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REVIEW ARTICLE

Non-Motor Fluctuations in Parkinson's Disease: Underdiagnosed Yet Important

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ABSTRACT

Non-motor fluctuations (NMFs) in Parkinson's disease (PD) significantly affect patients' well-being. Despite being identified over two decades ago, NMFs remain largely underrecognized, undertreated, and poorly understood. While they are often temporally associated with motor fluctuations (MFs) and can share common risk factors and pathophysiologic mechanisms, NMFs and MFs are currently considered distinct entities. The prevalence and severity of NMFs, often categorized into neuropsychiatric, sensory, and autonomic subtypes, vary significantly across studies due to the heterogeneous PD populations screened and the diverse evaluation tools applied. The consistent negative impact of NMFs on PD patients' quality of life underscores the importance of further investigations via focused and controlled studies, validated assessment instruments and novel digital technologies. High-quality research is essential to illuminate the complex pathophysiology and clinical nuances of NMFs, ultimately enhancing clinicians' diagnostic and treatment options in routine clinical practice.

Keywords Parkinson's disease; Fluctuations; Non-motor; Advanced; Therapy.

INTRODUCTION

The burden of non-motor symptoms (NMSs) in Parkinson's disease (PD) is now well established, with clinicians increasingly recognizing their importance and addressing them with equal attention to motor symptoms.[1] NMS play a critical role in determining treatment strategies for PD, as they can profoundly impact patients' quality of life (QoL).[2,3] However, the clinical presentation of PD is often dynamic, with symptoms fluctuating throughout the day in response to antiparkinsonian medications and other factors, such as food intake or circadian rhythm.[4,5] These fluctuations become more pronounced as the disease progresses, with the emergence of motor fluctuations and non-motor fluctuations (NMFs) marking the onset of advanced-stage PD.

In clinical practice, considerable effort is dedicated to identifying and accurately characterizing motor complications. Clinicians use semistructured interviews with validated and standardized tools to assess these manifestations, while patients and

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their caregivers are trained to recognize them. This awareness is crucial, as the appearance of MFs often signals the need for more focused and personalized therapeutic approaches, including device-aided therapies.

Despite this well-established approach to motor symptoms, only recently have NMFs in PD patients gained attention. In the NoMoFlu-PD study, clinical characterization of NMFs via home-based self-rating scales, including a visual analog scale, revealed the heterogeneity of NMFs and their patterns of fluctuation, with wider swings noted in neuropsychiatric NMS.[6] NMFs can coincide or even correlate with MFs and be equally or even more burdensome.[7,8] Despite their negative effects on patients' QoL, our understanding of NMFs remains limited; however, NMFs are often unappreciated or underreported in routine clinical practice.[9] Although much of the current knowledge is based on clinical intuition, as the systematic exploration of NMFs is still in an incipient stage, valuable progress has been made in this direction with the development and validation of targeted assessment tools. As this emerging field evolves, it presents new opportunities for interventions aimed at improving the overall QoL of PD patients and their caregivers.

In this descriptive review, we provide an overview of the current literature on NMFs in PD, examining various parameters and highlighting the need for further research to better understand and manage these complications.

MATERIALS & METHODS

We conducted a narrative review of papers written in English and indexed in the PubMed/MEDLINE database until October 13, 2024, referring to NMFs in PD. In the initial search strategy, we used the following combination of key terms: "Parkinson's disease" [Mesh] AND "fluctuat*" AND ("non-motor" OR "non-motor").

Our selection criteria included original research publications or post hoc analyses, reporting findings specifically focusing on NMFs in patients with PD, and reviews or meta-analyses presenting summative findings or original views and perspectives of movement disorder experts, avoiding duplications of research items. The references of any relevant publications were also screened for eligibility. The resulting findings were grouped and organized in the manuscript with respect to several NMF characteristics: definition, epidemiology traits, associations with MFs, risk factors, impact on disability/QoL, clinical characteristics and subtyping, diagnostic issues, focused assessment tools, and management/response to therapy. Publications reporting findings on pathophysiology and NMF-related digital technology were limited, so we included them separately in the discussion section. No automation tools were used in either the selection or data collection process.

RESULTS

During our initial screening process, we reviewed 492 records. We excluded 175 studies based on the title and an additional 180 studies based on the abstract, as these studies fell outside the scope of our review. An additional 2 papers were excluded because they were written in foreign languages (French and Hungarian). One study, written in Russian, was retained because its English abstract provided sufficient relevant information. A total of 135 full-text papers were subsequently assessed for eligibility, leading to the exclusion of 42 for various reasons (Figure 1). This process resulted in 93 papers meeting our inclusion criteria. Additionally, 13 papers identified through screening the reference lists of relevant publications were included. These 106 papers included 89 original research papers (including three post hoc analyses) and 17 reviews and/or meta-analyses, as presented below.

Definition of NMFs

NMF in PD refers to the fluctuations or swings of one or more NMS throughout the day in patients receiving long-term levodopa therapy.[10] Some NMSs exhibit a range of intensities, oscillating from a heightened to a reduced level, such as upregulated to downregulated emotion fluctuations. Other NMFs, such as pain or excessive sweating, are characterized by their intermittent presence or absence, although these may also vary along a severity spectrum.

NMFs were originally recognized in the context of MFs. Levodopa-induced "mood swings", associated with wearing-off motor phenomena, were originally described by Marsden and Parkes[11] in 1976, although they did not use the NMF terminology. The existence of NMF was subsequently corroborated by the scientific community, with researchers describing PD patients experiencing a deterioration of particular NMS during OFF periods but also, although less frequently, during the ON state.[12,13] These initiatives were specifically enhanced by the work of Storch et al.[6] and the Movement Disorders Society (MDS) Non-Motor Study Group, who aimed to qualify and subcategorize NMFs, as well as to develop simple, scale-based tools for clinical assessment. The dynamic nature of NMFs aligns with the principles underlying PD-related MFs, although MFs and NMFs are now conceptually distinct phenomena.[14]

