REVIEW ARTICLE

Falls in Synucleinopathies

Stephen Joza, Richard Camicioli, Fang Ba

ABSTRACT: Parkinson's disease (PD) and other synucleinopathies, namely dementia with Lewy bodies (DLB) and multiple system atrophy (MSA), are common degenerative neurological disorders that share synuclein pathology. Although certain cardinal features of parkinsonism, including bradykinesia and rigidity, respond well to levodopa, axial features, such as gait and balance impairment, are less reliably responsive to dopaminergic therapy and surgical interventions. Consequently, falls are common in PD and other synucleinopathies and are a major contributor toward injury and loss of independence. This underscores the need for appropriate fall risk assessment and implementation of preventative measures in all patients with parkinsonism. The aim of this review is therefore to explore modifiable and non-modifiable risk factors for falls in synucleinopathies. We next review and evaluate the evidence for pharmacological, nonpharmacological, and surgical approaches for fall prevention, and emphasize individualized and multifaceted approaches.

RÉSUMÉ: Les risques de chute dans le cas des synucléinopathies. La maladie de Parkinson (MP), de même que d'autres synucléinopathies comme la démence à corps de Lewy (DCL) et l'atrophie multi-systématisée (AMS), sont des troubles neurologiques dégénératifs courants qui ont en commun l'accumulation anormale de protéine synucléine. Bien que certains des principaux symptômes caractéristiques de la MP, par exemple la bradykinésie et la rigidité, répondent bien à la lévodopa, d'autres signes axiaux, par exemple une altération de l'équilibre et de la démarche, vont répondre de façon moins efficace à un traitement dopaminergique et à des interventions chirurgicales. Il s'ensuit que les chutes de patients atteints de la MP et d'autres synucléinopathies contribuent grandement à leur perte d'autonomie, et ce, en raison de blessures. Cette situation met en évidence la nécessité de procéder à une évaluation appropriée des risques de chute chez ces patients et de mettre en œuvre des mesures préventives destinées à tous les patients souffrant de parkinsonisme. L'objectif de cette étude consiste donc, dans le cas des synucléinopathies, à examiner les facteurs de risque modifiables et non-modifiables liés aux chutes. Nous passerons ainsi en revue et évaluerons les approches pharmacologiques, non-pharmacologiques et chirurgicales dans la prévention des chutes pour ensuite mettre en relief des approches individuelles et multidimensionnelles.

Keywords: Parkinson's disease, Dementia with Lewy bodies, Multiple system atrophy, Falls, Risk, Prevention, Management

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Introduction

Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) are common pathologically overlapping neurodegenerative disorders associated with α-synuclein aggregates at autopsy. Parkinsonism is defined as bradykinesia in combination with rest tremor, rigidity, or both. These features must be clearly demonstrable and not attributable to confounding factors.[1] DLB is defined as dementia (cognitive dysfunction affecting activities of daily living), concurrent with or preceding parkinsonism,[2] associated with the triad of fluctuating attention, hallucinations and parkinsonism with recent inclusion of rapid eye movement (REM) sleep behavior disorder as a supportive criterion.[3] By contrast, dementia occurring in the setting of well-established parkinsonism, pragmatically defined by at least 1 year of symptoms, is considered to define Parkinson's disease dementia (PDD), although this "1-year rule" remains contentious.[4] The revised diagnostic MSA criteria continue to categorize MSA with predominant parkinsonism (MSA-P) or with predominant cerebellar ataxia (MSA-C). Clinical diagnosis of possible MSA requires rigorously-defined dysautonomia and parkinsonism that is poorly responsive to levodopa, or cerebellar ataxia with neuroimaging abnormalities representing a supporting feature.[5,6]

While motor symptoms define parkinsonism, nonmotor features, including mild cognitive impairment (MCI), neuropsychiatric features, dysautonomia, and REM sleep behavior disorder, can precede synucleinopathy diagnosis[7–9] and may enhance diagnostic accuracy.[10] While bradykinesia and rigidity in PD respond to dopaminergic treatment, tremor, gait, and postural impairment do not always improve as consistently; less is known about levodopa response in DLB and MSA, though some response is possible, especially in early MSA-P.[11,12] Nonmotor symptoms (NMS) do not consistently respond to dopaminergic therapy,[13] while the response to motor symptoms becomes less complete as cognitive impairment worsens.[14] Some features, such as sleepiness, orthostatic hypotension (OH), and freezing of gait (FOG), may in fact be exacerbated by dopaminergic medications.

