

Cognitive impairment in multiple sclerosis

The role of the general practitioner in cognitive screening and care coordination



CPD 

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Background

Cognitive impairment is common in multiple sclerosis (MS) and can have an impact on all aspects of daily life. It is also an early marker of increased MS disease activity and indicates the need to optimise disease-modifying therapies to slow progression and preserve brain functioning. However, it is difficult to detect on clinical interview alone, and patient self-report is unreliable.

Objective

General practitioners (GP) can have a key role in the screening and initial management of cognitive impairment, but they need the right tools to do so. This aim of this article is to describe the best cognitive screening tools to use in MS and some psychological screening tools that can provide useful additional clinical information.

Discussion

The various ways in which information gleaned from applying these tools can guide GPs' care plans related to the effective management and treatment of cognitive impairment during three stages in the trajectory of cognitive change in MS are discussed.

COGNITIVE IMPAIRMENT is a common symptom of multiple sclerosis (MS). Affecting at least 65% of individuals, it occurs in all MS disease phenotypes, including the prodromal phases.¹ Up to 58% of Australians with MS self-report a range of cognitive difficulties,²⁻⁴ the most common of which relate to memory and concentration (58%), but also planning (36%) and judgement (41%).³ Five cognitive impairment phenotypes (with evidence of characteristic neurobiological evidence on magnetic resonance imaging) have recently been proposed on the basis of the findings from a large sample of community-dwelling people with MS in Italy between 2010 and 2019.⁵ These cognitive phenotypes include: 1) preserved cognition (19.4%), 2) mild verbal memory and semantic fluency difficulties (29.9%), 3) mild multidomain difficulties (19.5%), 4) severe executive/attention difficulties (13.8%) and 5) severe multidomain difficulties (17.5%). While most articles on MS tend to focus on the milder forms of cognitive impairment, it is clear from these findings that approximately 30% of people with MS may have severe enough impairments to be classified as a form of dementia (or Major Neurocognitive Disorder, as per the *Diagnostic and statistical manual of mental disorders*, 5th edition). This estimate is consistent

with other studies on the prevalence of dementia caused by MS.^{6,7} Yet, for unknown reasons, this terminology is rarely used to label cognitive phenotypes in MS. Consequently, the unique vulnerability of this severely impaired subgroup remains largely overlooked.^{7,8}

Recent research has added social cognition to the list of impaired cognitive domains in MS. Such impairment may include difficulties in perceiving emotions in others and reduced theory of mind (ie understanding of what others might be thinking or feeling), particularly in those with progressive MS disease phenotypes.⁹ It remains unclear how social cognitive impairment fits into the aforementioned cognitive phenotypes, although the social, community and employment-related implications are concerning.

The trajectory of cognitive change in MS, while varied, is somewhat predictable once it emerges. Initially there may be mild difficulties confined largely to processing speed. Over a number of years, these difficulties typically worsen and expand to include additional domains such as complex attention, learning, memory and executive function.¹⁰ Cognitive impairment occurs more frequently in people with progressive MS disease phenotypes, driven primarily by widespread brain pathology (ie when

compared with relapsing remitting MS) and advancing age.¹

Cognitive impairment can have an impact on many aspects of everyday functioning in MS. It can make performing household activities, maintaining family and community relationships, managing finances, making sound medical and health decisions, driving safely and sustaining paid employment arduous if not impossible.^{1,11} It makes self-management of other MS symptoms much more challenging, particularly given that there are typically multiple different symptoms to manage simultaneously.¹² Furthermore, rates of mood dysfunction and psychological distress, including suicidality, are high in MS and often co-occur with cognitive impairment and MS fatigue. Indeed, the frequent co-occurrence of these 'invisible' symptoms argues for the need for well-integrated multidisciplinary intervention whenever cognitive impairment is detected.¹³

One of the challenges of detecting cognitive impairment in MS is that it is difficult to identify on clinical consultation alone.⁷ Even when the overall level of cognitive impairment is severe, there is usually preservation of abilities in simple attention, orientation, routine language and communication skills and well-learned general knowledge. As a result, people can present as more cognitively capable than they are in actual daily life. Further, insight into cognitive difficulties can be compromised; thus, some people may not self-report any cognitive difficulties or may dismiss the concerns of others.¹ Objective cognitive screening is important for these reasons.

In contrast to the subgroup of 30% who develop MS-related dementia, a different subgroup of 20% experience no cognitive impairment nor much decrement in their functioning over time. As a result of this variability, the detection, treatment and management of cognitive impairment needs to occur on an individual, case-by-case basis. The general practitioner (GP) is the ideal health professional to oversee the screening, monitoring, and coordination of care of patients with MS.

