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Falls in People with Multiple Sclerosis: Risk Identification, Intervention, and Future Directions

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Practice Points

- Falls are prevalent among people with MS and have significant negative consequences, clinicians should ask about them at all stages of the condition and refer for appropriate interventions in a timely manner.
- Falls are multifactorial and complex and there are many, varied, risk factors. The most reliable predictor of future falls is a history of falls.
- Interventions should target physiological risk (e.g. balance and strength impairments) and personal risk (e.g. fear of falling, matching physical ability to the task) and environmental factors (e.g. use of appropriate assistive devices).

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Abstract

Falls are highly prevalent for people with Multiple Sclerosis (MS) and result in a range of negative consequences such as injury, activity curtailment, reduced quality of life, increased need for care and time off work. This narrative review aims to summarise key literature and to discuss future work needed in the area of falls prevention for people with MS. The incidence of falls is estimated to be over 50%; similar to the rate of falls in adults over 80 years. The consequences of falls are considerable as rate of injury is high, and fear of falling and low self-efficacy are significant problems that lead to activity curtailment. A wide range of physiological, personal and environmental factors have been highlighted as potential risk factors and predictors of falls. Falls are individual and multifactorial, and hence approaches to interventions will likely need to adopt a multi-factorial approach. However, the literature to date has largely focused on exercise-based interventions, with newer more comprehensive interventions using both education and exercise showing promising results. Several gaps remain in the topic of falls in MS and in particular the lack of standardisation of definitions and outcome measures to enable data pooling and comparison. In future, the involvement of people with MS in the design and evaluation of programmes is essential, as are approaches to intervention development that consider implementation from the outset.

The incidence of falls amongst people with MS is high, and the consequences of falls are far reaching for both the person and the healthcare system. This important topic has received increasing attention as researchers and health care professionals aim to identify the risk factors, context and consequences, and to use these data to develop theory-based interventions. This narrative review and position paper is written by members of the Special Interest Group on Mobility of the RIMS (European Network for best practice and research in MS) and aims to summarise the key literature in the area and to identify gaps in knowledge, challenges and ways forward.

Incidence of Falls

Falls are common among people with MS with a large international data set demonstrating 56% fall at least once within a three-month period,[1] with 37% of individuals categorised as frequent fallers. Notably, people with MS fall more frequently, are more likely to suffer injurious falls, and have different fall circumstances compared to their healthy peers [2]. Over a 6-month study period, 71% of people with MS reported falling versus 41% of healthy controls, with the MS group more likely to attribute their falls to tripping and distraction. Fall rates in MS are similar to those of community dwelling stroke survivors (55%),[3] over 80-year-old older adults (50%)[4] and people with Parkinson's disease (46%).[5]

Interestingly, there is a non-linear association between falls and the level of neurologic disability with peaks in falls incidence occurring at EDSS 4.0 and 6.0,[6] with the highest rate of recurrent falls occurring in those who do not yet use a mobility device.[7] Falls are not limited to

people with MS who are ambulatory and whilst there is less research evaluating falls in people with more advanced MS, studies show that wheelchair and scooter users also have a high incidence of falls (75%).[8] People with progressive MS have a higher incidence of falls[1] and falls have been proposed as a critical incident that signifies a worsening of symptoms that requires clinical attention. Those restricting their activity and avoiding risky behaviours may have a lower falls rate, however this practice is not without consequences and is not a solution to falls prevention.[9]

A key consideration when considering the prevalence and incidence of falls is the way in which falls data are collected. There is a notable underestimation of number of falls by people with MS. Dibble et al[10] found that 6-month recall was 17% accurate and 63% underestimated the number of falls they had. This underestimation when retrospective recall is used is confirmed by Nilsagård et al.[11] who found that using retrospective recall 34% were fallers, but using prospective diaries, 63% were. This consistent underestimation of number of falls when using retrospective recall led to recommendations that falls data be collected prospectively using diary-based methods.[12] However , the poor correlation between diary and electronic fall logging with a button push[13] suggests that a truly objective method of falls recording is required to advance this field.

