Modifiable risk factors for poor health outcomes in multiple sclerosis: the urgent need for research to maximise smoking cessation success

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Abstract

Tobacco smoking is a well-established risk factor for multiple sclerosis (MS) onset, progression, and poor health outcomes in people with MS. Despite smoking being a modifiable risk factor, no research has been undertaken to understand how, or who is best placed, to assess or understand smoking behaviour in people with MS, or how healthcare professionals can best assist people with MS to quit. People with MS may have unique motivators to continue smoking, or unique barriers to smoking cessation, that are not addressed by existing cessation tools. Research is urgently needed in this area if the aim is to maximise health outcomes for all people with MS.

Introduction

Multiple sclerosis (MS) is a chronic neurological condition with no known cause, although evidence suggests it occurs due to genetic vulnerability coupled with environmental factors[1]. The manifestations of the disease are heterogeneous, although common symptoms include fatigue, sensory disturbances, muscle weakness, and cognitive impairment. Following a diagnosis of MS, often early in adulthood, a person experiences uncertainty about the expected course of their disease and impact on their future. While there are more than a dozen disease modifying therapies for people with relapsing remitting MS (RRMS), pharmacological treatment for people with progressive disease is limited with one approved therapy for primary progressive MS and none for secondary progressive MS (SPMS) without relapses. None of these therapies provide 100% efficacy.[2] Recent developments of new and repurposed drugs, and new biomarkers to monitor progression, show promising results for future treatment of MS[2]. However, few treatments specifically target neurodegeneration and none reverse damage in the central nervous system. Unfortunately, most people with MS still experience accumulation of disabling symptoms over the course of the disease[3].

A recent topical review in the Multiple Sclerosis Journal highlighted the role of tobacco smoking as a key determinant of MS onset, increasing the risk by approximately 50%.[4] Observational cross-sectional and cohort studies show that modifiable lifestyle or health risk factors, including tobacco smoking, but also sedentary behaviour, obesity and low serum vitamin D levels, are associated with disability worsening.[5] This suggests the potential to modify risk factors and improve health outcomes for people with MS.[6]

Tobacco smoking and health outcomes

A meta-analysis of 8 datasets showed that smokers had an increased hazard ratio of 1.55 (95% confidence interval (CI) 1.1, 2.2) for faster progression compared to non-smokers. The authors concluded that although the evidence was of moderate quality due to heterogeneity, smoking is an important modifiable risk factor for MS progression.[5] Smoking is also associated with lower quality of life,[7] increased depression and anxiety[8] and higher premature mortality.[9] A prospective study of more than 900 people with MS showed that the hazard ratio for death in smokers compared to never smokers was 2.7 (95%CI 1.6 to 4.6). Further, the standardised mortality ratio for smokers with MS was 1.8 (95%CI 1.2, 2.7) compared with smokers without MS, while there was no difference between non-smokers with or without MS.[9] Smoking may also adversely impact on the efficacy of disease modifying drugs.[10, 11] Quitting smoking has significant benefits for people with MS. Persistent smokers reached the progressive stage of MS eight years earlier compared with those who quit at time of diagnosis, accelerating time from RRMS to SPMS by 4.7% (95% CI 2.3-7.2) for each successive year smoked.[12] Another study showed that smoking cessation significantly reduces the risk of reaching disability milestones, and the earlier people with MS or clinically isolated syndrome (CIS) quit, the stronger this effect (risk reduction is approximately 30% per 10 years).[13] Given that increased disability leads to exponentially higher economic costs in MS,[14] lowering smoking rates may lead to substantial economic benefits, in addition to improvements to health outcomes and quality of life. Economic modelling for people with Crohn's disease, another chronic immune relapsing-remitting disorder, shows cost effectiveness and improved health outcomes of all potential smoking cessation strategies over no strategy[15]. Further, smoking cessation could decrease the risk of MS in family members who may be genetically susceptible for developing MS, a risk further increased by being exposed to passive smoking.[16] Indeed, the risk of childhood-onset MS is reduced in children whose parent stops smoking.[17]