The importance of screening and monitoring of cognitive impairment for better care coordination

The management and treatment of cognitive impairment in MS has advanced significantly in the past few years. As a consequence, GPs can take a more active role in the screening and monitoring of cognitive symptoms. This can be useful in several ways.

Detection of early stage mild cognitive impairment to optimise pharmacological treatment of MS disease activity

Cognitive impairment is an early marker of increased MS disease activity and progression and of further cognitive decline,^{11,14} so its early detection is vital for optimising the use of disease-modifying therapies (DMTs). When cognitive impairment is first detected, a referral for neurological review should be instigated without delay. The fine-tuning of DMTs by a neurologist is essential for slowing MS disease activity and preserving brain functioning.¹⁵ However, the specific benefits of DMTs in preserving or delaying cognitive impairment, per se, are less clear, as outlined later in this article.

Detection of mild-to-moderate cognitive impairment to ensure access to non-pharmacological management and treatment

A diagnosis of probable mild-to-moderate cognitive impairment may trigger a person with MS to engage in a more 'brain-healthy' lifestyle, if they have not already done so. GPs can encourage this by sharing the following research findings with their patients: there is good evidence that the brain health of people with MS can benefit from avoiding or quitting smoking, maintaining a healthy weight, keeping up regular exercise, getting enough sleep and staying psychologically well. This brain-healthy lifestyle may also protect against further progression of MS.¹⁵

When possible cognitive impairment is indicated on cognitive screening, international guidelines recommend referral for a more comprehensive neuropsychological assessment.¹¹ Neuropsychological assessment is more

thorough and reliable than cognitive screening,¹⁶ and this information can be used to confirm or dismiss suspected impairment. It can also objectively clarify a person's cognitive strengths and weaknesses, likely aetiology of any deficits (including the influence of depression, anxiety and stress) and practical implications,¹⁷ including explaining the development of behaviours that others might find challenging. Most neuropsychologists provide psychoeducational feedback after the testing to help patients and carers to better understand these issues. They also recommend ways to manage or treat the impairments. This detailed information can then be used by GPs, in collaboration with their patients, to develop a more precise, individually tailored care plan for management and treatment, including seeking cognitive rehabilitation interventions.¹⁸

It is important to note that neuropsychological assessments are time consuming (typically taking 2-4 hours for the testing component alone), and the cost (refer to psychology.org.au for Australian Psychological Society [APS]-recommended rates) is not subsidised by the Medicare Benefits Schedule (MBS) despite decades of advocacy by the APS. These factors may limit the accessibility of this type of assessment for some patients. However, there is a range of other ways in which patients can access them, and the psychoeducational feedback component can be subsidised by the MBS.¹⁸

Detection of transition to later-stage severe cognitive impairment to ensure patient safety and quality of life

Monitoring cognitive changes via regular (eg biannual) objective screening can also identify the transition to more severe cognitive impairment, which can in turn cue GPs to introduce appropriate support services in a timely manner to maintain the patients' safety and quality of life and to prevent avoidable secondary harms (eg accidents).¹¹

When severe impairment is detected, referrals to other specialists (eg for further assessment) and relevant health and

community, National Disability Insurance Scheme, private sector and aged care services should be considered. At this point, the potential risks of stigma and distress induced by the introduction of dementia terminology are outweighed by the benefits of obtaining timely access to vital services, as has been shown in people with other forms of dementia.¹⁹ In particular, dementia terminology use can permit access to dementia-specific support services (including younger onset dementia services) and can reinforce to all those involved in providing care to the person the severity of their practical and decision-making support requirements and their extreme vulnerability.⁷ For example, there is a concerning overrepresentation of people with younger onset MS-related dementia living in residential care facilities in Australia.²⁰ It is possible that earlier detection, medical intervention using DMTs and access to dementia-focused services within their own homes could have prevented or delayed this outcome.

Finally, cognitive screening results can be used to support applications for the disability support pension, medical disability insurance, early release of superannuation funds and other financial entitlements. Alternately, if impaired decision making is putting a person at risk of harm, then their screening results, along with other evidence, can be used to support the activation of Enduring Guardian or Enduring Power of Attorney instruments, or to support applications for the appointment of a Guardian, Financial Manager or Administrator via the various state and territories' Civil and Administrative Tribunals to ensure that well-informed decisions are made in the person's best interests.