The definition of a faller is inconsistent in MS falls research. Some researchers in falls risk in MS define a faller as a person with 1 or more falls,[11,14,15] others define it as the occurrence of 2 or more falls[1617,18] and still others classify a faller as a person with 3 or more falls.[19] Likewise, there are a wide range of fall definitions utilised; with some defining a fall as an unexpected event that results in the person ending up on the ground, floor, or any lower

surface,[20-22] others defining it as unintentionally coming to the ground or other lower level and other than a consequence of sustaining a violent blow, loss of consciousness, sudden onset of paralysis as in stroke or epileptic or seizure[23] and still others defining it 'as any unexpected loss of balance that resulted in whole body contact with the ground.[24] In some studies the fall definition used is not stated.[25,26] This heterogeneity in fall definition and classification limits comparison between studies and data pooling. One potential way to overcome these discrepancies in faller classifications utilised is to report falls data as falls rate per person-year. Falls rate per person-year can be calculated using the following formula[27] [falls rate = (total number of falls/total number of person-days [all participants]) multiplied by 365].

Consequences of Falls

Falls can have significant physical, social and psychological consequences for the individual. In terms of physical impact, injurious falls among pwMS are common with rates of 0.18-0.23 per person per year.[6,28] The majority of injurious falls related injuries are relatively minor, for example sprains and contusions, however the risk of serious injury is pervasive with head injuries and fractures also reported by pwMS who have fallen.[2829] A population based cohort study found that people with MS have a threefold higher risk of hip fracture than age and gender matched peers with a greater risk for those prescribed steroids in the previous six months.[30] Injurious falls can result in increased healthcare utilisation and decreased labour force productivity which both contribute to the high socio-economic cost associated with MS [31,32]. These high rates of injurious falls (42% to 58% - ([2,19]) are much greater than those seen in the

elderly where rates of 23%[33] to 30%[34] have been reported and post stroke where rates of 10% have been reported.[3]

The psychological impact of falls presents predominantly as a high level of fear of falling and associated activity modification both in those who have[35] and who have not experienced an actual fall.[36] Fear of falling has multiple definitions that reflect a multidimensional construct with physiological, cognitive and behavioural components.[3738] Based on a cross-sectional study, pwMS with elevated fear of falling are less likely to participate in leisure-time physical activities.[39] This behaviour might be explained as a protective mechanism. However, this protective response may result in some people with MS curtailing their activities inappropriately, resulting in further deconditioning and adversely affecting physical function and independence s.[40] This adverse response should be avoided especially due to the growing body of evidence highlighting the benefits of regular physical activity for MS.[41] Most concerning is that studies have consistently found that fallers have lower quality of life than non-fallers[14,42] Lower quality of life, in turn, has higher associated socio-economic costs, and contributes significantly to the intangible costs and burden for the person with MS related to issues around self-care, pain, anxiety and depression.[32] Nilsagard et al.[43] qualitatively explored the context and impact of accidental falls in pwMS, with participants describing falls as limiting, restrictive and embarrassing.

Factors Associated with and Predictive of Falls

Understanding the factors associated with and predictive of falls can assist in the development of interventions, and also identify those in need of treatment. There are many varied falls risk factors highlighted in the literature confirming the complexity and individual nature of falls prevention. Broadly, falls risk can be considered in terms of physiological, personal and behavioural risk factors.

Unsurprisingly, the most frequently reported physiological risk is impaired balance. Two meta-analyses[44,45] which considered data from cross sectional and from prospective studies confirmed that balance is a risk factor for falls. In addition, other indicators of reduced postural control such as reduced walking speed, increased static postural sway while standing and the use of a mobility aid were also identified as falls risk factors in those reviews. These findings are accompanied by prospective cohort studies where reduced lower limb strength,[16] reactive stepping[18] and dual-task ability[17] were identified as risk factors for falls. Worth noting, although visual problems are often one of the first symptoms noticed by pwMS and good vision is essential for maintaining balance control, testing of known visual risk factors in other groups (such as edge contrast sensitivity) are not considered a predictor for falls in pwMS.[46] It is possible that other aspects of vision could be an issue for pwMS, however most risk factors studies in MS to date topic have not included specific visual tests. Nevertheless, visual function is integrated in the EDSS score and traditional balance tests such as the Berg Balance Scale (BBS) and the Physiological Profile Assessment (PPA). A prospective study with 100 participants found that *not* having a visual problem (via self-report) was associated with a greater falls risk.[47] This may indicate that those with visual problems are inherently more cautious and have a resulting lower risk of falls.

