Management of neuropsychiatric symptoms in multiple sclerosis

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Multiple sclerosis is associated with a high prevalence of psychiatric comorbidity, including affective, psychotic and cognitive disorders. In this review, Dr Sommerlad and colleagues discuss the epidemiology, aetiology and management of neuropsychiatric symptoms in multiple sclerosis, using case vignettes to demonstrate the wide range of clinical presentations.

Multiple sclerosis (MS) is the commonest cause of neurological disability in young and middle-aged adults.¹ The characteristic pathological features are demyelinating plaques, astrocytic gliosis and immune-mediated inflammation anywhere within the CNS, with the periventricular region, brainstem, juxtacortical region, optic nerves and spinal cord being particularly common targets. The neurological manifestations are diverse, although they usually reflect the function of the affected anatomical site, and the course of the illness is variable and initially difficult to predict with accuracy.

In 80-90 per cent of cases, MS is relapsing-remitting in nature with two-thirds of these cases developing a secondary progressive form of the condition a variable number of years after onset and a third having a relapsing-remitting course that does not result in long-term serious disability. The remaining 10-20 per cent of patients have a primary progressive course with gradually worsening symptoms.² The prognosis can be poor in the long term but progression is frequently slow; recent evidence suggests a median of 28 years before a stick is required for walking.³

The UK annual incidence of MS is 10 in 100 000 with a prevalence of 200 in 100 000.⁴ There is estimated to be over 100 000 people suffering from the condition in the UK. The median age of onset is 31 years and it is approximately twice as common in women.⁵ It has a multifactorial aetiology with genetic and environmental factors shown to be important. There is 31 per cent monozygotic concordance compared to 5 per cent in dizygotic twins⁶ while the environmental influence is demonstrated by marked variations in prevalence in genetically homogenous populations.⁷ Prevalence increases with increasing distance from the equator and those who emigrate in childhood have prevalence rates consistent with their adopted country.⁸

MS commonly presents with weakness, tingling or numbness in the limbs; diplopia, visual loss or impaired visual acuity; vertigo; dysarthria and ataxia; fatigue; and bladder and bowel disturbance.⁹ The array of presenting symptoms in MS can lead to diagnostic uncertainty and neuropsychiatric conditions such as somatisation disorder are sometimes suspected. A study demonstrated that 16 per cent of patients with MS had been referred to a psychiatrist between the onset of neurological symptoms and diagnosis of MS. In spite of neurological symptoms being present in the majority of cases, these remained largely overlooked and diagnoses of conversion disorder and hysterical personality disorder were applied,⁹ although the increased use of MRI scans since this finding was reported has improved diagnostic accuracy. While neurological features are the most recognised manifestations of MS, psychopathology, including affective, psychotic and cognitive disorders, is also common. The identification of these symptoms is often more difficult and diagnosis can be delayed. Psychiatric symptoms can occur at onset or later in the MS disease process and initial psychiatric symptoms tend to improve later than neurological symptoms and frequently never resolve.¹⁰

In this review, we will describe a range of neuropsychiatric disorders that can develop in MS, illustrated by case vignettes from our own clinical practice, and consider the most appropriate management.

Mood disorders
Depression

Depressive symptoms are common in patients with significant disability but distinction should be made between sufferers with these symptoms and those with the syndrome of major depression, which is characterised by pervasive mood change, diurnal mood variation, altered sleep and appetite, and distorted beliefs...
including feelings of guilt and worthlessness and suicidal ideation. The lifetime prevalence of major depression in MS, replicated in a number of studies, is around 50 per cent with a point prevalence of 14 per cent, which is higher than matched populations with neurological disability and around three times higher than the general population.

Due to the potential overlap between somatic symptoms of depression and features of MS, clinicians should use a screening tool that gives weight to depressive thoughts to identify patients at risk of depression who warrant more detailed clinical interview. The Beck Depression Inventory and Hospital Anxiety and Depression Scale are both suitable and have been validated for patients with MS.

The identification of depression in people with MS is important as it is linked with lower quality of life, more functional impairment, potentially reversible impaired cognitive function and reduced adherence to medication regimens as well as higher rates of suicide than the general population. Suicidal ideation is common in MS, with a quarter of patients considering suicide at some point during their illness. Young males within five years of diagnosis are at highest risk of completed suicide while presence and severity of depression, social isolation and alcohol abuse are other notable risk factors.