Falls are common in synucleinopathies and can lead to significant morbidity and mortality. This underscores the need

From the Division of Neurology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

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Correspondence to: Fang Ba, Division of Neurology, Department of Medicine, University of Alberta, 7-112 Clinical Sciences Building, 11350 – 83 Avenue, Edmonton, Alberta, Canada T6G 2G3. Email: fb@ualberta.ca

Table 1: Falls latency (duration from first symptom to falls onset) in the synucleinopathies

	N	Age at disease onset, years (range)	Falls latency, months (range)
PD	485	58 (29–84)	113 (0–384)
DLB	60	69 (40–87)	51 (0–287)
MSA	106	56 (33–79)	33 (0–165)

Data adapted from refs. [19,20]
PD: Parkinson's disease; DLB: dementia with Lewy bodies; MSA: multiple system atrophy.

for fall risk assessment and the implementation of preventative measures in any patient with parkinsonism. Non-synuclein-related conditions, such as corticobasal ganglionic degeneration and progressive supranuclear palsy (PSP), also feature falls and can be misdiagnosed as synucleinopathies.[15] This review focuses on synucleinopathies since it is a distinct group of movement disorders with shared pathogenic features associated with parkinsonism, gait impairment, and dysautonomia that increase fall risk. The aim is to review modifiable risk factors as well as medical, surgical, and nonpharmacological approaches to the prevention and treatment of falls in these disorders.

Falls Epidemiology in Synucleinopathies

Falls are common in synucleinopathies. Thirty-five to 90% of PD patients fell at least once over 12 months (average 60.5%), with two-thirds recurrent fallers.[16] Likewise, those with DLB sustained sixfold more falls compared to healthy controls.[17] In MSA, frequent falls were the commonest milestone of disease advancement and mortality progression, with an estimated probability of at least daily falls of 23% 5 years from disease onset, and years to death of 1–2 years when falls occur.[18]

Recurrent falls and postural instability (PI) are supportive clinical features of DLB and MSA, and conversely, are considered red flags early in the course of PD. Correspondingly, falls incidence is roughly double in DLB relative to those with PD without dementia.[17,18] Studies assessing postmortem-confirmed parkinsonian disorders noted that the latency between symptom onset to recurrent falling was far shorter in DLB and MSA compared with PD (Table 1). The latency between recurrent falling and death was not significantly different between groups, suggesting that recurrent falls herald an advanced stage of disease with poor prognosis.

Fall Risk Factors in PD, DLB, and MSA

Fall Risk Factors in PD

Given the impact falls have in synucleinopathies, a systematic way to identify those most likely to fall would be ideal to proactively mitigate risk. Numerous risk factors have been proposed; however, the relative contribution of any factor in particular is difficult to assess given the interplay between them and their tendency to change over time. Many studies have devised prediction models for falling in PD,[21–31] and although these have highlighted various risk factors, their relative degree of contribution is inconsistent for several reasons. Many studies rely on subjectively collected questionnaires or one-time neurological assessments. Often, falls are self-reported in fall diaries with considerable heterogeneity between subjects. Some studies evaluate not easily accessible or practical physiological measurements.[32] Recently, a clinical prediction tool to discriminate future fallers from non-fallers was developed[33] and validated,[34,35] using a history of at least one fall within the past year, FOG in the past month, and slowed gait speed as fall risk determinants. This allows the simple classification of PD patients into low (17%), moderate (51%), and high (85%) fall risk in the ensuing 6 months, which can be effectively communicated and introduce strategies for fall prevention. This provides a benchmark for the development for other predictive models but doesn't identify all factors that might be targeted for interventions. Other simple models, such as recent fall history, pull test, tandem gait and dyskinesias, and Frontal Assessment Battery (FAB), have also been examined.[35,36]

Preemptively identifying modifiable risk factors to implement preventative strategies is essential. Over the past decade, many small to moderately sized prospective studies have attempted to elucidate this by comparing potential risk factor profiles between fallers and non-fallers (Supplementary Table S1). Prior studies have been reviewed previously.[16,37] The evidence for the prevention of falls through the remediation of these risk factors is reviewed in the next section.

Non-modifiable risk factors inconsistently associated with increased fall risk in PD include advanced age[22,26,27,30,38–45] and gender,[21,22,24,27,38–44,46,47] although they are known risk factors in the general population.[48] Conversely, the rate at which non-motor and motor symptoms develop can depend on sex and age at diagnosis, with dramatic rates in the development of axial symptoms after age 70.[49] Thus, the patient population studied may influence findings in observational studies. Other risk factors consistently associated with falls in PD include disease severity as measured by H&Y scale,[22,22,25–27,31,38,42–44,46,47,50–52] UPDRS total score,[22,23,27,30,39,44–46,50,51,53] and UPDRS motor subscore.[21–23,25,27,30,38,41,42,47,51,52,54,55] Studies where no association was found[24,26,39,43,44,53] may be explained by the fact that as motor features progress, the fall risk decreases as the patient becomes more sedentary. Moreover, tremor might decrease leading to lower scores in the setting of worsening gait and PI subscores with paradoxically better overall scores in fallers.[26] Similarly, proxies for disease severity, including higher levodopa equivalent doses[22–24,26,27,30,39,42,44,47,52,53,55] and disease duration, have been variably identified as risk factors,[21–23,27,30,31,38,40,42–44,46,47,50–55] although the degree of levodopa response is not usually directly assessed. Falls can be observed preceding diagnosis[24,25] and prior to initiation of levodopa,[21] particularly in those with the postural instability and gait difficulties (PIGD) subtype.[21,22,24,25,30,42,46] Injurious falls and hip fractures may in fact precede PD diagnosis by a decade or more.[56]

