (2013) Anxiety and depression in patients with Parkinson's disease. *Intern Med* 52:539–545. <https://doi.org/10.2169/internalmedicine.52.8617>
- Yoon J-E, Kim JS, Jang W et al (2017) Gender differences of nonmotor symptoms affecting quality of life in Parkinson disease. *Neurodegener Dis* 17:276–280. <https://doi.org/10.1159/000479111>
- Zaaroor M, Sinai A, Goldsher D et al (2018) Magnetic resonance-guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases. *J Neurosurg* 128:202–210. <https://doi.org/10.3171/2016.10.JNS16758>
- Żach M, Friedman A, Sławek J, Derejko M (2004) Quality of life in Polish patients with long-lasting Parkinson's disease. *Mov Disord* 19:667–672. <https://doi.org/10.1002/mds.10698>
- Zahodne LB, Okun MS, Foote KD et al (2009) Greater improvement in quality of life following unilateral deep brain stimulation surgery in the globus pallidus as compared to the subthalamic nucleus. *J Neurol* 256:1321–1329. <https://doi.org/10.1007/s00415-009-5121-7>
- Zhang J, Li J, Chen F et al (2021) STN versus GPi deep brain stimulation for dyskinesia improvement in advanced Parkinson's disease: a meta-analysis of randomized controlled trials. *Clin Neurol Neurosurg* 201:106450. <https://doi.org/10.1016/j.clineuro.2020.106450>
- Zhao N, Yang Y, Zhang L et al (2021) Quality of life in Parkinson's disease: a systematic review and meta-analysis of comparative studies. *CNS Neurosci Ther* 27:270–279. <https://doi.org/10.1111/cns.13549>

Žiropađa L, Stefanova E, Potrebić A, Kostić VS (2009) Quality of life in Serbian patients with Parkinson's disease. *Qual Life Res* 18:833–839. <https://doi.org/10.1007/s11136-009-9500-4>

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