Interestingly, though balance is impaired in MS fallers, a recent review found that clinical balance measures in isolation are poor at identifying future fallers.[48] This suggests that other factors are also important when identifying those at risk of falling and when designing treatments for preventing falls. Other MS symptoms related to falls include fatigue,[49] cognitive impairment,[50] spasticity,[11] and urinary incontinence,[22] although, again the relationship may not be linear in nature. Similar to the literature in elderly populations, medications, in terms of quantity and class, are associated with higher falls rates in most studies published on this topic.[51,52] During the last decade a wide variety of disease modifying drugs (DMD's) have been introduced in MS. The challenge is to examine whether immunomodulatory drugs differ when examining falls in the MS community. This issue was partly addressed by Comber et al[52] who investigated the effect of medication usage on falls in MS. They reported that participants taking medications categorised as genitourinary and sex hormones or centrally acting muscle relaxant medications had increased odds of being a faller.

When considering personal factors associated with and predictive of falls, reduced balance confidence[53] and reduced falls self-efficacy[54] have been shown to be predictive of future falls in pwMS, with concerns about falling being associated with changes in postural control in fallers.[55] Other personal factors which have also been highlighted as contributing factors for falls in MS are unrealistic appraisal of ability, poor organisation/planning of activities, adjustment/replacement of activities and emotional adaption through awareness and acceptance of limitations.[29,56] Gunn et al examined physiological risk and perceived risk in 416 pwMS and found that approximately 50% of individuals had disparities between their physiological risk (using the Physiological Profile Assessment) and perceptual risk of falls (using the Falls Efficacy

Scale (international)), with the majority having a perceived perceptual risk greater than their physiological risk.[57] It is hypothesised that those with excessive perceptual risk may be at increased likelihood of fear of falling and associated activity curtailment, whereas those with excessive physiological risk may engage in risk-taking behaviours through an unrealistic appraisal of ability.[58]

Understanding the environmental context of falls will improve management of falls in MS. Studies suggest that falls most often occur inside the home, in the morning or afternoon and during general mobility without the execution of any other specific task.[6,29,59] It is likely that the circumstances associated with falls differ amongst those who are ambulant or wheelchair users with one study suggesting that most falls occur during transfers for wheelchair users.[60]

An additional method to uncover risk factors of falls in MS can be achieved by asking the individual what they attribute their falls to. According to Matsuda et al.,[29], pwMS attribute their falls to trips/slips, fatigue, failing to use an assistive device when needed, rushing and not paying attention. Similarly, Peterson et al[61] found that poor balance, lower extremity malfunction and use of assistive devices were the leading causes of falls. More recently, Gunn et al[6] reported that 1/3 of falls were associated with being feeling fatigued and/ or loss of balance, with tripping, legs giving way and being distracted each accounting for 10% of falls.

While cognitive impairment in isolation has been identified as an independent risk[50], difficulty with dual tasking has also been shown to be associated with falls in people with MS.[62,63] Interestingly, those that prioritise cognitive tasks over walking are at greater risk of falling[64] which similarly has been found in other populations,[65] resulting in strategies such as balance first or slow down and concentrate.[66]

The proliferation of factors associated with and predictive of falling has led to several authors investigating multivariate risk prediction models using prospective study designs in order to identify those at future risk of falls, and hence treatment. Models included simple clinical variables such as the EDSS score, Ashworth score and fine motor control assessed with nine-hole peg test.[67] Some of these models require instrumented tools such as gait analysis devices, strength assessment using the Biodex Multipoint System and the Physiological Profile Assessment.[16,19,68] Regarding clinical utility these falls risk prediction models have varying levels of sensitivity and specificity ranging from 69% to 71 % and 70% to 88%, with 80% sensitivity regarded as an important cut-off level for falls screening tools.[69] Only two studies reported the area under the receiving operating characteristic curve (AUC); reporting values of 0.71[19] and 0.73[16] suggesting moderate and acceptable levels of discriminative ability as it is greater than 0.7.[70] Despite these many well designed multivariable studies, Cameron et al advocate identifying those at risk of future falls by simply asking about history of previous falls.[49] A fall in the past year was the best predictor of falls or injurious falls in the following 6 months. However, limitations of this approach are that predicting future falls based on previous falls requires the person to fall at least once (and therefore experience the negative consequences associated with this), pwMS with memory deficits might not report accurately. Asking a simple question also relates to the recent emphasis on patient reported outcomes; with a previous study demonstrating self-report measures having higher levels of discriminative ability than performance based measures[22] although they did not report corresponding measures of clinical utility.