Association of NMFs with MFs

Most patients with PD who experience MFs also experience

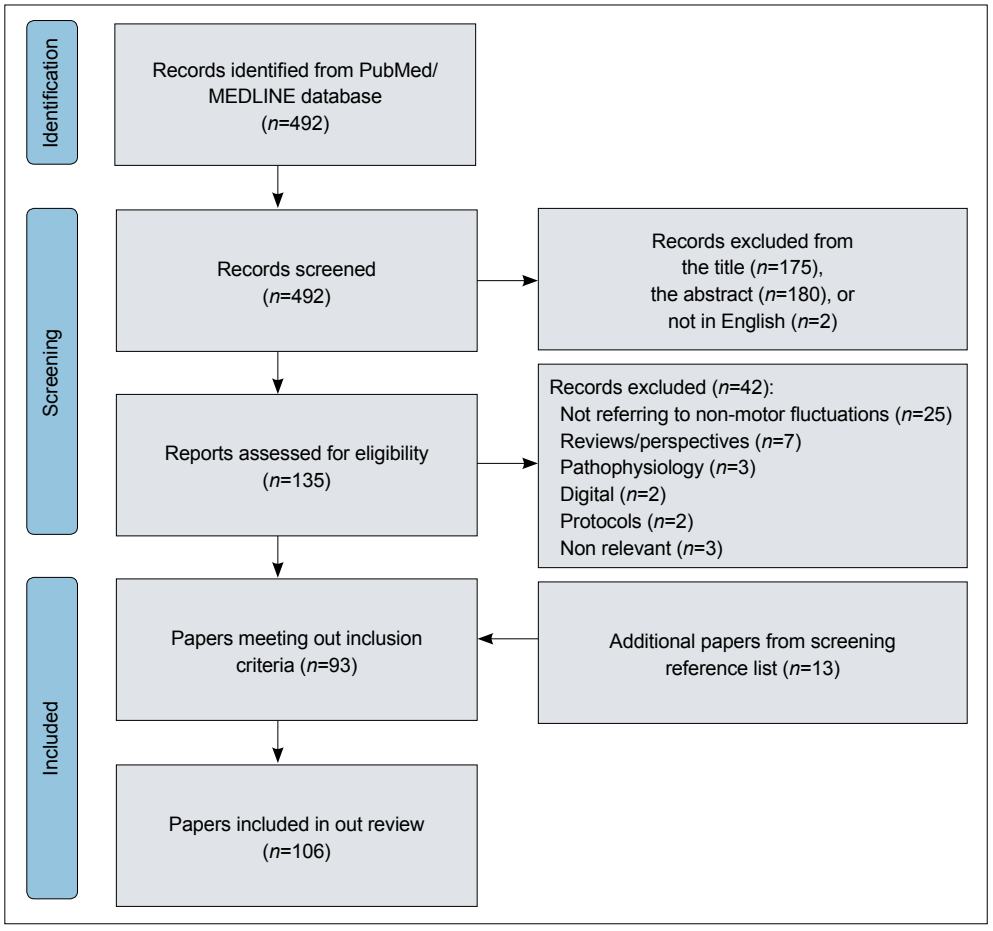

Figure 1. Prisma flowchart for a review of articles on Parkinson's disease-related non-motor fluctuations. PubMed database on October 13, 2024.

NMFs.[10] A prospective study (*n*=307) revealed that NMFs appeared either simultaneously or following MFs in nearly all patients with PD who developed fluctuations over the three-year study period.[15] Earlier studies reported that NMFs could not occur independently of MFs.[16,17] The idea that specific NMFs were secondary to motor complications, such as OFF-related anxiety associated with social embarrassment or fear of falling, was also raised[18-21]. Fernie et al.[22] introduced the concept of "metacognitions" to describe patients' anticipatory thinking about the upcoming OFF period as a stress-inducing factor precipitated by the MFs. Moreover, Witjas et al.[8] reported a significant correlation between the total burden of NMFs and motor disability.

The current understanding, however, suggests that aspects of NMFs are distinct entities that can occasionally occur in the absence of MFs, despite their frequent temporal association, the so-called "isolated NMF".[10,23,24] Ossig et al.[17] explored the frequency of NMFs and MFs throughout the day, along with their temporal relationships in groups of patients with fluctuating (*n*=15) PD, nonfluctuating (*n*=17) PD, and controls (*n*=15). They reported that switches in the NMS state were largely unrelated to motor state switches, although NMFs were observed only in patients with PD with MFs. In a small cohort of 17 patients with fluctuating PD, although OFF-related NMFs, such as anxiety, depression, poor cognitive performance, and bladder urgency, were temporally linked to motor OFF periods, they did not precisely overlap, as non-motor OFF periods were nearly twice as long.[25] Plasma levels of levodopa were closely monitored in two groups of PD patients (*n*=13) without clinically evident NMFs but with comparable motor performance and MFs, one receiving oral levodopa and the other receiving levodopa carbidopa intestinal gel (LCIG) infusion.[26] Greater fluctuations in levodopa levels were detected in the former group, whereas cognitive and affective fluctuations exhibited a more favorable pattern in the LCIG group, suggesting a link between NMFs and the fluctuating pharmacokinetics, and potentially the pharmacodynamics, of levodopa independent of MFs.

In addition to their temporal link, NMFs can be correlated with MFs, as poor OFF-related motor performance can coincide with low mood and high anxiety.[27] This latter presentation,

also referred to as "episodic anxiety", may not meet the criteria for an anxiety disorder and is considered unique to patients with PD.[20] Rizos et al.[28] reported that the majority of early-morning-OFF (EMO) periods, such as anxiety, urinary urgency, drooling, pain/paresthesia, low mood, and dizziness, are accompanied by NMS. Del Prete et al.[29] used wearable sensors to detect ON and OFF states in 18 patients with PD, tracking NMFs in real time over several days. They reported that upregulated neuropsychiatric manifestations, such as self-confidence, motivation, and competency, were typical of the ON motor state, whereas the opposite symptoms, such as anxiety, depression, and apathy, were more commonly OFF-related phenomena. Although these patterns are frequent, they are not universal.[30]

Nocturnal motor and NMSs in patients with PD, including pain, sleep impairment, and restlessness, could also reflect wearing-OFF phenomena, especially given their good response to sustained-release dopaminergic formulations or continuous dopaminergic drug infusions.[31] While motor phenomena play a role in such manifestations, it remains unclear whether these symptoms should also be classified within the NMF spectrum (e.g., wearing-OFF pain), warranting further investigation with focused assessment tools.