Screening tools: Cognition, mood and work difficulties

When conducting cognitive screening of patients with MS in the general practice clinic, the same principles apply as when conducting screening for early stage dementia caused by more common conditions such as Alzheimer's disease.²¹ Points to consider when conducting

cognitive screening with people with MS specifically are listed in Box 1.

There is a plethora of cognitive screening tools that have shown sensitivity to detect the early signs of cognitive impairment in MS.^{22,23} The current international consensus tends to favour the Brief International Cognitive Assessment for MS (BICAMS) and Symbol Digit Modalities Test (SDMT) as the most effective brief objective screening tools^{11,23} to use in MS clinics. There is no reason why GPs could not use the SDMT in particular, as it is unrestricted for general clinical use and easy to access, administer, score and interpret. Despite

the international recommendations, MS-specific instruments are not routinely used in clinical practice, even in many specialist MS clinics.²⁴ Instead, the most frequently used tools are those with which physicians are already familiar: the Montreal Cognitive Assessment (MoCA) and Addenbrooke's Cognitive Assessment-III (ACE-III). Both are rather confusingly called 'assessments' but are, in fact, just brief screening tools. The MoCA is reasonably sensitive in detecting early cognitive changes in MS,²⁵ and preliminary evidence supports the potential usefulness of the ACE-III.²⁶ However, these two tools were designed

Box 1. Points to consider when using cognitive screening tools with people with multiple sclerosis

1. Cognitive screening involves administering a limited number of brief 'bedside tests' (eg of memory, orientation to time and place, and other short tasks) in order to obtain a single summary score reflecting a person's general level of cognitive functioning.
 2. Interpretation is binary (pass/fail) and based on whether the person's total score falls above or below a specified cut-off criterion. However, test cut-off criteria are initially established on the basis of a study sample with a specific age range, so adjustments in interpretation might need to be made when using these tools in the clinic for people in a different age range. For instance, the cut-off criterion might be lowered for older people, on the basis of normative data,³⁴ to allow them to make more errors before classifying their performance as a 'fail'.
 3. Although the brevity of cognitive screening is attractive, it is narrow in scope, and reliability is low when compared with more comprehensive cognitive assessments such as neuropsychological assessments.
 4. Cut-off scores are pitched to detect impairment in people of average intellect and/or average education level. Thus, early signs of impairment in people whose usual level of intellectual functioning (including speed of thinking) is well above average may be missed. They can also inaccurately label a person as 'probably impaired' in those whose usual level of intellectual functioning is well below average. Care in interpretation is therefore needed.
 5. Special care needs to be exercised when interpreting indicators of new or worsening cognitive impairment in the context of multiple sclerosis (MS) exacerbations. These new MS symptoms may lessen at least partially over time as the inflammatory exacerbation remits, so it is prudent to repeat initial screening following remission of relapse symptoms (on average after approximately six weeks). Making major lifestyle decisions (eg giving up work) must be delayed until this further screening, or more thorough assessment, has been conducted.
 6. Special care must also be taken to ensure that other physical MS symptoms (eg poor vision or reduced dexterity) are considered when interpreting results. While most MS-specific screening tools minimise the influence of typical physical MS symptoms, this is not absolute. Fatigue is not usually a problem with these brief screening tests.
 7. Psychological symptoms, such as major depression or anxiety, can also affect performance.
 8. Interpreting change in cognitive functioning over time via repeated administration of the same screening tool is possible. However, consideration of what constitutes a clinically meaningful change is required (eg a four-point deterioration on the Symbol Digit Modalities Test³⁵ for predicting risk of loss of employment). A clinically meaningful change in scores will differ for each screening tool, so reference to the scientific literature for this information is recommended.
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to detect common types of dementia (eg Alzheimer's disease); thus, they are less efficient and sensitive than specifically developed MS tools. The most common cognitive screening tests used in MS, and the recommendations for use (or not), are listed in Table 1.

The challenge for GPs is not just choosing which of these screening tools to administer (we support the international consensus opinion on this), but also knowing how best to introduce the topic of the need to screen for cognitive impairment in the first place in this younger cohort of patients with MS. Initiating this discussion can be challenging for many GPs who might not have experience in screening for cognitive impairment in younger adults. To assist, the following approach is suggested.