Mazumder et al identified contextual differences in falls between middle aged pwMS and healthy controls.[71] The authors found that healthy adults most often fall outdoors whereas pwMS showed a higher rate of indoor falls. Additionally, healthy adults were more likely to report falls due to a slippery surface whereas pwMS were more likely to report falls due to a distraction or tripping, fatigue or excess heat. This suggests that when designing fall prevention programs for pwMS they need to address the unique risk factors for falling for this cohort.

Treatment

Given the complexity in causes and risk factors of falls in MS, a multi factorial approach seems the most appropriate strategy, however much research to date considers exercise only. Two systematic reviews of interventions to reduce falls exist.[72,73] Sosnoff and Sung (2015) identified 10 studies, four were randomised controlled trials with a total of 524 participants. The increased focus on this topic resulted in 13 RCT's being included in the recently published Cochrane review.[73] In contrast, a systematic review of exercise interventions for falls prevention in older adults included 108 RCTs with 23,407 participants living in the community in 25 countries.[74] The majority of MS studies with exercise interventions included conventional balance, sensory-specific and game-based exercises. The majority of trials demonstrated a reduction in actual falls and/or fall risk, most often with a concurrent improvement in balance and/or mobility. Despite these encouraging findings, firm conclusions could not be drawn due to the heterogeneity in study designs, small sample sizes, lack of assessor blinding and limited use of prospective falls monitoring. The review authors highlight the need for additional knowledge

regarding risk factors for falls in pwMS and suggest implementation of targeted multifactorial interventions examining both physiological and behavioural risk, as advocated by the International Multiple Sclerosis Falls Prevention Research Network (IMSFPRN).[75]

A related review concerns interventions to improve balance among people with MS[76] which found that specificity is important (i.e. balance and functional exercises had the largest effect on balance) and that dose of intervention is related to outcome. Sherrington et al[77] suggest over 50 hours of intervention is required to improve balance, yet, to the best of our knowledge, no study in the MS field has examined an intervention program at this dose. The older adults' literature consistently finds that exercise interventions though effective, are more impactful as part of multiple component or multifactorial interventions.[78]

Unfortunately, the strong evidence for multifactorial and multiple component interventions in older fallers, are sparsely replicated in MS. To date, only four multifactorial interventions have been published in MS.[26,79,80,81] Hugos et al.[80] performed a retrospective evaluation of an existing exercise and education programme for falls prevention in pwMS using the 'Free from falls' for older adults programme with adaptations made for MS specific symptoms such as fatigue. However, the retrospective nature of the study and the lack of a control group, requires caution when interpreting these findings, which were a reduction in fall rates, improved balance performance and confidence. Sosnoff et al.[82] evaluated a multifactorial approach based on the "Safe at Home BAASE" programme.[83] Their pilot randomised controlled trial including 34 participants compared four groups; waitlist control, home exercise alone, education targeting behavioural risk and a combination of home exercise and education. The authors found a reduction in risk of falls and falls risk for the groups engaged in an exercise

component, although with mixed findings for the combined exercise and education arms. Limitations included underpowered sample size and lack of prospective falls monitoring before intervention. Thus, further research examining multicomponent falls prevention interventions for pwMS is needed.

Interventions addressing personal and environmental factors associated with falls are lacking. For example, fear of falling and falls risk is not only associated with falls, but is an independent falls risk factor[84,42,85] yet to date it has had limited attention in interventions. The strong evidence from older person's literature and our increasing understanding of the role of psychological and environmental aspects of falls in MS suggests that future interventions should address both aspects and be tailored to the individual risk factors and physiological/psychological profile. Therefore, we encourage future trials to investigate the efficacy of adding supportive features (e.g. grab bars or handrails) in locations such as stairs and bathrooms in homes of pwMS. Additionally, future research should examine the impact of fall prevention programs that include education around the use and training of walking aids or increasing awareness of the outdoor environment and situations that might lead to falls. Other environmental harm minimization elements, such as fall monitoring devices or pressure sensors have also not been addressed to date. Another element is that of harm minimization through fracture prevention through routine preventative bone density assessment and intervention to improve bone loss if it presents.