Biological and psychosocial factors are implicated in the aetiology of depression in MS. Evidence suggests that the individual’s adjustment to adversity and their coping strategies is more closely related to physical deterioration than the severity of depression; loss of recreational opportunities and poor quality relationships are also important. Studies have not demonstrated a significant correlation between depression and plaque load but the location of brain lesions is significant. A higher lesion load in the anterior temporal lobe and inferior medial prefrontal cortex of the dominant hemisphere as well as dominant anterior temporal lobe atrophy are associated with depression. Genetic factors have not been shown to be relevant, while some have proposed that dysfunction in the hypothalamic-pituitary-adrenal axis underlies the increased risk of depression in MS.

There has been some concern in the past that the use of disease-modifying drugs (DMDs), particularly interferon beta, resulted in increased risk of depression and suicide. However, recent evidence suggests that this is not the case and the value of interferon in maintaining remission in MS means that it should remain a treatment option in all individuals, including those with a past history of depression, but used with caution in those with severe depression. It is appropriate to screen high-risk individuals for depression following the initiation of treatment with DMDs and, if depression develops, the agent need not be stopped automatically, but depression should be treated using standard options.

Several treatment options seem to be effective in treating depression in MS but the strength of evidence for any particular treatment is poor. Although open-label trials and case reports suggest efficacy of many different antidepressants in the treatment of depression in MS, there have been only two previous blinded randomised controlled trials (RCTs) of desipramine and paroxetine, which have shown only a non-statistically significant trend towards improvement compared with placebo. Electroconvulsive therapy (ECT) has been shown to be effective in severe depression but can result in exacerbation of symptoms of MS. Results from trials of individual or group psychological treatments have shown more promise and cognitive behavioural therapy (CBT) can be helpful in mild to moderate depression and as effective as treatment with the SSRI sertraline. A well-conducted RCT of telephone-administered CBT compared with a control group of supportive therapy by telephone demonstrated a significant reduction in cases of depression and depressive symptoms after CBT but the difference between the groups was no longer significant at one year follow-up.

Treatment of depression in MS remains difficult and is poorly guided by evidence but the Golman Consensus Group recommends individualised treatment of moderate to severe depression with a combination of an antidepressant and a form of psychotherapy: either supportive therapy, CBT or interpersonal therapy.

**Bipolar affective disorder**

Co-occurrence of bipolar affective disorder (bipolar disorder) and MS is uncommon but prevalence of bipolar disorder in people with MS is at least double the expected rate and a number of potential explanations have been proposed, although none fully explains the association. Some can be attributed to the mania-inducing properties of steroids but a
Neuropsychiatric symptoms in MS

**Case vignette 2 – Euphoria**

A 22-year-old woman with secondary progressive MS characterised by optic neuritis and limb weakness presented to the neurology outpatient clinic with her mother, who was concerned about her inappropriate public behaviour; she would react with extreme excitement to unremarkable situations. She was inappropriate and incongruously optimistic during assessment while neuropsychological assessment showed mild frontal and subcortical deficit. Symptomatic treatment with sodium valproate yielded little benefit.

**Disorders of affect**

**Pseudobulbar affect**

Pseudobulbar affect (PBA), synonymous with the condition of ‘pathological laughing and crying’, is characterised by uncontrollable laughing and/or crying without the associated subjective feelings of happiness or sadness and usually without any discernable stressor. PBA is socially and occupationally disabling and distressing for patients and their families. It is seen in around 10 per cent of MS patients and is associated with long disease duration, a progressive course, cognitive impairment and greater physical disability. PBA is also seen in other neurological conditions, including Parkinson’s disease, motor neurone disease and stroke. Cognitive assessment usually demonstrates poor performance on tasks involving prefrontal function. Structural brain changes predict pseudobulbar affect; bilateral medial inferior frontal and bilateral parietal hyperintense lesions and brainstem hypointense lesions are seen.

Use of the Centre for Neurologic Study Emotional Lability Scale, a seven-item self-report tool, is recommended for screening. While treatment with small doses of amitriptyline, fluoxetine or levodopa has previously shown some benefit, new guidelines from the American Academy of Neurology propose the use of a combination of dextromethorphan and quinidine, which was shown in two RCTs to reduce emotional lability and significantly improve quality of life.

**Euphoria**

In possibly the earliest large study of neuropsychiatric problems in MS in 1926, Cottrell and Kinnier Wilson reported the presence of euphoria in 63 of 100 consecutive cases of disseminated sclerosis at Queen Square, London, although recent studies have suggested the prevalence in MS sufferers to be around 10 per cent. Euphoria should not be confused with hypomania or mania seen in bipolar affective disorder. It is a fixed mental state change (rather than fluctuating as in mania) distinguished by lack of concern over physical disability and incongruous optimism and is associated with more severe MS, greater physical disability, cognitive dysfunction, lack of insight and a severe, often frontal, brain lesion load. It is seen in around 10 per cent of MS sufferers and is likely to be related to impairment of the self-regulatory orbito-frontal network.