Epidemiology of NMFs

The prevalence and severity of NMFs varies significantly, not only because of the particular characteristics of patients with PD in selected cohorts but also because of marked heterogeneity in screening tools, characterized by a wide spectrum of sensitivity and specificity values. Large cross-sectional studies have reported NMFs in 19%–47% of patients with PD, with pain, anxiety, depression, fatigue, and sweating being the most commonly reported NMFs.[23,32-36] Higher percentages, even up to 100%, have also been detected.[8,37,38] Faggianelli et al.[7] reported that NMFs accompanied 83.8%–93.4% of the NMSs reported by individual patients with PD, with the highest prevalence corresponding to fatigue and the lowest to excessive sweating.

Clinical spectrum and subtypes of NMFs

Capturing and quantifying NMFs is challenging, not only due to the variety of available assessment tools but also because of the inherent heterogeneity of NMF. This umbrella term encompasses a broad spectrum of NMS, which fluctuate in different patterns and degrees of severity and frequency, while they can even fluctuate within individual patients with PD.[39] There is a clinical impression that certain combinations of NMFs commonly cooccur.[28,32] Researchers generally categorize NMFs into three subgroups: (neuro) psychiatric, autonomic, and sensory.[8,10,32,40,41]

Neuropsychiatric fluctuations

Neuropsychiatric fluctuations, such as anxiety, concentration difficulties, inner restlessness, and mood swings, are considered, by some researchers, to be the most common and pronounced NMFs, while they are reported as the most disabling.[6,14] Upregulated symptoms, such as hypomania or euphoria, are more typical of the ON state, whereas downregulated symptoms, such as low mood, anxiety, or irritability, are often OFF related.[41] Franke and Storch[14] referred to this discrimination as "plus" (related to the motor ON state or dyskinesia) and "minus" symptoms (related to the motor OFF state). A U.S.-based research group analyzed the neuropsychiatric profile of 200 patients with PD with fluctuating anxiety.[42] Although nearly 70% of them had a "typical ON–OFF response" to medication, a subgroup labeled "anxious fluctuators" exhibited significant anxiety exacerbation, more depressive symptoms, greater disability, and poorer ON-related performance in fluctuating symptoms. Fluctuating anxiety can also be levodopa-induced or episodic.[8,19,27] A systematic review examining the prevalence of fluctuating anxiety in patients with PD reported a weighted mean of 34.2% (range 3.8%–100.0%); this value exceeds the average overall prevalence of PD-related anxiety disorders (31%).[27] Panic attacks, which mostly occur in the OFF state, have also been reported.[1]

A systematic review reported that fluctuating anxiety and depressive symptoms, mostly encountered in the OFF phase, were found in up to 67.7% and 71.4% of patients with PD with MFs, respectively.[43] The association of neuropsychiatric fluctuations with MFs is one of the reasons for their dopaminergic basis.[25,27] Costa et al.[44] reported that PD patients with fluctuating cognition performed better in high-flexibility tasks after receiving a levodopa dose, further supporting the role of dopamine in early cognitive issues in PD. In a cohort of 102 fluctuating PD patients, neuropsychiatric fluctuations, particularly ON-related euphoria, were more commonly associated with dopamine and behavioral addictions.[45] "Dopamine dysregulation syndrome" is a particular form of ON-related elevated emotion, euphoria and alertness; these features can escalate to psychomotor agitation and hyperactivity or even a hypomanic or manic state.[46] This condition is associated with impulsive, addictive or stereotypical behaviors and a higher levodopa equivalent daily dose (LEDD) than is actually needed for the management of PD symptoms.

Pain and sensory fluctuations

Sensory fluctuations include different levels and types of pain and discomfort, such as burning or tingling sensations, and can occur in either the ON or OFF state (Figure 2).[10] Higher rates and severity levels of pain have been particularly linked to the OFF motor state, including dystonia-related pain.[33,47-49] In a study of 47 patients with fluctuating PD who were meticulously moni-

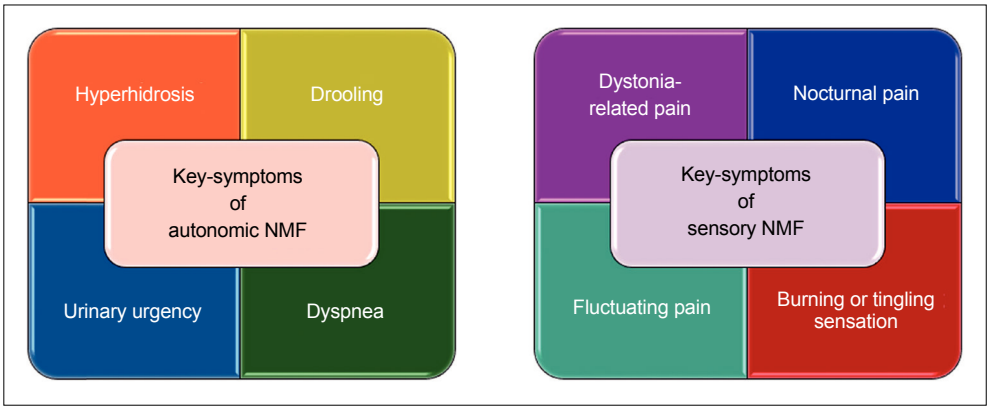

Figure 2. Key features of autonomic and sensory NMFs. NMF, non-motor fluctuation.

tored with pain-targeting tools, pain was detected in 35% of waking hours, with nearly half of all OFF motor periods characterized by pain.[50] A distinct peak was noted during the EMO time. Interestingly, pain was associated with disease severity solely in the motor ON state and in the presence of dyskinesia, highlighting the need to address ON-related pain in routine clinical practice. Nocturnal pain, often associated with EMO episodes, and fluctuation-related pain are quite prevalent among patients with PD (43.9% and 34.6%, respectively), particularly at advanced stages (Hoehn & Yahr [H&Y]≥3).[51] Fluctuating pain was more commonly reported among patients with PD who had an abnormal axial posture, such as Pisa syndrome or camptocormia, indicating different pathways in pain origin and, possibly, alternative therapeutic approaches.[52] Dopaminergic deficits are thought to mediate sensory NMFs to some extent, as suggested by a good response of pain symptoms to dopaminergic therapy.[53,54] For other sensory symptoms, such as hyposmia or vision disturbances, no signs of fluctuation have been reported.[14]