Recent studies[86,87] have investigated the views and opinions of persons with MS in relation to what they would consider the optimal fall prevention program, highlighting their preference for practical, personalised interventions with peer interaction and ongoing support

(either within groups or by other media). Balance/strength exercises and fall prevention/management techniques might be included as well as services regarding mobility aids and home modification from trained professionals (for example occupational therapists and physiotherapists). Something remarkable is that pwMS recognise personal factors such as the competence of knowing and accepting their capacity to engage in activities are crucial in preventing falls.

Gaps in Knowledge

In order to increase our understanding of falls in pwMS and hence their treatment, there are several gaps in knowledge that require attention. Balance impairment is associated with and predictive of falls, however, our understanding of what particular postural control deficits are associated with falls is limited.[88,89] Determining what postural control deficit or what element of balance (e.g. proprioceptive deficits, reduced strength, cognitive motor interference or reaction time) are most associated with falls will allow more targeted and tailored approaches and potentially increase efficacy of exercise interventions.

Additionally, our understanding of the protective versus predictive nature of these deficits and their contribution to falls is limited. For example, if an individual walks at a slower gait speed with a wider base of support this may be a compensatory mechanism to increase stability. Therefore, attempts to 'normalise' this pattern of gait, such as increasing speed, may be inherently disadvantageous to reducing fall risk. Similarly, if imbalance occurs due to fast walking speed, a reduction in gait speed may be seen as a positive outcome of intervention.

Longitudinal observational studies of clinical measures and posturography should be implemented with falls incidence assessed prospectively before and after assessment. Such investigations may enable more targeted rehabilitation strategies for falls prevention in pwMS.

An associated issue is the choice of balance measures used to establish fall risk. For example, people with MS fall while standing, turning and walking[296] yet many balance measures capture balance with feet in a static position. Posturography appears promising as a falls risk tool[90] however the static foot plate does not mirror the dynamic activities where falls occur and access to this in many clinics is limited with some systems requiring technical expertise. The use of sensor-based measures of balance during gait[91] may be an option worth pursing as it would allow the collection of ecologically valid postural control data, potentially in remote settings.

When conducting studies to evaluate multicomponent risk prediction tools firstly the model needs to be developed, and it subsequently needs to be validated; none of the existing MS fall risk prediction tools have been validated to date. The predictive ability of a model often tends to be overestimated during the model development study, usually due to overfitting if the sample size is small and there are too few outcome events relative to the number of predictor variables.[70] External validation involves applying the model to a new cohort of individuals that were not involved in the model development study and assessing its predictive performance. Model impact studies are recommended after external validation to assess the impact on the change in behaviour of clinicians and also on cost effectiveness and on health outcomes[92]. When measuring the impact of a prediction model it is not enough to only include analysis of the traditional predictive values (e.g. sensitivity, specificity, AUC), but impact studies must also consider safety and efficiency.[93]

Arguably falls prevention interventions for people with MS are in their infancy, though the start is promising. One concern is the mismatch between the range of physiological and psychological risk factors and the predominance to date of exercise only interventions, however more recent interventions are acknowledging this and evaluate multiple component and multifactorial interventions. Intervention development is complex, and for this multifactorial, variable, and individualised problem the challenges will be many. Frameworks such as the Medical Research Council (MRC) development of complex interventions[94] may assist with this challenging process. An additional consideration as this field progresses is the need to articulate the theory behind the interventions; an aspect of intervention development that the rehabilitation field has previously been criticised for. It is essential that transparent dissemination of the development processes behind complex interventions occurs, and that theoretical underpinnings and mechanisms of intended action are clearly articulated so that the intervention is developed in line with best practice.[95,96]

It is likely that a range of interventions considering either group or individual treatment, using face to face or remote methods, and in hospital, outpatient and community settings, and a range of international healthcare and social contexts will be needed – one size certainly will not fit all for the issue of falls in MS.

