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Symptom management of patients with multiple sclerosis in primary care:

focus on overlooked symptoms

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Submitted: 13 November 2020; **Editor's response:** 10 December 2020; **final acceptance:** 22 December 2020.

71: 139–141.

DOI: https://doi.org/10.3399/bjgp21X715193

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative condition of the central nervous system. Its prevalence varies from 50–300 per 100 000 people, and it is estimated that around 2.3 million people worldwide live with MS.[1] In 2020, Public Health England released new MS prevalence data from GP records. This revealed that the number of adults with MS in the UK has risen to 131 720.[2] Each year there are on average 4950 new cases of MS diagnosed and recorded in UK primary care records.[2] Treatment of MS comprises disease-modifying drugs (DMDs) that reduce the inflammation and management of MS relapses and symptoms. The clinical decisions about DMDs and their complex monitoring dominate consultations with MS specialists, leaving less time for the management of patients' daily symptoms. Therefore, GPs currently have a unique role in managing patients' symptoms in primary care. This article focuses on the most under-recognised symptoms of MS.

WHICH ARE THE MOST OVERLOOKED SYMPTOMS?

Cognitive dysfunction, fatigue, and depression are often overlooked by healthcare professionals.[3–8] These symptoms are linked and profoundly affect patients' quality of life, especially at the early stages of the disease.[3–8]

Cognitive dysfunction

Cognitive impairment is prevalent in up to 65% of patients with MS.[4] The most common cognitive domains affected are processing speed and memory.[4] Other cognitive symptoms include deficits in attention, executive functioning, and verbal fluency.[4,5] There is a robust correlation between cognitive deficits and quality of life, including employment status in patients with MS.[4,5] Patients' self-reported cognitive function is not considered a reliable measure, as it correlates with depression, rather than cognition.[4] An informant report about patients' cognition correlates better with objectively measured cognitive function and should be sought in primary care.[4] In the suspicion of cognitive dysfunction, an objective neuropsychological assessment is essential.[4] There are many tools available for objective cognitive screening; however, the Symbol Digit Modalities Test, or a similarly validated test (Box 1), is recommended as the best rapid-assessment tool in clinical practice.[4]

A few small randomised controlled trials (RCTs) studying acetylcholinesterase inhibitors (donepezil and rivastigmine), NMDA receptor (memantine), dalfampridine, amantadine, *Gingko biloba*, and L-amphetamine have shown conflicting effects or have been disappointing.[3,5] Consequently, there is no pharmacological treatment approved for cognitive dysfunction in patients with MS.[5] In recent years there is increasing evidence that cognitive rehabilitation is having a positive impact on patients' cognition.[4,5] For patients with cognitive changes, the US Medical Advisory Committee of the National MS Society[4] and the UK National Institute for Health and Care Excellence (NICE) guidelines (Box 1) recommend a referral to a neuropsychologist (although access can be limited) and/or occupational therapist, ideally with MS expertise. Physical exercise is also recommended, as it has shown a potential benefit in MS-related cognitive dysfunction.[4,5]

Other factors impacting cognition are anxiety, depression, fatigue, pain, sleep problems, and illicit-drug and alcohol misuse,[4] thus effective management of each of these factors is likely to improve cognitive impairment. A thorough review of a patient's medication list is essential, as many drugs can cause cognitive deficits and/or fatigue. In particular, anticholinergic medication (used for an overactive bladder), anticonvulsants and opioids (used for neuropathic pain), as well as

Box 1. Resources for healthcare professionals and patients

- **National Institute for Health and Care Excellence recommendations of managing MS symptoms in an interactive flowchart:**

https://pathways.nice.org.uk/pathways/multiple-sclerosis#path=view%3A/pathways/ multiple-sclerosis/managing-multiple-sclerosis-symptoms.xml&content=view-index

- Free mobile application (for iPhone and Android) from the National Multiple Sclerosis Society (NMSS). It provides advice for managing MS symptoms and a clinical assessment tool for depression (two-question screening), fatigue (modified fatigue impact scale), and pain (pain effects scale). It has a separate section for primary care:

https://apps.apple.com/us/app/multiple-sclerosis-diagnosis/id480116542

https://play.google.com/store/apps/details?id=com.bbi.national_multiple_sclerosis_society&feature=search_result#?t=W251bGwsMSwxLDEsImNvbS5iYmkubmF0aW9uY WxfbXVsdGl wbGVfc2NsZXJvc2l zX3NvY2lldHkiXQ...