Autonomic fluctuations

Compared with neuropsychiatric or sensory symptoms, autonomic fluctuations display greater heterogeneity, with fewer autonomic NMSs fluctuating (Figure 2).[32] Some of these symptoms, such as constipation or sexual dysfunction, are less prone to fluctuate; others, such as urinary urgency, excessive sweating, dyspnea, drooling, or abdominal disturbances (e.g., bloating), are most commonly encountered in the OFF state,[8,14,25,28,32,55] although these findings are not unanimous.[48] Notably, sweating can be ON-related when associated with dyskinesia.[56] Less common symptoms, such as wearing-OFF shortness of breath or stridor, have also been reported.[8,57] Disability induced by autonomic NMFs has been correlated with levodopa therapy,[8] whereas excessive sweating, attributed to thermoregulatory dysfunction, is thought to be more directly linked to dopaminergic medication.[24]

Other distinctive clinical features

Grouping NMFs into three subgroups offers some practical benefits, as symptoms within each group often share common pathophysiological mechanisms and similar frequency rates or treatment options. However, this is not a standardized categorization, which is consistently encountered across different studies, while the description of each NMF subtype remains imprecise and somewhat subjective. Several limitations should also be acknowledged. Some NMFs cannot be easily assigned to a single category.[14] Fatigue, which is often OFF related, has been reported as one of the most prevalent NMFs.[36,38] Although it is sometimes categorized as a neuropsychiatric NMF, other researchers examine it separately in a fourth category, alongside symptoms of sleep impairment.[14] This distinction has pathophysiological value, as fatigue is less responsive to dopaminergic variations than other neuropsychiatric fluctuations are.[24] Nocturnal symptoms, motor or non-motor, are frequently associated with sleep impairment and linked to wearing-OFF phenomena, while they show overlapping patterns with all three NMF subtypes (e.g., nocturnal pain, anxiety, low mood, excessive sweating, drooling, and urinary urgency).[28,58] However, excessive daytime sleepiness can be a secondary ON-state complication of dopaminergic therapy, although it has also been associated with circadian dysfunction.[5]

Perceptual problems, such as hallucinations, seem to fluctuate less.[59] Hallucinations are often related to higher LEDDs and are mostly considered drug-induced.[60] However, OFF-related cases have also been described, and MF and dyskinesia are considered independent risk factors.[60,61]

Burden of NMFs and QoL

NMFs have been consistently found to negatively impact QoL in PD patients, often to a similar or even greater degree than MFs do, particularly when pain and mood fluctuations are considered.[8,45,48,62] In a multicenter study in France (n=310), approxi-

mately one-third of patients with PD reported that NMFs were more troublesome than MFs were, whether in the ON- or OFF-medication state (34.9% and 37.5%, respectively).[7] These results were in line with those of another French study (*n*=136), which reported a strong correlation between poor QoL and NMFs, which was particularly significant for OFF-related NMFs and neuropsychiatric symptoms.[8,62] In a Mexican cross-sectional study of 271 patients with PD with various motor disabilities (H&Y=1–5), approximately three-quarters experienced wearing-off phenomena, whereas almost half exhibited both MFs and NMFs.[35] Those with both types of fluctuations reported significantly worse QoL than those with only MFs.

Fluctuating salivation, particularly deteriorating during the OFF motor state, is associated with dysautonomia and worse QoL.[63] The effect of fluctuating fatigue on PD patients' QoL is debated.[7,48] Interestingly, significantly worse QoL was found among patients with PD who experienced solely ON-related fatigue than among those with either solely OFF-related fatigue or both ON- and OFF-related fatigue.[48] Rastgardani et al.[64] explored the impact of OFF-related symptoms on patients with PD, their caregivers, and treating physicians; although motor symptoms were perceived as more burdensome overall, a wide range of NMSs was revealedduring OFF periods, with cognitive impairment posing the greatest burden on caregivers. OFF-related fatigue, affect (anxiety/irritation, sadness, apathy), and sleepiness were also noted as troublesome in more than 40% of the caregivers. Only a small number of clinicians, mostly movement disorder specialists, identified pain, anxiety, and sweating as potential OFF-related NMSs.

Gender differences and other risk factors of NMFs

Female sex appears to be a risk factor for the development of NMFs in patients with PD. In a recent post hoc analysis (*n*=380), an increased burden of wearing-OFF NMSs was detected among female patients with PD, which was particularly relevant to behavioral and anxiety-related NMFs.[65] This higher risk of NMFs in women was corroborated by a multivariate analysis of an Italian study, which revealed a greater NMF burden among female patients with PD, particularly in the domains of depression/anxiety, sleep/fatigue, and dysautonomia.[38] Other studies using validated NMF assessment tools also reported higher scores among female patients with PD, who were occasionally underdiagnosed and undertreated.[7,66] On the other hand, male sex was identified as a risk factor for more severe anxiety fluctuations in a focused U.S. cohort of selected patients with PD with fluctuating anxiety.[42]

Similar to MFs, younger onset age, higher LEDD, longer disease duration and extended levodopa therapy were associated with increased vulnerability to developing NMFs.[8,23,24,32,36,59,67-69] Brun et al.[23] suggested that MFs, as well as dysautonomia, constitute independent predictors of the development of NMF.

Frame of NMFs

Different phases in the course of PD may be characterized by various types or combinations of NMSs. A recent study (*n*=137) revealed that the ON state was associated with unpleasant NMSs early in the PD course (less than 7 years of PD) but with pleasant NMSs at later stages.[70] The frequency of NMFs at different PD stages is conflicting; some researchers argue that the prevalence of both NMSs and NMFs increases with PD progression.[23,36,45] An Italian study reported a correlation between combined MF and NMF scores and motor performance, as expressed by the Unified PD Rating Scale Part III (UPDRS-III) and H&Y, suggesting that advanced PD patients are more vulnerable to fluctuations.[71] A meta-analysis of a German and Swedish study of patients with PD (*n*=101) of all motor stages (H&Y=1–5) with documented NMF showed that although the overall burden of NMS increased proportionally to disease progression, an opposite trend was revealed for NMF; the amplitude of NMF decreased with disease progression to subside at the most advanced stage (H&Y=5).[6] The authors attributed this pattern to the continuous deterioration of ON-related NMSs until they matched the levels of OFF-related NMSs. This observation is in line with previous findings.[72] However, great methodological heterogeneity is found in relevant studies, as disabling, typically drug-induced NMSs, such as orthostatic hypotension and sleepiness, which are often more pronounced at this late stage, are not always considered.[72] Other researchers detected NMF in patients with PD with H&Y stages 4 and 5, even when the response of motor performance to dopaminergic therapy was poor, highlighting the need to optimize dopaminergic therapy even at advanced stages.[73]