Certain motor symptoms and signs of parkinsonism are potentially modifiable risk factors. Numerous studies have identified impaired balance as a key risk factor by assessing composite measures of PI,[21,22,24,25,30,42,43,46,47,52–55,57] anticipatory balance maneuvers,[22–25,27,31,41,42,44,52,55,57–59] reactive balance maneuvers,[35,54,57–59] and slowed mobility.[24–26,41,44,54,58] FOG is also reliably associated,[21–23,27,35,42,43,47,50,54,55,58–60] while conversely, tremor, axial rigidity, and dyskinesias are not convincingly associated.[22–24,27,30,31,50,54,55,58]

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Dementia is a significant fall risk factor in the general population and in PD,[61] although data are less comprehensive in MCI. Some studies correlated increased fall risk with lower scores on global cognitive assessments[21,23,30,41,50,58,60] while others have not.[22,24–27,38,40,43,44,50,51,53,55] However, many studies excluded patients with cognitive impairment *a priori* based on mini-Mental State Exam (MMSE) screening (i.e., less than 24).[62] This is problematic since MCI and dementia are common in PD,[63] and the MMSE is insensitive to attention and executive function, both of which are more prominently affected in PD-related cognitive impairment.[64] The few studies that examined specific cognitive domains found mixed data to suggest possible correlations with frontal,[23,25,45,47,53,58] visuospatial,[25] working memory,[24,31,58] verbal function,[31,58] and dual-tasking impairment.[40,41,54]

OH is prevalent in PD and may have a reversible effect upon cognition secondary to CNS hypoperfusion.[65] A few studies showed involvement of OH in falls.[24,27,45,51,53] One recent study focusing on cardiovascular dysautonomia in PD fallers found an adjusted tenfold increased probability of falling in those with OH.[66] Dopaminergic medications can exacerbate OH and further increase fall risks. Likewise, one study investigating urinary dysfunction in PD fallers found mild (but not severe) urinary urgency was associated with a fivefold increased fall risk,[51] presumably given the balance between the need to ambulate quickly versus the presence of activity and environmental factors.

With respect to neuropsychiatric symptoms, depression has been proposed as a potential factor, as it may influence motivation to ambulate in addition to psychomotor slowing,[21,46,51] although numerous other studies have not found a correlation.[24,26,39,40,43,44,47,53] Depression is a risk factor for falls in older people without PD.[48]

Other potentially modifiable risk factors include a fear of falling, which can be related to anxiety,[24–26,30,39,42,44,46,47,52–55] impaired activities of daily living and reduced quality of life,[22,24,26,27,30,31,38,39,42,46,50,52–55] reduced lower extremity strength,[23,58] and sensory dysfunction.[23,46,51,58]

Fall Risk Factors in DLB

The onset of recurrent falling is much shorter in DLB relative to PD, with repeated falls a supportive criterion for DLB. Although both are neuropathologically characterized by Lewy bodies and Lewy neurites, their symptomatology and clinical course differ substantially. Similar to PD, the presenting features may be broadly subdivided into four categories: cognitive impairment, physical symptoms, dysautonomia, and neuropsychiatric phenomena.

DLB is the second-most common form of neurodegenerative dementia, after Alzheimer's disease (AD), and consequently, studies of fall risk tend to directly compare the two. Distinct from AD, in which early anterograde amnesia is sine qua non, those with DLB display variable memory impairment; fluctuating cognitive impairment; and early dysfunction of attention, executive, and visuospatial domains.[3] While a decline in global cognitive function is associated with increasing fall risk in heterogeneous general populations,[67–70] a more careful examination of dementia subtypes has demonstrated a far greater fall risk and a shorter latency period from diagnosis to onset of recurrent falls in DLB relative to AD.[17,71–73] The reason does not seem to be from a more aggressive rate of overall cognitive decline in DLB.[73,74] More likely, the decline of specific cognitive domains characteristic of DLB, as well as autonomic and motor features, might explain the discrepancy. Patients with DLB have disproportionately more severe visuospatial impairment.[75] This was substantiated by one study that demonstrated dysfunction in constructional praxis increased fall risk in DLB, and in particular, those without parkinsonism.[76] Other disproportionately affected cognitive domains in DLB, such as judgment and executive function, likely contribute to fall risk as they do in the general population.[70,77] The positive effects of cholinesterase inhibitors upon cognition and behavior[78] may extend to reducing fall risk, although this is not clearly demonstrated.[79] Finally, fluctuating cognition in DLB is likely to impact upon fall risk, as fall-related injuries may occur during cognitive "down" periods in patients without evidence of parkinsonism or PI.[80]