- **The NMSS summary of cognitive screening recommendations, including information about rapid screening tools and how to obtain them:**

https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Cognition_rec_provider_brochure.pdf

- The Royal College of General Practitioners provides an e-learning module regarding management of MS in primary and secondary care:

https://elearning.rcgp.org.uk/mod/lesson/view.php?id=5147 [registration required]

It also provides an online clinical course, in partnership with the MS Society:

https://elearning.rcgp.org.uk/course/view.php?id=94 [registration required]

- **The MS Society provides patient advice about memory, thinking problems, and fatigue:**

https://www.mssociety.org.uk/about-ms/signs-and-symptoms/memory-and-thinking/tips-for-dealing-with-memory-and-thinking-problems

https://www.mssociety.org.uk/about-ms/signs-and-symptoms/fatigue/managing-fatigue

https://www.mssociety.org.uk/about-ms/signs-and-symptoms/fatigue/managing-fatigue/online-fatigue-management-course

benzodiazepines and anti-spasticity drugs should be reviewed to ensure that the benefits outweigh any side effects.

Fatigue

Fatigue is the most commonly reported symptom in MS, affecting up to 80% of patients.[6,7] It impacts quality of life, with 66% of patients reporting fatigue as their most disabling symptom.[7] Fatigue has been described as *'a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities'*.[8] A variety of different scales have been used to measure fatigue, with fatigue severity scale and modified fatigue impact scale (Box 1) being the most widely used.[8,9]

Among all pharmacological treatments, amantadine is considered the most effective in MS-related fatigue (MSRF),[10] although the evidence base is low, because of trial design limitations.[3] Small trials of modafinil showed some preliminary positive results; however, these were not confirmed in a large double-blind placebo controlled RCT.[10] Other medicines that have been studied in MSRF but did not show positive results are pemoline, 4-aminopyridine, L-carnitine, and Prokarin.[3,10] Various non-pharmacological treatments have been studied in patients with MSRF.[10] Energy conservation, fatigue management programmes, yoga, and cognitive behavioural therapy (CBT) are considered effective interventions, despite the lack of standardisation in these techniques and the small sample size of the studies.[7,10] Exercise therapy has also shown benefits in patients with MSRF.[11]

Other factors that can cause fatigue, such as sleep problems, thyroid disease, anaemia, coexistent depression, and medicines (as for cognitive dysfunction above), need to be addressed.

NICE guidelines recommend amantadine, mindfulness-based training, CBT, fatigue management, aerobic, balance, and stretching exercises, as well as yoga (Box 1). The American Academy of Neurology (AAN) has assessed the evidence base for alternative therapies and recommends *Ginkgo biloba* and magnetic therapy as possibly effective options for MSRF.[12]

Depression

Patients with MS are at high risk of emotional disorders, with an estimated prevalence of depression up to 50%.[7] Suicide rates are twice as high compared with the general population.[8] Depression in MS is a major determinant of quality of life and overlaps with cognitive dysfunction, fatigue, and sleep changes.[7] The AAN recommends a two-question screening tool

(Box 1) for detecting depression in primary health. One question is about depressed mood and the other about diminished interest or pleasure. A positive response to either question indicates depression.[13] Antidepressant medication in MS-related depression showed modest benefits.[14] However, in everyday clinical practice the usual antidepressants are offered, based on efficacy in non-MS individuals with depression.[3,7,13] CBT has shown more robust evidence and has been recommended by the AAN for the treatment of depression in patients with MS.[13] Exercise is helpful in depression; however, the data from patients with MS are mixed.[13,15]

Clinicians are strongly advised to look for underlying depression in every consultation with patients with MS and ensure it is adequately treated.

APPROACHES FOR MANAGING PATIENTS' SYMPTOMS IN EVERYDAY CLINICAL PRACTICE

Symptom management in MS can be challenging. Patients may not spontaneously talk about all their symptoms, and clinicians can overlook some aspects of MS that they are not familiar with, and/or that are difficult to manage. In the experience of the authors, acknowledging a symptom and its impact on a patient's quality of life is important even in the absence of an easy solution.

There are numerous pharmacological treatments available; however, the evidence base is modest. Ultimately, drugs may not be effective, and their unevaluated use leads to polypharmacy, which is a common pitfall in daily clinical practice. As discussed, medications used to manage other MS symptoms can affect fatigue and cognitive function, thus regular review of medication efficacy and optimisation is recommended. Also suggested is a combined holistic approach with emphasis on non-pharmacological treatments (for example, CBT, counselling, neuropsychology, occupational therapy, physiotherapy, and exercise).

Patients are encouraged to have an active involvement in the management of their symptoms; it might be helpful for patients to have diaries regarding severity and impact on daily activities. This approach enables a thorough evaluation of symptoms (and their treatment) and leads to a productive clinical relationship with the best possible therapeutic outcome.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests. The corresponding author is the clinical guarantor and takes overall responsibility for the content of this article.

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