Differential diagnosis of NMFs

Accurate detection of NMFs is one of the unique challenges encountered in managing PD. While the concept of isolated NMF is recognized,[23] it remains less clearly defined, carrying a risk of misdiagnosis.[74] NMFs can overlap with the dynamic and heterogeneous presentations of common PD-related neuropsychiatric symptoms, such as depression, fatigue, apathy, or dementia.[75] Neuropsychiatric symptoms and behavioral disorders can masquerade as NMFs or dopamine dysregulation syndrome. Interestingly, patients with PD experiencing NMFs, particularly of a neuropsychiatric nature, had higher rates of depression, drug-induced psychosis, and cognitive impairment, further complicating accurate diagnosis and comprehensive management.[59,68]

Cognitive fluctuations, a core diagnostic feature in dementia with Lewy bodies, need to be distinguished from potential NMF.[76] Additionally, differential diagnosis from dopamine agonist withdrawal syndrome (DAWS), which presents with neuropsychiatric

symptoms, including severe apathy, anhedonia, and depression, should be considered in patients with PD following abrupt cessation of dopamine agonists, such as after the implementation of device-aided therapies.[77] Finally, it is important to differentiate between NMFs and suboptimal titration of the antiparkinsonian regimen in patients responsive to dopaminergic therapy.[78]

Assessment tools for NMF

The largely subjective nature of NMFs, their heterogeneity, and the occasional absence of insight from clinicians may explain why NMFs are often unappreciated or difficult to diagnose despite their pronounced effect on the QoL of patients with PD (Table 1).[79] Many validated instruments are currently available to assess the NMS burden either in the ON or OFF state, without particularly focusing on NMFs. The Non-Motor Symptoms Scale (NMSS),[80] for example, administered separately in the ON and OFF states, was used in a cohort of 100 patients with PD to detect NMFs, indicating a greater load of OFF-related NMSs.[37] Although the clinimetric characteristics of this tool in patients with fluctuating PD are similar to those of the original NMSS, this modified use of the NMSS is not considered specific or comprehensive when evaluating NMFs.

Similarly to MFs, descriptive methods of NMFs, which use self-reported daily diaries, have also been used in research.[17,50,81] On most occasions, a training session would take place to train patients with PD and their caregivers on how to fill out the diary to increase their reliability. These diaries offer the advantage of providing real-time descriptions of NMFs without any recall bias, as they are completed by patients at home. Although they are not standardized and are highly subjective, they can offer great insight into patients experiencing NMFs under real-life circumstances.

The quantification of NMFs in a practical and standardized way is crucial, as it may facilitate its recognition and assessment in routine clinical practice. Several types of such evaluation tools have been created thus far; tools that evaluate NMSs separately in the ON or OFF phase constitute a step toward the recognition of NMFs. The Non-Motor Symptoms-ON scale (NoMoS-ON) is a novel questionnaire focused on the assessment of NMSs solely during the ON phase with acceptable clinimetric characteristics (internal consistency/Cronbach's alpha=0.61, test-retest stability/intraclass correlation coefficient=0.77, diagnostic accuracy=76.6%).[70] The older Wearing-Off Questionnaire (WOQ) was recommended by the MDS as a validated screening tool for MFs and NMFs, even in early PD stages.[82] Two versions of the WOQ are now used: the 19-item (WOQ-19), also known as "QUICK", and the 9-item (WOQ-9), which focus on 19 and nine symptoms, respectively, that are believed to be the most crucial.[83,84] Both assessments are considered highly sensitive in detecting wearing-OFF motor or NMSs; the former exhibits better specificity values (0.39–0.8), although the latter is often preferred because it has the shortest duration.[85] Test-retest reliability was only available for the WOQ-19 (intraclass correlation coefficient of 0.86).

Some of these tools attempt to capture the whole range of fluctuating NMSs, which are commonly encountered in PD, whereas others are tailored to detect specific fluctuating NMSs. The MDS Non-Motor Rating Scale is a validated, updated version of the NMSS that has been amended to address several previous limitations, including NMF evaluation.[86] The values of internal consistency (Cronbach's alpha 0.84), interrater reliability (intraclass correlation coefficient>0.95), test-retest stability (intraclass correlation 0.70), and precision (standard error of measurement 7.06) for NMFs ranged from adequate to excellent. The Non-Motor Fluctuation Assessment Questionnaire (NoMoFa) is a validated questionnaire that captures both the static and dynamic (fluctuating) nature of NMSs[9]; one of its applications was to monitor the response of NMSs and NMFs to treatment, while it has been validated both in cognitively intact and impaired PD populations. NoMoFa exhibits an adequate level of internal consistency (Cronbach's alpha=0.89) and test-retest reliability (intraclass correlation coefficient of 0.73).

The PREDISTIM study group in France devised an original questionnaire, the Non-Motor Fluctuations Park questionnaire, which was validated in three groups of patients with PD (drug-naïve, with and without MFs).[87] The questionnaire particularly focuses on the association of a series of selected NMFs with dopaminergic treatment, highlighting the role of autonomic, cognitive, and psychiatric parameters. An updated and validated version, the Non-Motor Fluctuations Severity Scale, is completed by patients while they are OFF- and then ON-medicated to describe their NMSs in real time.[7] The same approach is used by the NFS, a scale that focuses particularly on neuropsychiatric fluctuations.[88,89] Minus or hypodopaminergic neuropsychiatric manifestations, including anxiety, fatigue, slow thinking, depression, impaired attention, and nonmotivation, which are often associated with the OFF-medication state, are sought separately from plus or hyperdopaminergic or ON-medication symptoms, such as hyperactivity, well-being, and elevated mood. The final score arises from the combination of the aforementioned subscores, thus expressing the amplitude of neuropsychiatric fluctuations between the ON- and OFF-medication states. The internal consistency of the scale was satisfactory (Cronbach's alpha>0.80), but other psychometric qualities, such as test-retest stability, were not reported. Such applications resemble the use of the UPDRS in the ON and OFF states to assess and compare motor manifestations. These are valuable characteristics among other validated tools, offering a more focused reflec-

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Table 1. Tools aiming at non-motor fluctuations assessment, either solely or as part of an overall questionnaire