More severe parkinsonism is associated with an increased falls in DLB.[81] However, while the essential motor features of PD can be present in DLB, they are not strictly required to diagnose "probable DLB,"[3] and as only one cardinal feature is required to meet criteria for parkinsonism in DLB, many patients would not meet criteria for clinical PD.[82] In fact, cross-sectional studies have shown that approximately 20%–30% of patients have minimal or no signs of parkinsonism during their disease course.[83,84] When parkinsonism is present, extrapyramidal motor features in DLB more often take the form of prominent axial symptoms rather than resting tremor as compared with PD.[85,86] Correspondingly, a cross-sectional analysis found that those with Lewy body dementias (either DLB or PDD) had a greater fall risk and poorer scores on gait and balance relative to those with AD.[71] Other studies have similarly shown poorer scores on gait and balance when comparing those with DLB versus AD and PDD, and likewise correlated these measures to fall risk.[87,88] A prospective assessment of baseline risk factors in DLB recapitulated these findings and noted that abnormalities in gait and balance correlated with increasing fall risk.[17] FOG is usually a sign of advanced PD and is frequently seen in atypical parkinsonism, including DLB.[89,90]

The NMS profile of DLB includes dysautonomia, neuropsychiatric symptoms, and REM sleep behavior disorders. A prospective assessment of baseline risk factors in DLB demonstrated that fall risk was related to the duration of dementia, use of cardioactive medications, and dysautonomia.[88] Dysautonomia, particularly OH and exaggerated carotid sinus reflex, is more common in DLB compared with PD and other forms of dementia,[91,92] and together caused the majority of syncopal episodes in those with DLB in a prospective observational study.[93] Part of this may relate to the exaggerated period of hypotension following orthostatic challenge seen in DLB relative to other forms of dementia.[94] Furthermore, dysautonomia was associated with significantly reduced survival within 3 years of a prospective longitudinal study.[95] Persistently untreated OH may in fact precipitate or worsen dementia secondary to prolonged regional cerebral hypoperfusion.[96,97] OH and consequent falls can be further exacerbated by medications used to treat the neuropsychiatric manifestations of DLB, including psychotropic medication, and the use of psychotropic medications is an independent risk factor in falls in DLB.[17] Cholinesterase inhibitors may induce bradycardia and syncope leading to fall-related injuries including hip fractures in patients with dementia,[98] which is of particular significance in DLB considering the association with neurocardiovascular instability.[91] Benzodiazepines are often used to treat

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Table 2: Therapy interventions and monitoring of falls in PD and DLB

Intrinsic	Extrinsic
Optimize medical treatment for PD	Environmental assessment and modification
Cognitive strategies	Wearable sensors
Surgical treatment – (DBS at novel targets)	Embedded home sensors
Non-invasive brain stimulation	Virtual reality training, combined with complex motor tasks
Exercise	
Physiotherapy	

REM sleep behavior disorder but also increase falls risk and hip fractures in the elderly population.[99] Finally, dopaminergic drugs are also well recognized to cause hypotension or exacerbations of OH[100] that lead to increased falls risk.

Fall Risk Factors in MSA

Fall risks have not been as extensively studied in MSA when compared to PD, which may reflect the early onset and high frequency of falls in this disease[19] in addition to its relative rarity. Moreover, its rapid progression, particularly early in the course of the disease, necessitates the use of gait aids and confinement to wheelchair by 3 and 5 years, respectively.[101] One retrospective study examined fall risk factors in atypical parkinsonism, including MSA.[20] In this study, univariate analysis distinguished fallers from non-fallers using clinical features of MSA including limb rigidity, speech disturbance, dysphagia, and pyramidal tract signs. Further, the latency to first fall was independently influenced by age of disease onset and PI. The presence of cerebellar signs, as seen prominently in MSA-C, is likely also to be a risk factor, particularly given the broad-based ataxic gait commonly associated with this condition,[6] but was underrepresented in this study sample. Finally, dysautonomia was not found to be a fall risk factor; however, this is likely a reflection of its early and severe prominence in both fallers and non-fallers, particularly in the urogenital and cardiovascular domains.[102]

Other prominent features of MSA that may be early risk factors for falls may be extrapolated from the preceding discussions on PD and DLB. Motor risks include PI (89% at presentation), FOG (38%), postural tremor (54%), and dystonia (10%).[102] Likewise, nonmotor potential risks include depression (41% at presentation), executive dysfunction (49%), and dementia (4.5%).[102,103]

Approaches to Fall Prevention

Although the majority of the evidence toward disease management comes from studies in PD, there is substantial overlap in the challenges faced, and therefore, the strategies are broadly applicable to other synucleinopathies (Table 2). Pharmacological, nonpharmacological, and surgical treatment options are described later and are summarized in Table 3.