In the first instance, it is important that the patient is fully informed about the risks and benefits of engaging in cognitive screening and provides consent. This necessitates a careful discussion about the likelihood of them developing some degree of cognitive impairment as a symptom of MS and the benefits of detecting this early, as outlined previously. As a useful practical example, information gleaned from cognitive screening can be used to guide clinical interventions for minimising the risk of premature loss of paid employment,²⁷ which may affect as many as 80% of people with MS.²⁸ Further, it may reduce the high rate of 'presenteeism' (ie working while sick), which contributes to almost three times more work productivity loss in people with MS when compared with absenteeism (ie number of work days missed).²⁹ On the other hand, this initial discussion may open up concerns about the emergence of cognitive symptoms and how they might affect the patient's life goals, which may, understandably, lead to some anxiety or other distress that will also need to be managed sensitively. Referrals to clinical psychology or counselling services might also be useful in this situation.

A useful next step is to administer other brief psychological screening tools before cognitive screening to gather contextual information that can help to

inform further discussion. The 15-item Multiple Sclerosis Neuropsychological Questionnaire (MSNQ)³⁰ measures the patient's perception of their everyday cognitive problems. It is best given along with a brief screening tool for depression (eg Depression, Anxiety and Stress Scales-21 [DASS-21] or Beck Depression Inventory - Fast Screen [BDI-FS]).^{11,31} This is because scores on the MSNQ are influenced by depression symptoms. Asking a patient's family member or carer to fill in the observer ('informant') version of the MSNQ can enhance the ability to detect the presence of cognitive impairment, since carers' ratings correlate well with objective cognitive test results. Likewise, administering the MS Work Difficulties Questionnaire-23 (MSWDQ-23)³² to track a patient's work difficulties over time is also recommended. This psychometrically strong instrument was developed in an Australian sample of patients with MS to assess three core dimensions of work difficulties including psychological/cognitive barriers, physical barriers as well as external barriers (eg work-life balance, financial difficulties).

If any concerns are identified via this brief psychological screening process, this information can reinforce the value of further objective cognitive screening. Regardless of the findings detected via cognitive screening, this exercise can reassure patients that they are being listened to and that information obtained from these screening tools is being used to inform the GP's care discussions with them. It can also provide useful baseline information about the patient for future comparison. Details of useful self- and informant-report instruments are provided in Table 2.

Treatment of cognitive impairment in MS

The latest DMTs for MS should theoretically lower the incidence of cognitive impairment via their ability to reduce the number of relapses and slow disease progression in the brain. There are some indications that this might be the case.^{1,11} However, there is currently

no clear evidence of this despite decades of effective DMTs use, as illustrated by the results of the aforementioned recent study on cognitive phenotypes.⁵ Furthermore, there is currently no compelling evidence to support the use of any specific medication for the treatment of cognitive symptoms per se in MS,²³ although there are some promising candidates.¹¹ Fortunately, there is now good evidence that a range of compensatory and restorative cognitive rehabilitation interventions is effective in remediating mild-to-moderate cognitive impairment in MS to at least some degree.^{1,11,14,23,33} These interventions offer some hope for people learning how to live with this common, complex, invisible and disabling symptom of MS.

Conclusion

Cognitive impairment is common in MS. It ranges widely in its severity, presents in all types of MS and yet is difficult to detect on clinical interview alone, so is considered to be one of the main 'invisible' symptoms of MS. It can have an impact on all aspects of daily life, so early detection is important to allow for effective management and treatment. Screening for cognitive impairment is best achieved by the GP administering brief objective screening tools such as SDMT or BICAMs, alongside brief psychological screening tools such as MSNQ, DASS-21, BDI-FS, and MSWDQ-23. Screening is clinically useful at any stage in the trajectory of cognitive change to guide GPs' care plans related to interventions aimed at preserving brain reserve; managing the impact of cognitive impairment on everyday functioning and quality of life; and accessing effective treatments, such as cognitive rehabilitation, and relevant support services. It is also a useful precursor to comprehensive neuropsychological assessment. The GP is the ideal health professional to oversee the screening, monitoring and coordination of care of patients with MS, so cognitive screening should be a routine activity for GPs caring for people with MS in their clinics.