Full name	Abbreviation	Reference	Items	Phase	Result	Details
Non-Motor Symptoms-ON scale	NoMoS-ON	Donzuso et al.[70], 2024	17 items	ON	0%–100%	Validated, rater-administered
Wearing-Off Questionnaire	WOQ-19 (QUICK/QQ); WOQ-9	Stacy et al.[82], 2008 Martinez-Martin et al.[84], 2008	10 NMS (+9 motor) items; 4 NMS (+5 motor) items	OFF	0–10 (total 0–19); 0–4 (total 0–9)	Patient-rated, some foreign versions are validated
Movement Disorders Society Non Motor Rating Scale	MDS-NMS	Chaudhuri et al.[86], 2020	NMF subscale (8 items)	ON & OFF	0–128 (total 0–832)	Rater-administered, validated
Movement Disorders Society Non-Motor Fluctuation Assessment Questionnaire	(MDS-) NoMoFa	Kleiner et al.[9], 2021	27 items	ON & OFF (separate scores)	0–81 [NMF (ON+OFF)+NMS (static)=total NoMoFa]	Patient-rated, validated
Non-Motor Fluctuations Park	NMF-Park	Faggianelli et al.[87], 2022	22 items	ON & OFF	0–100	Patient-rated, validated
Non-Motor Fluctuations Severity Scale	NMF2S	Faggianelli et al.[7], 2024	11 items	ON & OFF (separate scores)	0–110	Patient-rated, real-time assessment, validated
Neuropsychiatric Fluctuation Scale	NFS	Schmitt et al.[88], 2018	20 items (ON/plus & OFF/minus-10 items each)	ON & OFF (separate scores)	-30 to +30 (0–30 each) <0: OFF-dominant >0: ON-dominant	Patient-rated, real-time assessment, not validated
Ardouin Scale of Behavior in Parkinson's disease	ASBPD	Rieu et al.[90], 2015	Part III (2 items) (total of 21 items)	ON & OFF	0–8 (total 0–44)	Rater administered/semi-structured interview, validated
King's PD Pain Scale	KPPS	Chaudhuri et al.[135], 2015	Domain 3 (3 items): fluctuation-related pain	ON & OFF	0–36 (total 0–168)	Different versions for patient- or rater-administered, validated
Seoul National University Hospital Fluctuations Questionnaire	SNUH-Fluctuations Questionnaire	Kim et al.[15], 2018	20 NMF items (+9 motor)	-	-	Adopted & modified from WOQ-19 and NMSQ

NMS, non-motor symptom; NMF, non-motor fluctuation; NMSQ, non-motor symptoms questionnaire.

tion of the NMF response to treatment; however, one should bear in mind that it represents NMSs of patients with PD during test completion and not necessarily their overall condition (e.g., anxiety-related NMFs, not necessarily anxiety disorders).

The Ardouin Scale of Behavior in PD is a validated questionnaire aimed at detecting and quantifying mood and behavioral disturbances in patients with PD in the context of dopaminergic therapy (hypodopaminergic or hyperdopaminergic symptoms).[90] It is considered a reproducible instrument with satisfactory internal consistency (Cronbach's alpha 0.69–0.78), test-retest reliability (kappa coefficient>0.4) and inter-rater reliability (kappa coefficient>0.5) for most items. Apart from part II, which evaluates the ON- and OFF-state psychological states, part IV is focused on potential dopamine-induced behavioral disorders, such as excessive motivation and diurnal somnolence.

Clinical observations, professional experience, and movement disorder experts' opinions played a central role in the design of the aforementioned tools to support their use as an adjunct to standard clinical practice. These tools are intended to complement history-taking and facilitate efficient and targeted clinical assessment. Although the selected array of non-motor items can flag specific areas of interest for individual patients with PD, their role is assistive and cannot under any circumstances replace a comprehensive medical history.

Management of NMF

It is important for clinicians to recognize NMFs as crucial parameters that affect the selection of the optimum treatment strategy (Table 2), including patients' eligibility for interventional therapies.[91] Since strong correlations between NMFs and MFs are acknowledged, any strategies aimed at efficiently managing MFs are highly likely to address NMFs as well. Overwhelming NMFs, such as panic attacks or apathy, may overshadow motor OFF phenomena; thus, a balanced and holistic approach is advised.[74] The inherent diversity of NMFs needs to be considered, as does secondary NMFs (e.g., drug-induced NMFs).[14] A significant percentage of NMFs exhibit a good response to dopaminergic treatment, although cases of deterioration in the ON-medication state have also been described (e.g., dyspnea, restless legs syndrome).[7] The optimization of dopaminergic therapy with strategies aimed at continuous drug delivery, such as extended-release formulations and redistribution of dosing, are reason-

Table 2. Treatment options in managing non-motor fluctuations

Strategy used	Study title	Effects noted	Reference
Rotigotine transdermal patch	• RECOVER study post hoc analysis • DELORES study	• Sleep benefit • Pain • Drooling • Mood • Fatigue • Depression • Anhedonia • Apathy	• Trenkwalder et al.[136], 2011 • Chaudhuri et al.[137], 2013 • Kassubek et al.[97], 2014 • Rascol et al.[96], 2016
Safinamide	• VALE-SAFI study • Secondary analysis of SAFINONMOTOR	• Pain • Mood • Sleep quality • Fatigue • Depression	• Labandeira et al.[138], 2021 • De Masi et al.[139], 2022
Opicapone	• BIPARK-1 & BIPARK-2 post-hoc analysis • OPTIPARK sub-analysis	• Mood/apathy domain • Sleep/fatigue domain	• Schofield et al.[92], 2022 • Santos García et al.[140], 2022 • Hauser et al.[141], 2024
Subcutaneous apomorphine infusion	• Post-hoc analysis of APOMORPHEE study • Euroinf-1 & Euroinf-2	• Insomnia • Sleep disturbances • Excessive sweating • Weight change	• De Cock et al.[142], 2022 • Martinez-Martin et al.[118], 2015 • Dafsari et al.[143], 2019
Intrajejunal levodopa-carbidopa intestinal gel infusion	• GLORIA • DUOGLOBE post-hoc analysis • COSMOS long-term effect	• Sleep/fatigue • Mood/cognition • Gastrointestinal tract domain • Miscellaneous domain • Constipation • Dopamine dysregulation syndrome	• Antonini et al.[144], 2017 • Chaudhuri et al.[145], 2023 • Fasano et al.[146], 2023 • Standaert et al.[147], 2021
Subthalamic nucleus deep brain stimulation	• 36-month quality of life data	• Anhedonia • Concentration impairments	• Jost et al.[148], 2021
Subcutaneous foslevodopa-foscarbidopa infusion	• Phase 3 RCT • Open-label, 12-month	• Sleep • Early morning akinesia • Nocturia	• Soileau et al.[149], 2022 • Aldred et al.[150], 2023

able initial approaches for the management of NMFs, at least those with a dopaminergic origin, such as mood impairment, anxiety, and pain,[7,24] and are presented below.