Clinical Approaches to Fall Classification

Key to establishing a treatment plan in such a multifactorial phenomenon is to classify falls to understand and manage risk. In practice, establishing fall circumstances can be challenging, as this is often self-reported and retrospective, and therefore subject to the vagaries of memory,[141] particularly in a population with cognitive challenges. Moreover, it is important to document the events leading toward a fall, rather than simply assessing fall frequency, as the latter does not have a clear relationship with fall etiology.[26] Instead, the use of fall diaries to record both the frequency and circumstances of falling can be successfully used, at least in those without major cognitive impairment.[142,143]

Establishing the environment and type of movements leading to a fall is important, as for example, those falling during transitional movements or in the home tend to have a higher burden of disease than those who fall during higher-risk activities or in the community.[26,38] Falls occurring during multitasking, at a particular time suggestive of cognitive fluctuations, or in the presence of neuropsychiatric disturbances might suggest the need for neurocognitive treatment. A review of medications and "on" or "off" status can be helpful for medication selection and titration. Preceding symptoms, such as presyncope or dizziness, may suggest the need for management of OH, bearing in mind that OH can be asymptomatic. Finally, other mitigating circumstances, such as urinary urgency, proprioceptive loss, or visual impairment, can trigger management of comorbid disease.

Recently, a simplified approach toward falls classification was developed, which divides falls into those involving transitional movements (e.g., rising from a chair), complex motor activities (e.g., skiing), and combined movements (e.g., garden work).[144] Describing falls in this manner may simplify the approach toward management by categorizing physical differences between fallers and thereby allowing the detection and targeting of fall risk factors. For example, those with consistent transitional falls may benefit from strength or simple balance training, while those with consistent falls during combined movements may benefit from targeted neurocognitive strategies.

Optimizing Medical Management of Parkinsonism

Levodopa remains the agent of choice in the treatment of parkinsonism, particularly in PD, although short-lived, if less robust, responses are seen in as many as half of patients with DLB and MSA.[11,12,102] However, PI may respond less reliably,[48,49,145] and fall risk and PI may persist and progressively worsen despite levodopa.[146] This may, in part, arise from levodopa-induced dyskinesias.[147] In patients responding well to antiparkinsonian drugs (i.e., >30% change in UPDRS-III with treatment), axial features were found to respond partially to levodopa.[148] Decreased levodopa efficacy with disease progression has been attributed to worsening axial symptoms (i.e., gait disorders and PI)[145,149] and is considered to result from the increasing severity of non-dopaminergic deficits affecting brain regions and systems localized outside of the striatal output pathways.[150] Conversely, levodopa improves rigidity and bradykinesia, and thus enhances patient mobility. As PD fallers have higher impulsivity scores compared to non-fallers,[151] this imbalance between the persistence of PI and improved ambulation with levodopa can potentially increase the likelihood of falling.[26]

FOG is common in synucleinopathies and remains difficult to treat.[89,90] In PD, FOG can occur in the "on" or "off" states,

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Table 3: Pharmacological, nonpharmacological, and surgical interventions

Medication/ treatment	Effects	Reference	Level of evidence
DA agonists			
Ropinirole	↑ incidence of FOG vs. levodopa	104	A2
Pramipexole	↑ incidence of FOG vs. levodopa	105	A2
MAO-B inhibitors			
Selegiline	↓ risk of FOG	106, 107	A2
Rasagiline	↓ risk of FOG	108	A2
NMDA antagonists			
Amantadine	Some evidence for ↓ fall risk in PSP; inconsistent data in PD	109–112	B, C
NE precursor			
Droxidopa	↓ fall risk possibly due to improvement in postural hypotension	113, 114	A2, B
Anticholinergics			
Donepezil	↓ fall risk in PD patients without FOG	115	B
Rivastigmine	Improvement in gait parameters	116	B
Any drug	↑ emergency room visits, admissions, and fractures	117	C
Antidepressants			
Any drug	↑ fall risk	118	B
CNS stimulants			
Methylphenidate	Inconsistent benefit; effect thought to be due to improved attention	119–121	B, C
DBS stimulation			
STN or GPi	Levodopa-resistant postural instability and falls are unlikely to respond to DBS, and may worsen. If seen, there is unsustained benefit in posture, FOG, and gait	122, 123	A1
PPN	Inconsistent data	124–126	B
SNr	Limited data suggest improvement in FOG but not in other axial symptoms if combined with STN stimulation	127	B
Cognitive training	Dual-task training and virtual reality training may improve gait speed in elderly adults. Unknown effect in PD	128–131	B
Physiotherapy			
Tai chi	Tai chi improved balance and reduced falls in mild-moderate PD	132	A2
Resistance training	Resistance strength training reduced falls in mild-moderate PD	133	B
Balance training	Outpatient or home-based physiotherapy programs may reduce the number of injurious falls	134–138	B
Dance	Tango dancing may improve mobility and motor severity in PD	139	B
Occupational therapy	Insufficient evidence supports the use of occupational therapy in falls prevention	140	D

A1=meta-analysis containing at least some trials with evidence level A2, with consistency in trial results; A2=good quality randomized comparative clinical trials (randomized double-blind controlled trials) of sufficient size and consistency; B=moderate (weak) quality randomized clinical trials of insufficient size or other comparative trials (non-randomized trials, cohort studies, patient-control studies); C=non-comparative trials; D=expert opinion.