As smoking is a key risk factor for MS onset, it is not surprising that smoking rates are high at time of diagnosis. A UK study reported that 49% of 895 people smoked at time of MS diagnosis, with 22% still smoking 17 years later.[18] Whether smoking remains more prevalent among people with MS compared to people with other chronic disease, or the general population is not well studied. However, some data from case-control studies suggests this is the case. An Australian case-control study of 282 people with first demyelinating event and 558 controls matched on age, sex and study region reported that 27.4% of people with MS smoked at time of enrolment versus 22.4% of controls,[19] with 25.6% of people with MS still smoking 5 years

later.[20] Data from a case-control study from Sweden also suggests that people with MS are more likely to smoke than controls matched for age, sex, and residential area; 36.5% of 902 people with MS vs 28.6% of 1855 controls.[21] In addition, the increasing interest in cannabis to manage MS symptoms (one in five use cannabis regularly in the UK and Canada) may further increase the use of tobacco,[22] as smoking a mix of tobacco and cannabis is common (although more evidence is needed in this area). It is a cause for considerable concern that around 20% of people with MS smoke cigarettes regularly, given the adverse consequences. We currently do not know what the barriers are to smoking cessation, what the motivators are to continue to smoke, whether people with MS are aware of the extent to which smoking contributes to their health outcomes, and what their needs are to receive smoking cessation assistance.

MS-specific motivators and barriers

It is possible that there are MS-specific motivators to continue smoking, as well as MS-specific barriers to smoking cessation and that interventions designed for the general population are not meeting the needs of people with MS. Some motivators may be similar to those in other chronic disease populations (e.g. stress, boredom, coping, self-medication, perceived pain relief), while some may be unique to MS.[23, 24] For people with acute health problems, the motivation to change behaviour should be higher, but if their health condition presents unique challenges that prevent them from quitting successfully,[25] many will find themselves unable to quit unless these challenges are adequately addressed. Several common symptoms such as cognitive dysfunction,[26] pain and depression[27] may be both motivators to continue smoking, and barriers to sustained smoking cessation. While smoking tobacco is harmful, nicotine may have actual and/or perceived benefits for symptoms,[21, 28] as has been found in people with schizophrenia[29] and depression,[30] and in animal models for MS.[31] Evidence from Swedish snuff users (smokeless tobacco) suggests that it is not the nicotine in tobacco that is responsible for an increased chance of MS onset, but other elements in the smoke.[21] One key issue that is likely important with MS, and may be for some other conditions, is the role of nicotine. Nicotine may ameliorate deficits in cognitive function such as inhibitory control, which can be impaired following abstinence.[32] Similarly, depressive symptoms reduce cessation success[25] and there is a complex relationship between cognitive function, coping and depression in people with MS.[33, 34] Finally, there is a clear association between smoking and pain,[35] which has been summarized as a positive feedback loop where smoking may be a risk factor for pain, while pain is a powerful motivator to continue

smoking due to anti-nociceptive effects.[36] These feedback loops may be especially hard to break for people experiencing depression or anxiety who may have increased pain sensitivity (all common symptoms in MS) when attempting smoking cessation.[37] If indeed nicotine is actually or perceived to be helping with these issues, then this is likely to be one area where providing cessation assistance for those with MS may differ to the generic advice provided for all smokers. They also point to a potentially important role for nicotine replacement products. However, we have been unable to find any studies on the role of nicotine in ameliorating MS symptoms. In addition to the potential role of nicotine, there may be other disease specific barriers, but this has not been investigated. We need to understand what additional or augmented resources people with MS may need (if any) on top of generic smoking cessation interventions if we are to maximise the likelihood of cessation programs being successful.

MS management

Calls have been made for smoking cessation to be urgently advised to people with MS.[6, 13, 38, 39] At present we do not know to what extent people with MS receive assessment, advice and assistance by health professionals to quit smoking, but there is some evidence of an unmet need[40]. We currently do not know whether MS clinicians, or other health professionals are aware of the specific consequences of smoking on MS health outcomes, or if they feel able or willing to assist people with MS to quit smoking. The most effective method to offer smoking assessment and cessation intervention is also unclear (e.g. through a general practitioner, MS nurse, or neurologist). Anecdotally, time, resource or knowledge barriers may exist for health practitioners to assess smoking behaviour, refer to, or provide interventions. Further, there may be a lack of confidence that existing smoking cessation interventions or tools available are effective for people with MS, which may be true to a degree if such interventions miss important MS-specific issues. Understanding current knowledge and practice, including gaps and barriers to assessing and addressing smoking from a healthcare provider perspective are essential in guideline or intervention development. Important aspects that need to be considered include: assessing smoking behaviour, referring for intervention, delivering the intervention and follow-up; the best method, which healthcare professional is best placed, and when the best time is for each of these steps. From the perspective of the person with MS, there may be disease and sociodemographic considerations for smoking cessation management, such as whether people with specific symptoms, e.g. cognitive impairment, depression or pain, require different levels of provider support.

The answers to these questions may differ between countries depending on the structure of the healthcare system and/or access to generic smoking cessation programmes.