Drug-based approaches

Defining whether NMFs are drug-induced is an important step, as lowering LEDD or discontinuing selected medication might be applicable to ON-related NMFs, such as dyskinesia-induced sweating or hallucinations.[56] For primarily OFF-related NMFs, any strategies focused on decreasing OFF periods overall, such as dopamine-enhancing therapies (e.g., adding a catechol-O-methyltransferase inhibitor), are essential.[10,81] This approach is particularly relevant to fluctuating anxiety.[19] A subanalysis of the OPTIPARK study indicated that opicapone may be effective in alleviating wearing-OFF NMSs, including mood changes.[92] A randomized, double-blind placebo-controlled clinical trial is currently underway to explore the effect of opicapone on fluctuations focusing on pain (OCEAN trial; EudraCT number 2020-001175-32).[93]

With respect to neuropsychiatric symptoms, it is important to establish whether depression or low moods are fluctuating, particularly OFF-related, as fluctuating depression may respond to specific adjustments in dopaminergic medication, such as the introduction of pramipexole, a dopamine agonist with potential antidepressant effects, before depression-specific therapies are considered.[75] A post hoc analysis of patients with PD with a fluctuating mood revealed a beneficial effect of safinamide, a drug with both dopaminergic and nondopaminergic properties, on mood; this effect was suggested to be mediated by a reduction in OFF periods.[94] Nonpharmaceutical approaches, such as focused physiotherapy or training programs, are also beneficial for emotional wellbeing and balance management in patients with PD with fluctuating anxiety.[95] On the other hand, the response of fluctuating fatigue to dopaminergic therapy is conflicting.[7]

With respect to sensory NMFs, fluctuating dystonic pain shows a good response to dopaminergic therapy.[24] A beneficial effect on fluctuating pain was achieved with the use of transdermal rotigotine in the DOLORES study and a post hoc analysis of the RECOVER study.[96,97] Moreover, safinamide was found to improve fluctuation-related pain, including dystonia-related pain in the OFF state.[98,99]

Device-aided therapies: deep brain stimulation

Fluctuating NMF, such as anxiety, pain, apathy, slow thinking or impaired concentration, can be relieved by device-aided therapies, including subthalamic nucleus deep brain stimulation (STN-DBS)[100,101] and apomorphine[102] or LCIG infusion.[103] A recent prospective study (*n*=20) reported a statistically significant improvement of almost 45% in overall NMFs at 6 months after DBS implementation.[104] This improvement, which was strongly correlated with both motor complications and QoL, was attributed mainly to the reduction in the unpredictable OFF time. The same trend was observed for the severity of OFF-related sensory NMFs. Witjas et al.[105] reported a positive overall effect of STN-DBS on NMFs at the 1-year follow-up, particularly regarding sensory, autonomic, and cognitive NMFs, whereas the response of other neuropsychiatric fluctuations (e.g., anxiety, fatigue) was less consistent. Notably, rare debilitating fluctuating symptoms such as akathisia or drenching sweats substantially improved as well. Researchers also attributed this benefit to shorter OFF periods, as the majority of NMFs were detected in the OFF state preoperatively. An older, prospective study (PD, *n*=20) revealed a significantly decreased frequency and severity of autonomic and psychiatric OFF-related NMFs 2 years after STN-DBS implementation.[106] In a small pilot study (PD, *n*=18), nocturnal and fluctuating pain significantly improved 6 months following either STN- or globus pallidus internus-DBS.[107]

The acute psychostimulant effects of levodopa, as measured by a euphoria subscale, were significantly reduced in 36 patients with PD 1 year after STN-DBS and gradually lowered their LEDD, suggesting that continuous subthalamic stimulation can have a beneficial effect on drug-induced upregulated emotion compared with pulsatile treatment.[108] In a recent retrospective study, Magalhães et al.[109] reported that the acute psychotropic effects of STN-DBS were similar to those induced by oral levodopa. In a prospective study of 63 patients with PD, neuropsychiatric NMFs were significantly alleviated 1 year after the implementation of STN-DBS, with reductions in OFF-related dysphoria and ON-related euphoria.[110] The same findings were replicated in subsequent studies by the same (follow-up at 6 months) and different (follow-up at 1 year) research groups.[108,109,111] Researchers have suggested that although NMFs are partly improved by lowering the use of dopaminergic medications, they were also affected by direct stimulation of non-motor STN regions.[110]

In a case–control study of patients with PD (PD, *n*=494), DBS candidates were more likely to experience fluctuations in the psychological state associated with motor performance either in the ON or OFF state but also hyperdopaminergic symptoms, such as compulsive behaviors or elevated motivation.[112] The presence of fluctuating apathy, depression and anxiety was found to significantly predict the development of postoperative apathy, with researchers suggesting that this phenomenon could be attributed to delayed DAWS.[113] Therefore, the presence of neuropsychiatric fluctuations in DBS candidates could be an indication for long-term neuropsychological monitoring postoperatively, as postoperative apathy can be associated with postoperative depression with increased suicide risk in patients with PD.[114]

Device-aided therapies: intrajejunal infusion of LCIG

Like motor complications, continuous drug delivery can benefit NMFs.[26,115] A prospective, multicenter study in Spain (*n*=72) with up to 4 years of follow-up revealed that LCIG significantly improved NMF, particularly anxiety, irritability, and pain, in patients with PD.[116] Additionally, stable levodopa plasma levels were found to mitigate the "overdosing" effect observed with oral levodopa in patients with fluctuating PD, leading to poor cognitive performance soon after an oral levodopa dose.[117]

Device-aided therapies: apomorphine pump

Apomorphine infusion can also be considered in patients with PD with severe MFs and NMFs.[118] Growing evidence from nonrandomized studies suggests that it can have a positive effect on OFF-related NMS, including pain, mood impairment and cognitive fog.[119] It was found to effectively address nocturnal pain in the long term in a prospective, multicenter Indian study (*n*=51) of patients with advanced PD.[120] Apomorphine injections could also be considered for rapid relief of OFF-related NMS, such as pain.[119] The initiation of OFF-related NMS has been reported as a signal to determine the right moment to administer apomorphine injections as a rescue therapy for motor OFF symptoms.[121]

DISCUSSION

Although the concept of NMFs has been well known for more than two decades, their contribution to therapeutic decisions is still minimal.[59,122] In 1996, Hillen and Sage[34] underscored the presence of wearing-OFF NMSs in nearly 20% of 130 patients with PD with MFs. Notably, these manifestations, although initially undetected or little appreciated, improved in three-quarters of the patients after being specifically addressed.