with off-freezing potentially improving with dopaminergic medications. Levodopa has been shown to be a better agent of choice compared to dopamine agonists: an increased risk of freezing was observed in a pramipexole group compared with the levodopa group (hazard ratio 1:7) in a phase-III, prospective, double-blind, placebo-controlled trial.[152] A similar observation was reported with ropinirole in patients with early PD in a prospective, double-blind, placebo-controlled trial with a 5-year follow-up.[104] Selegiline was effective in reducing the risk of developing FOG,[106] and in decreasing the number of patients who develop FOG as a late complication of disease progression in a 2-year prospective follow-up.[107] Rasagiline showed a 1.17 point improvement on the FOG-Questionnaire (FOG-Q) total score, in a prospective, double blind, placebo-controlled study.[108] In both studies, however, falls were not directly addressed, and therefore the clinical significance is unclear. In the case of DLB, dopamine agonists are not preferable because of their propensity to cause hallucinations and somnolence.[153] Moreover, monoamine oxidase type-B inhibitors may cause OH and thus might precipitate falls. There are conflicting results regarding Amantadine in FOG and subsequent falls risk, but there is some evidence for fall risk reduction in PSP.[109] The norepinephrine precursor, droxidopa, was shown to reduce fall risk in PD,[113] with the mechanism attributed to improvement in postural hypotension, though other effects have not been extensively examined.

Optimizing Surgical Management

Multiple randomized controlled studies have demonstrated that deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus interna (GPi) is superior to medical treatment alone in the treatment of a number of cardinal PD symptoms and motor complications from therapy.[154–156] The benefit of DBS on axial symptoms, however, is less clear.[157] Several reports have indicated improvement of posture, gait, and balance control after STN- or GPi-DBS, when these symptoms were responsive to levodopa treatment before DBS surgery;[158–163] however, the benefit on PI and gait is not sustained.[158] Moreover, a significant number of patients report post-operative worsening of gait despite concurrent improvement in motor scores and global outcomes after bilateral STN-DBS.[164] Further, falls risk has been demonstrated to increase and levodopa-resistant FOG to persist or worsen.[165–171] To complicate matters further, stimulation

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parameters (i.e., high-frequency stimulation) can also lead to adverse axial effects in patients.

The pedunculopontine nucleus (PPN) is considered a key component of the mesencephalic locomotor region (MLR).[172] Widespread projections involving the PPN include direct glutamatergic inputs from the motor cortex, and GABAergic inputs from substantia nigra, GPi, STN, and deep nuclei of the cerebellum.[173] Previous work suggests that the PPN is underactive in PD due to degeneration and inhibition, and that this underactivity relates to axial motor impairment.[174] Since the first report of PPN-DBS,[175] multiple studies have shown clinical improvement in patients with PD who have PI and FOG, but results have been variable.[176–179] Despite more than 10 years of experience, PPN-DBS remains experimental and the number of implanted patients remains limited since the outcome varies considerably. A heterogeneous dataset has been published so far including case reports, open label series, double-blinded single time point single-center study, and longer-term double-blinded studies. The heterogeneous study designs, differences in outcome measures to assess FOG, falls, and PI, the different targeting strategies and stimulation sites (caudal vs. rostral PPN), the variability in DBS settings (including unilateral PPN vs. bilateral, lone bilateral PPN-DBS, and combined bilateral PPN-DBS with other targets, i.e., STN or caudal zona Incerta) may explain the inconsistencies. In addition, different stimulation parameters contribute to variable results. For instance, low-frequency PPN-DBS can improve axial motor symptoms presumably by partly reversing PPN underactivity.[178,180] More precise targeting strategies with improved technology (i.e., improved imaging and programming) are required. Structural and functional neuroimaging may have a role in patient selection to determine if PPN degeneration is too severe for PPN-DBS to work.[181] In addition, to improve axial symptoms, that is, FOG, multitarget DBS strategies have been trialed allowing the modulation of cortico-basal ganglia loops, and subsequently aiming to improve falls.[182] Since falls and gait impairment are likely related to multiple failing neural circuits, combined PPN and STN stimulation may have greater beneficial effects on gait and PI than either target alone.[176] Targeting multiple sites can potentially synchronize different circuits and promote neuroplasticity; however, the risk/benefit trade-offs have yet to be determined.[183] Although there is scarce evidence of PPN-DBS reducing falls and FOG in PD, whether and how to modulate the PPN remains to be determined.

The substantia nigra pars reticulata (SNr) is another key player in the MLR, via its significant efferent GABAergic input to the PPN.[184] Axial motor symptomatology, including gait impairment and PI, responds favorably to SNr stimulation in the literature.[127,185–187] One of the more recent double-blind, cross-over, randomized controlled trials with combined STN and SNr stimulation showed significant improvement in FOG, but not in other axial symptoms when compared to STN-DBS alone.[127] With SNr-DBS, one should be cautious about the possibility of worsening akinesia, as increased immobility and recurrent falls were reported with combined STN and SNr stimulation.[127]

Spinal cord stimulation has recently been investigated in PD.[188] Although presently studied only in small open-label case studies, there has been early evidence to suggest improvement in FOG and PI,[189,190] although falls were not assessed as an outcome.