Table 1. Screening instruments commonly used to detect possible cognitive impairment and change in people with multiple sclerosis

| Screening instrument | Administration time (minutes) | Cost* | Available from | Comments |
|---|-------------------------------|--|---|---|
| <p>Symbol Digit Modalities Test (SDMT) oral version</p> <p>This test presents a series of nine symbols, each paired with a single digit in a key at the top of a sheet of paper. The adapted oral version is suitable for use in patients with multiple sclerosis (MS). Patients are asked to voice the digit associated with each symbol as rapidly as possible for 90 seconds.</p> | 3 | SDMT Kit \$275; pack of 25 forms \$143 | https://paa.com.au | This instrument is highly recommended for use by medical practitioners to screen for cognitive impairment and change. ^{11,23} While sensitive to the hallmark feature of MS (processing speed), it is unable to detect difficulties in other the domains of cognition including memory and executive functioning. So, if likely impairment is detected, referral for more comprehensive assessment is required. Poor performances are not obvious to the patient, so this test rarely causes distress. |
| <p>Brief International Cognitive Assessment for MS (BICAMS)</p> <p>This brief test screening battery includes a test of processing speed (SDMT oral version) and memory (California Verbal Learning Test, third edition [CVLT3] and the Brief Visuospatial Memory Test-Revised [BVMT-R]).</p> | 15–25 | SDMT as above; CVLT3 Kit \$813, pack of 25 \$202; BVMT-R Kit \$913, pack of 25 forms \$187 | https://paa.com.au (SDMT, BVMT-R) www.pearsonclinical.com.au (CVLT3) https://bicams.net | The addition of the memory tests in this brief battery, while offering some greater precision in the detection of impairments, requires training and a background in clinical psychology. No overall score is obtained, and impairment may be detected in any one of its subtests. While highly recommended for use in MS clinics, ^{12,23} this tool is most appropriately administered by psychologists. |
| <p>Montreal Cognitive Assessment (MoCA)</p> <p>This is a screening instrument for mild cognitive impairment. It assesses overall cognitive functioning on the basis of performance in the following cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations and orientation.</p> | 10 | Free once training and certification achieved | https://mocatest.org | This is not an ideal instrument for screening in MS as it is less efficient and less sensitive than the screening instruments specifically developed for MS. However, there is some evidence supporting its utility in MS. ²⁵ Administrators must be trained and certified and should adhere closely to the official manual. |
| <p>Addenbrookes Cognitive Assessment-III (ACE-III)</p> <p>This brief cognitive screening instrument assesses overall cognitive function on the basis of performance across five cognitive domains: attention, memory, verbal fluency, language and visuospatial abilities.</p> | 15 | Free | www.sydney.edu.au/brain-mind/resources-for-clinicians/dementia-test.html | This is not an ideal instrument for screening in MS as it is less efficient and less sensitive than the screening instruments specifically developed for MS. There is only preliminary support for its utility in MS. ²⁶ The instrument is freely accessible. It should only be administered and scored according to the official manual. |
| <p>Mini Mental State Examination (MMSE)</p> <p>This screening instrument is widely used, particularly to assess overall cognitive function among the elderly; it includes brief tests of orientation, attention, memory, language and visual-spatial skills.</p> | 5–10 | Free | www.ihoa.gov.au/what-we-do/standardised-mini-mental-state-examination-smmse | This instrument is not recommended to detect cognitive impairments in MS because of its lack of sensitivity, ²³ despite it being freely accessible for non-commercial use. It will only reliably detect severe cognitive impairment in people with MS. |

*Cost is accurate at time of publication. Please refer to websites for current cost.

Table 2. Other psychological screening instruments recommended to complement cognitive screening and monitoring in people with multiple sclerosis

| Instrument | Description | Length | Administration time (mins) | Accessible from |
|---|--|----------|----------------------------|---|
| Multiple Sclerosis Neuropsychological Questionnaire | Measures neuropsychological competence during activities of daily living. Cognitive functioning is assessed in several domains including attention and processing speed, memory and other cognitive functions. Self-report and informant-report versions are available. | 15 items | 5 | Refer to Benedict et al (2003; 2004). ^{30,36} |
| Depression, Anxiety and Stress Scale-21 | Measures the negative emotional states of depression, anxiety and stress that typically co-occur with cognitive impairment. Available in self-report only. | 21 items | 6–7 | www2.psy.unsw.edu.au/dass |
| Beck Depression Inventory – Fast Screen | Measures depressive symptoms. Helps quantify depression while excluding symptoms that might be related to multiple sclerosis (MS). | 7 items | 2–3 | www.pearsonassessments.com |
| Multiple Sclerosis Work Difficulties Questionnaire-23 | Measure of subjective difficulties experienced in a work setting by people with MS. The scale consists of three subscales: psychological/cognitive, physical and external barriers. A 50-item version with 12 subscales (some of which include general cognitive difficulties, fatigue, interpersonal difficulties) is also available. | 23 items | 6–7 | Permission for non-commercial use can be obtained from Sage publications. Scale can be obtained by contacting the test's primary author (CA Honan). |

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