Fluctuations may persist despite optimum therapy.[123] However, our understanding of NMFs appears to be in the early stages, with a focus on preliminary awareness rather than effective treatment. Implementing appropriate treatment strategies is challenging without a prior clear definition of NMFs and a comprehensive understanding of its full extent. Refinement of definitions, accurate use of relevant terms, and targeted research are necessary, as NMFs are commonly grouped under the broad "umbrella" term of fluctuations without distinguishing them from MFs. Researchers and clinicians specify the type of PD fluctuations (e.g., wearing-OFF phenomena, delayed-ON, EMO, dyskinesia, unpredictable OFF episodes, and dose failures), including whether they present as motor or non-motor phenomena, is essential, as the therapeutic approach may change.

Wearing-OFF phenomena can start with either motor or NMSs; however, if the latter are subtle, patients with PD may not realize that they are associated with antiparkinsonian medication and, thus, may not discuss them with their treating physician.[78] Clinicians need to be vigilant for the timely recognition of NMFs, as it can develop early in the disease course, even in patients who are considered nonfluctuating.[67] The lack of established assessment tools for NMFs has been criticized in the past.[14] Although the NMSS is typically used by the majority of studies to evaluate the NMS burden, this questionnaire is not specific for NMFs. As shown above, several validated tools focusing on NMFs are currently available. The diagnosis of NMFs can be challenging, even for experienced movement disorder specialists; although the use of validated screening tools is strongly encouraged, they cannot replace careful history taking and semistructured interviews with treating physicians.[124]

Various and heterogeneous pathophysiological mechanisms, often shared with those mediating MFs in the advanced PD stage, are believed to be involved.[14,79] Gastrointestinal dysfunction and erratic absorption of dopaminergic medications can, at least in part, predispose patients to both MFs and NMFs, which explains why nonorally delivered dopaminergic medications are effective in NMFs.[115,125] The temporal association of some NMFs with MFs also highlights a potential impairment in dopaminergic neurotransmission, either in a direct or indirect way.[14] Downregulated neuropsychiatric symptoms, such as depression and brain fog, are thought to result from low dopaminergic reserves, as they are often alleviated or even reversed (e.g., euphoria, hyperactivity, and impulsivity) by dopaminergic stimulation.[10] However, this is not a straightforward mechanism and debilitating symptoms of anxiety, sleepiness, confusion, and hallucinations can emerge. A retrospective, longitudinal study (drug-naïve PD, *n*=29) showed that greater dopamine turnover, as assessed with 18Fluorodopa positron emission tomography imaging, was associated with the development of neuropsychiatric fluctuations approximately a decade later; this mechanism has also been associated with MFs and dyskinesia but not with autonomic and sensory fluctuations.[126] Moreover, Black et al.[127] measured regional cerebral blood flow before and after levodopa challenge, revealing increased perfusion of regions linked to the posterior cingulate cortex (caudate nucleus, anterior cingulate cortex, orbital frontal cortex) in patients with PD with mood fluctuations, an area also highlighted in the pathogenesis of neuropsychiatric symptoms in PD.[113]

The above findings support the dopaminergic basis of some, but not all, NMFs. Since NMFs are not fully coupled with the presence of MFs, other nondopaminergic mechanisms may also be involved in their pathophysiology. In a PD group of DBS candidates (*n*=33), poor OFF-related cognitive performance was associated with decreased structural integrity of the cholinergic nucleus basalis of Meynert, as expressed by mean diffusivity and

generalized fractional anisotropy; this association disappeared when ON-related cognitive scores overall were examined.[128]

Newer technologies have revolutionized diagnosis and monitoring procedures as an add-on to standard clinical care, offering additional clinical information that is not fully captured during a clinic visit.[129] To date, such technologies have focused mainly on motor aspects of PD; however, the focus is gradually shifting to NMFs, with digital means attempting to assist clinicians and researchers in accurately and timely detecting and quantifying NMFs.[130] Using sensors to measure NMFs seems more challenging than using sensors to measure MFs. Wearable devices, including kinetigraphs, have been successfully used to remotely monitor and assess dyskinesia and MFs in patients with PD, including undetected EMO periods.[131] Online NMF questionnaires could also be applied to remotely assess NMFs patientwise.[132] Devices tracking neuropsychiatric fluctuations, which are based on instant patient input throughout the day, are currently being developed in psychiatric research and employ mobile applications.[133] Smartphone sensors detecting usage patterns or language choices, as indirect indications of mood impairment, are also underway.[133] Smart watch measurements have been used for the detection of alterations in vital signs, such as heart rate, oxygen saturation and blood pressure, possibly paving the way for monitoring autonomic fluctuations in patients with PD.[130,134] Such applications are expected to be widely developed in the future, serving not only as research tools but also as extensions of treatment physician follow-up.

CONCLUSION

In summary, NMFs represent a significant aspect of PD that warrants greater attention from both researchers and clinicians. The diversity and complexity of NMFs, along with their substantial impact on the QoL of patients with PD, highlight the urgent need for systematic, large-sample studies using targeted assessment tools. Validated questionnaires are currently available and should be implemented more consistently in routine clinical practice to support clinicians in the accurate and timely detection of NMFs. Early identification of NMFs can influence therapeutic decisions, including indications for device-aided therapies. Additionally, digital technologies and online applications offer promising prospects for enhancing the detection, monitoring, and management of NMFs, with their contributions expected to grow as technology advances. By deepening our understanding of the clinical characteristics, risk factors, and pathophysiologic mechanisms associated with NMFs, we can improve diagnostic accuracy and treatment strategies. Ultimately, proactive identification and management of NMFs in clinical practice will contribute to better overall care for patients with PD, leading to improved health outcomes and well-being.

Conflicts of Interest

The authors have no financial conflicts of interest.

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