Challenges

One key challenge in pooling and comparing data is the lack of standardisation of fall definition, faller classification and falls outcomes to date. The use of frameworks such as

COMET[97] to develop and apply core outcome sets for MS falls interventions is recommended to overcome the current issue of multiple definitions, classifications and outcomes. Most concerning is the limited input to date from people with MS in deciding study outcomes and this requires attention in future work.

The issue of "dose" of intervention required to improve postural control is a challenge, and a fine balance between the optimal dose/duration and the practicalities involved in engaging with and delivering such a programme need to be considered. Evidence from a range of groups highlights sustained engagement as a major challenge to falls prevention interventions[98] and suggests that programmes need to be easy to access, easy to carry out and easy to embed into a person's daily life for initial improvements to be sustained.[99] There are also significant resource implications in the provision of such interventions which may challenge existing models of healthcare. Supplementing face-to-face delivery with the provision of web-based resources, telephone or email contact to support engagement appears promising,[100] as do programmes that embed a supported self-management approach.[10183]

Perhaps the greatest challenge in reducing falls risk and hence falls, is variability. MS presentations and symptoms (and thus falls risk factors) vary significantly between people and over time: this necessitates flexible intervention programmes which can be individually targeted, and which support people to be able to self-assess their changing symptoms and adjust their programmes effectively on an ongoing basis. Additional variability in personal, environmental and social factors mean that programmes need to be adaptable and responsive to needs and circumstances. Such programmes require input from highly trained clinicians who are supported to utilise a wide range of skills; and present feasibility and sustainability issues for many models

of healthcare delivery. For researchers, this degree of variability is also a significant challenge, particularly in achieving the high degree of flexibility in programme provision whilst maintaining the degree of standardisation and intervention fidelity necessary to ensure methodological rigour in clinical trials. Collaboration, both nationally and internationally will be vital to recruiting sufficient numbers of people in order to undertake the large-scale studies which are essential to develop a robust evidence base, although the variety of health care settings internationally adds an additional challenge.

The introduction of wearable electronic technology worn on the body or embedded into mobile and portable solutions (e.g. smartphones, watches, etc) creates a new challenge for those investigating falls in pwMS. Although the potential of these devices to identify risk factors of falls is clear, their benefits are still to be verified. Importantly, these devices enable the research field to detect movement behaviour of pwMS outside the laboratory and/or clinical facilities. This opportunity might uncover new "real-life" risk factors that were not previously considered.

Conclusion and Way Forward

It is probable that we cannot prevent all falls; however, our aim should be to prevent as many falls as possible. Falls that require medical attention are particularly burdensome for both the person and the healthcare system and might be prioritised, however even those minor falls may have a profound effect on well-being and on activity participation and therefore warrant intervention to prevent them.

Falls are common and have a wide range of negative impacts. Research to date suggest that there are a variety of physiological, personal and environmental factors that contribute to falls for people with MS; a better understanding of those will lead to improved risk prediction tools and interventions for this cohort. Interventions to date have largely comprised exercise only interventions: These show promise, and suggest that challenging, functional balance programmes targeting individual risk factors, which are structured to support people to engage at a high intensity over a long duration are most likely to be effective. However, large-scale effectiveness trials are urgently required to determine the key components which should form the basis of MS falls exercise interventions, regardless of delivery method or healthcare setting.

Given the range of issues contributing to falls in MS, future interventions should consider other aspects of falls risk, particularly the psychological and MS specific risk factors. This also necessitates a recognition that not all risk factors will be modifiable, and that people will often choose to accept a degree of risk in order to maintain their participation in daily activities. Alongside assessing and optimising modifiable individual falls risk factors, programmes need to support people to develop effective, realistic strategies to manage falls risk whilst maintaining engagement, to recognise when changes to their strategies are required and to access further support as necessary. As in other groups, perhaps the focus of programmes should move away from emphasising falls reduction and instead move towards approaches which aim to maximise 'safe mobility'.

The way forward is undoubtedly through collaboration; nationally, internationally, across disciplines and with people with MS. A better understanding of this complex, individual and

multifactorial issue will assist in designing, evaluating and implementing interventions to prevent or reduce falls for people with MS.

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