Managing Orthostatic Hypotension

The approach to treating OH includes correcting aggravating factors (discontinuing hypertensive medications and correcting anemia) and implementing nonpharmacological measures and pharmacological treatment. Levodopa and dopamine agonists have been variably reported to contribute toward OH (reviewed in[191]), which should be reviewed with patients when making dose adjustments. Nonpharmacological measures with volume expansion, lifestyle management, activity level, and diet adjustment are first-line recommendations. Physical counter-maneuvers are helpful.[192]

In patients with severe OH, pharmacologic therapies are advisable to minimize the fall risks leading to injuries.[193] Efficacious agents include the synthetic mineralocorticoid fludrocortisone and the pressor agents midodrine or droxidopa. All drugs that raise blood pressure when standing also raise blood pressure when supine, increasing the risk of supine hypertension. Although there are no specific reports on cardio- and cerebrovascular adverse events induced by supine hypertension in this cohort, one should be cautious about this potential side effect.

Cognitive Strategies

Emerging evidence indicates that deficits in multiple cognitive domains, such as attention, executive function, and working memory, are associated with low gait velocity, stability, and falls.[60] Medical treatment addressing the motor deficits in PD dementia and DLB can have cognitive side effects (i.e., decreasing verbal short-term memory, attention, reaction time and set-shifting, increasing impulsivity/worsened decision-making, impaired distractor resistance, hallucinations) that increase the propensity to fall.[194] Dopamine agonists and anti-cholinergics should be avoided in this population, given adverse effects on alertness and general cognition, and less improvement in overall motor function compared to levodopa. DLB patients are at heightened risk for complications of drug therapy, since they are prone to psychosis triggered by dopaminergic therapies and more susceptible to side effects of antipsychotics used to treat hallucinations. Atypical agents, such as olanzapine or quetiapine, are not risk-free but are preferred when an antipsychotic drug is indicated.[153,195] While quetiapine has less propensity to worsen parkinsonism, it has sedating and anti-cholinergic effects that might increase fall risk.

Nonpharmacologic treatment strategies for DLB are the same as in other dementia syndromes,[196,197] with a focus on ameliorating environmental, medical, psychological, and social factors that may exacerbate problem behaviors leading to falls. Many interventions for fall prevention do not translate successfully from cognitively normal older adults to those with dementia,[198] likely due to different underlying mechanisms for falls and treatments unable to adequately address cognitive deficits. Studies using nonpharmacological methods, including single motor task, dual-task, and complex motor task training, have shown some benefit reducing fall risk;[128–131] however, results vary from study to study. Large-scale studies with more standardized protocols are needed.

Cholinesterase inhibitors can offer clinically meaningful benefits to patients with cognitive issues, particularly in the domains of apathy, confusion, hallucinations, and somnolence,[199] and thus may improve fall risk. A small trial of donepezil suggested a reduction of falls in PD patients without FOG.[115] Another study

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showed improvements in gait parameters, but may have been inadequately powered to examine the impact on falls.[116] Memantine was investigated in patients with mild to moderate PD and DLB, with cognitive measures improving in the memantine group, but increased falls was a documented adverse effect.[200,201]

Conversely, anti-cholinergic burden is associated with adverse events, including emergency room visits, fractures, and falls.[117] Consistent with studies in older patients, antidepressants are associated with increased fall risk in PD,[118] but it is not clear if this is related to comorbid pathology or a medication effect. Methylphenidate was shown to improve FOG in PD presumably through improving attention,[119,120] although a randomized clinical trial showed negative results.[121]

Exercise/Physiotherapy

There is abundant evidence showing the benefits of physical activity for PD, and exercise can regulate neurotrophic factors and therefore potentially promote neuroprotection in PD.[202,203] Strength and balance training can reduce falls among the community-dwelling elderly.[204–208] Rhythmic visual or auditory clues[209–211] and mental singing during walking may also improve gait in PD.[212] Randomized control trials have shown falls reduction with Tai Chi,[132] and exercise programs for muscle strengthening and movement strategies.[133]

Physical therapy can improve fall prevention,[134–136] but benefit may be limited and short-lasting.[137,138] Dosage, training intensity, and duration may also affect results. A recent randomized trial of home program with strength and movement strategy training and falls education did not prevent falls.[213] Dance therapy can be beneficial and may have longer-lasting effects.[139,214,215] In particular, tango training improved mobility and other motor domains.[139]

One should be cautious in applying the results of therapeutic intervention studies to practice. Regular exercise, physiotherapy, and dance are helpful in mobility, but the right dosage and type of exercise should be individualized. Future studies should also focus on therapy content, repetitions, and effective duration, to optimize outcomes and cost-effectiveness for PD patients to further guide treatment. Falls should be included as on outcome in such studies.