Tailored smoking cessation interventions

In many other areas of health, tailoring basic smoking cessation interventions to include a focus on comorbidities or problem-specific barriers are showing evidence of improving outcomes. Interventions that are tailored to specific groups, and take into account social determinants, may be more successful in promoting cessation, e.g. tailoring to people with low literacy.[41] For example, a customised intervention, including behavioural therapy and nicotine replacement therapy (NRT) is effective in people with cardiovascular disease[42] and cancer.[43] While for people with psychotic illness, 8 sessions of intensive clinician-delivered therapies in combination with NRT were effective in a dose-response manner[44] and in chronic obstructive pulmonary disease interventions with specific behaviour change techniques were found to be most efficacious.[45] It has been suggested that a combination of NRT and behavioural mood management should be considered for people with depression, although more evidence is needed to confirm efficacy.[46] It is troubling that nothing is happening to provide similar interventions tailored for our priority population, those with (or at risk of) MS.

Tailoring interventions to people with MS

Despite the known risks for health outcomes and premature mortality, not one study of an intervention for smoking cessation has been undertaken in people with MS or CIS.[42, 45, 47] One smoking cessation trial was designed in 2012,[48] but this was halted due to a combination of recruitment difficulties including lack of interest in quitting, and funding restrictions (personal communication, J Ciccolo 2017). The dearth of research into this key modifiable risk factor is in stark contrast to other modifiable risk factors such as physical inactivity and low vitamin D, where dozens of studies including meta-analyses are published.

Future research in this area needs to address the following questions:
- Are people with MS more likely to smoke than people with other chronic disease or the general population?
- Are people with MS, especially smokers, aware of the additional risks of smoking for their MS?

- Are there MS/CIS-specific motivators for smoking behaviour? In particular what is the role of nicotine?
- Are there MS/CIS-specific barriers to smoking cessation? In particular, do specific MS symptoms impact cessation success?
- To what extent is smoking behaviour routinely assessed and addressed in clinical practice?
- What is the best method to assess smoking behaviour and refer people for smoking cessation?
- To what extent is the MS health workforce aware of the importance of smoking cessation for people with MS?
- Which healthcare provider is best placed to provide assessment and or cessation intervention?
- When (and how often) is the best time to assess, refer or intervene?
- To what extent are existing smoking cessation interventions effective in people with MS?
- Should and can existing smoking cessation interventions be adapted to better meet the needs of people with MS and CIS?

Given the paucity of evidence in the area currently, the priority would be to understand what MS/CIS-specific barriers to smoking cessation exist, and what barriers from healthcare professionals exist in assessing and referring for smoking cessation. This will enable learnings from smoking cessation research in other areas to be adapted and applied to the development of guidelines and interventions to be tested for efficacy in people with MS.

Challenges

There may be challenges in recruiting smokers for smoking cessation intervention studies, highlighting the importance of assessing the feasibility and acceptability of interventions, prior to phase III effectiveness trials. Smokers newly diagnosed with MS may be highly motivated to take action if made aware of the implications of the diagnosis and the evidence that smoking speeds progression. Combinations of the use of telephone Quitlines and online resources can help overcome challenges of accessing people with MS across a broad geographic region and in remote areas. Involvement of MS clinicians including neurologists, MS nurses and/or general practitioners are crucial to drive clinical change, depending on the healthcare setting. Models where MS clinicians work with smoking cessation experts to deliver high quality integrated services are possible, and these are increasingly being used by

Quitlines to help support groups requiring more than standard levels of assistance.[49, 50] Efforts to design and test smoking cessation interventions for priority groups are considered the last frontier in tobacco control in countries with low smoking rates such as Australia.[51] The savings to economic and healthcare costs, improvements to health outcomes and quality of life could be substantial given people often live with MS for 3-5 decades following diagnosis. This would justify intense interventions, as in other chronic disease[15].

Conclusion

Despite compelling evidence that smoking is a key risk factor for development, unfavourable health outcomes and premature mortality in people with MS, there is little focus in research or clinical practice on smoking cessation. There is an urgent need to understand whether there are MS-specific barriers for smoking cessation, whether there are real or perceived benefits from smoking or nicotine on MS symptoms, and what best practice is around assessing and addressing smoking in people with MS. We present this topical review to MS and smoking cessation researchers, as well as relevant funding bodies, to highlight that much needed research in this key modifiable lifestyle factor is required if we are to maximise health outcomes for all people with MS.

Declaration of Conflicting Interests

The authors declare no conflicting interests.

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