**Psychotic disorders**

Although psychosis in people with MS is a rare occurrence, studies suggest that the prevalence rate surpasses that expected by chance. The reason for this is unclear; it may be due to the direct effect of demyelinating lesions as patients with MS and psychosis are more likely to have plaques affecting the temporal horns bilaterally although a viral precursor to both conditions has also been proposed.
Affective and schizophrenia-like presentations are seen equally when MS patients become psychotic but the predominant presentation is one of positive psychotic symptoms (usually persecutory delusions) with a relative lack of negative symptoms (apathy, restricted affect and thought).\textsuperscript{26} In addition, compared to schizophrenia, MS-related psychosis tends to present later (mean age around 36 years) and there is quicker resolution of symptoms, fewer psychotic relapses and a better long-term outcome, with 60 per cent of patients having only one psychotic episode over six-year follow-up.\textsuperscript{26}

The evidence to favour a particular antipsychotic drug is scarce but atypical agents, eg olanzapine, quetiapine and risperidone, are preferred due to a lower risk of adverse neurological effects. As irritability and agitation is common in people with MS and psychosis, hospital admission is sometimes required and benzodiazepines are appropriate if added sedation is required.

**Cognitive disorders**

Cognitive deficit in MS was described by Charcot in 1877, who noted that MS causes ‘marked enfeeblement of the memory, conceptions are formed slowly, and intellectual and emotional faculties are blunted in their totality’.\textsuperscript{33} Slowed cognitive processing is present early in the disease and can be seen in people with clinically isolated syndromes – a single episode of demyelination in one area of the CNS, eg optic neuritis or brainstem or spinal cord syndrome – with asymptomatic lesions elsewhere in the brain on MRI.\textsuperscript{34} In people with established MS, around 40 per cent have cognitive abnormalities.\textsuperscript{35} Risk factors for impaired cognitive function in MS are age greater than 40 years, low premorbid intelligence or educational attainment, and depression. Cognitive impairment tends to develop alongside worsening physical disability, disease duration and the onset of a progressive disease course.\textsuperscript{35} Patients with a relapsing-remitting disease course generally perform better than those with progressive illness, in whom the predominant deficit is executive function, rather than memory, which is more affected in relapsing-remitting disease.\textsuperscript{36}

Cognitive dysfunction adversely affects daily functioning, employment and quality of life and is frequently missed in routine assessment. When a neurologist suspects cognitive impairment, they are correct in over 90 per cent of cases but when they do not suspect cognitive impairment, they are wrong in half of cases.\textsuperscript{37} Thorough neuropsychological assessment is time-consuming and costly so approaches have been proposed to assess those in greatest need.

**Case vignette 4 – Cognitive impairment**

A 20-year-old man with a five-year history of relapsing-remitting MS was admitted to the neuropsychiatry ward due to a two-month history of disorganised behaviour at home. During assessment, his behaviour was bizarre at times and he displayed fixed, concrete thinking and impaired attention. He scored 30/30 on MMSE but was slow to answer some aspects of this screen. Formal neuropsychological testing demonstrated significant impairment in executive functioning and information processing speed with reduced naming and facial recognition.

The Mini-Mental State Examination (MMSE) is not useful in screening MS patients for cognitive impairment but screening using the Multiple Sclerosis Neuropsychological Screening Questionnaire,\textsuperscript{37} a 15-item self- or informant-rated measure of cognitive and neuropsychiatric problems, which has been validated for use in MS, may be a helpful strategy. More thorough assessment using a battery of neuropsychological tests that assess the cognitive domains most affected in MS patients (processing speed, learning and memory, executive function, visuospatial processing and word retrieval) is recommended for people in whom cognitive dysfunction is suspected. The Minimal Assessment of Cognitive Function in MS battery is a valid approach to neuropsychological assessment in MS patients.\textsuperscript{38}

MS has been suspected to cause a subcortical pattern of cognitive deficit, ie forgetfulness, emotional or personality changes, slowed thought processes and impaired executive function, as it affects classic subcortical white matter tracts, such as periventricular white matter tracts and the corpus callosum, and this has been borne out by research. Information processing speed, verbal memory, cognitive flexibility and executive function are all impaired.\textsuperscript{39}