Risk Reduction in Osteoporosis

PD patients are older and therefore have a higher risk for metabolic bone disease. This predisposes PD patients to fall-related injuries, including fractures.[216,217] There are no specific guidelines related to management of osteoporosis and PD. A combination of bisphosphonates and vitamin D is recommended along with regular intake of calcium-containing food or supplements.[218] Medical treatment is mainly based on computed X-ray densitometry (DEXA; T score < -2.5) and FRAX scores (10-year risk for fracture $> 3\%$ hip, $> 20\%$ of any major osteoporotic fracture).[218] Two main types of pharmacological treatments are available to treat patients with osteoporosis: antiresorptive agents and anabolic agents. Dietary and nutritional manipulation is important, and vitamin D, B12, and folate status needs to be addressed and corrected if required. Lifestyle-related management, including smoking cessation and decreasing alcohol consumption and exercise, should be encouraged.

Extrinsic Risk Reduction

For PD, PDD, DLB, and MSA patients, fall prevention can benefit from occupation therapy input for improvement of home environment. This includes footwear, floor slipperiness, creating safe spaces and familiarization with furniture layouts, lighting, handrails conditions, bedroom/bathroom/kitchen adaptations.[219] Patient education for behavioral adaptations is also essential to avoid multitasking and to take time with postural change to prevent postural dizziness.

Other Risk Factors

Several studies have identified the need for multimodal interdisciplinary methods for fall prevention and the need for more accurate risk assessment instruments.[206,220–223] Multimodal assessments with targeted intervention reduced fall risk by 37%, and exercise interventions reduced fall risk by 14%.[206] A meta-analysis identified a benefit on fall prevention in the community when individualized management tailored to address individual risk factors was added to exercise interventions.[224]

Other individual prevention strategies include cataract surgery and cardiac pacing. Cataracts are common in PD and PD-related disorders,[225] and cataract disease is associated with a higher risk of developing PD.[226] Cataract surgery for the first eye was found to reduce the fall rate by 34% in general population, but not the number of fallers.[227] Moreover, surgery for the second eye did not reduce the fall rate further. Cardiac pacemakers in patients with cardio-inhibitory carotid sinus hypersensitivity reduced fall rate by 58%, but not the number of fallers.[228,229] For MSA with significant dysautonomia, cardiopulmonary arrest can occur.[230,231] Physicians should carefully review the history and risk factors and assess patients for indications for cardiac pacing.

Novel Experimental Approaches to Falls Prevention

Wearable Sensors

Wearable sensors (accelerometers and gyroscopes) have been used to test mobility. Gait and balance analysis can be extracted through daily activities for a real-time fall risk assessment.[232–234] Such evaluations are potentially more sensitive than conventional tests for recording activity.[235,236] Embedded home sensors are another approach to continuously monitor fall risk.[237,238] Experimental motion sensors to feedback and help with rehabilitation have been used. Virtual reality training, combined with complex motor tasks, has also been shown to provide some benefit to falls prevention.[239]

Non-Invasive Stimulation

Non-invasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), have been trialed in various neurologic and psychiatric disorders.[240] One recent meta-analysis demonstrated that rTMS can improve motor symptoms in PD with a moderate effect size.[241] However, few rTMS studies have focused on FOG and falls in PD.[242–246] One study with high-frequency rTMS over the lower leg primary motor cortex showed

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significant reduction in subjective FOG and improved gait performance.[246] However, results are inconsistent across studies with different stimulation targets, frequencies, and parameters having been applied. Further well-designed, large-scale studies are needed.

Transcranial direct current stimulation (tDCS) is another non-invasive stimulation technique. To date, a few studies have shown some benefit of tDCS in FOG. A double-blind, crossover, randomized sham-controlled study showed that applying 20-minute-long anodal 2 mA tDCS sessions on M1 during rest over 5 consecutive days significantly reduced dopamine-resistant FOG in 10 PD patients, and the benefit persisted at 1-month follow-up.[247] Simultaneous stimulation over M1 and left dorsolateral prefrontal cortex with tDCS was able to modulate consecutive motor and cognitive function and further improved FOG in 20 PD individuals with FOG when compared to sham or tDCS of either target alone.[248] In practice, given the simplicity of the technology and affordability of tDCS compared to TMS, the former may be a safer, more cost-efficient tool for treatment once stronger evidence is established.

Future Directions

The successful future treatment and research of falls in synucleinopathies will need to consider and integrate cognitive, behavioral, pharmacological, device-based and surgical treatments along with the support of a multidisciplinary team. Further research examining functional neuroanatomy and neurochemistry as well as novel imaging modalities will help with our understanding of the pathophysiology underlying gait disorders and falls, and guide better treatment strategies in the future. Clinical trials of interventions should include falls as an outcome and safety measure.

Disclosures

The authors have no relevant disclosures.

Statement of Authorship

All authors are responsible for writing the manuscript, for discussions and for reviewing the manuscript.

Supplementary Material

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