The presentation of cognitive deficit in MS is variable. Cognitive function tends not to correlate with other markers of relapse and remission and the syndrome of a rapidly progressive dementia is rare but there is usually a progressive course with more cognitive domains affected, as well as correlation with markers of physical disability and social dysfunction.\textsuperscript{40} Some patients can present with predominant severe cognitive impairment without significant impairment in other neurological domains. In these patients, brain atrophy is commonly seen on neuroimaging and DMDs are frequently ineffective.\textsuperscript{41}

Cognitive impairment can be predicted by brain atrophy on traditional MRI imaging but not by the degree or location of demyelinating lesions,\textsuperscript{12} although more advanced MRI techniques are showing more promise in this regard. The combination...
of structural and functional MRI imaging has demonstrated altered cerebral activation in MS patients performing as well as controls on tasks requiring attention, while MS patients who performed worse on a planning ability task did not have abnormal brain activation. This suggests that compensatory mechanisms related to neuronal plasticity can mitigate the pathological changes but can become overwhelmed, leading to the manifestation of cognitive symptoms. There is also increasing evidence that grey matter pathology, as reflected by atrophy, is implicated in cognitive dysfunction as MS progresses.

DMDs are the first-line of treatment for MS and secondary outcome data from some large RCTs have demonstrated that early treatment with interferon beta results in better processing speed and working memory but no RCTs have assessed this as a primary outcome so the methodology does not allow sound conclusions to be drawn. Initial enthusiasm for the use of cholinesterase inhibitors or memantine, which are used in dementia, has dispersed as they have been shown to be ineffective. Symptomatic treatment with the stimulants levodopa and methylphenidate has been proposed by some authors but this remains controversial.

Of the non-pharmacological treatments, cognitive rehabilitation is likely to be the most effective and has two components: restoration of function and compensation for loss of function. Relying on neuronal plasticity, restorative approaches aim to identify specific cognitive deficits and introduce remedial therapies to increase performance in a given area, such as graded practice for improving memory. Compensatory strategies aim to maximise the use of the retained cognitive abilities in order to improve social and occupational function, such as using notebooks or calendars to record important information or appointments and developing time management skills.

The changing socio-economic landscape of 21st century Britain, with the increasing role of new technologies and disappearance of manual jobs, means that cognitive performance and skills are of rising importance; the cognitive challenge of sustaining mental effort over the hours of a normal working day cannot be adequately tested in standardised neuropsychological assessment. Clinicians need to be vigilant for cognitive dysfunction and more effective treatments are urgently needed.

### Table 1. Useful assessment tools for neuropsychiatric disorders in multiple sclerosis

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<thead>
<tr>
<th>Disorder</th>
<th>Assessment Tool</th>
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<tbody>
<tr>
<td>Depression</td>
<td>Beck Depression Inventory, Hospital Anxiety and Depression Scale</td>
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<tr>
<td>Pseudobulbar affect</td>
<td>Centre for Neurologic Study Emotional Lability Scale</td>
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<tr>
<td>Cognitive function screening</td>
<td>Multiple Sclerosis Neuropsychological Screening Questionnaire</td>
</tr>
<tr>
<td>Neuropsychological assessment</td>
<td>Minimal Assessment of Cognitive Function in MS</td>
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### Table 2. Treatment options for neuropsychiatric disorders in multiple sclerosis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Depression</td>
<td>Sertraline, CBT</td>
</tr>
<tr>
<td>Mania</td>
<td>Lithium, sodium valproate</td>
</tr>
<tr>
<td>Pseudobulbar palsy</td>
<td>Dextromethorphan and quinidine</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Olanzapine, quetiapine, risperidone</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Disease-modifying drugs, cognitive rehabilitation</td>
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### Conclusion

An understanding of neuropsychiatric disorders in MS is important for all professionals involved in the care of people with MS. These disorders occur early in the disease, affect about half of patients at some point and have a significant impact on social and occupational function, and quality of life. Furthermore, they negatively affect patients’ ability to adhere to the recommended treatment regimens for other neurological symptoms in MS. Timely detection is essential as therapies can often be successful and improve quality of life, although the paucity of empirical treatment data demonstrates the need for targeted research on the management of these disorders.

### Declaration of interests

None declared.

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### References


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Key points

• Neuropsychiatric disorders are common in MS, especially depression and cognitive impairment, which affect around 50 per cent of individuals at some point
• They can occur at any time in the disease process but are rarely the first presenting symptom
• Untreated neuropsychiatric symptoms result in worse social and occupational function and reduced quality of life
• Neuropsychiatric symptoms are under-recognised but appropriate screening and diagnostic tools are available
• There should be close liaison between psychiatry and neurology teams to achieve holistic management of these disorders