Neuropsychiatric syndromes of multiple sclerosis

Ruth Murphy,1 Stefani O’Donoghue,2 Timothy Counihan,3 Colm McDonald,2 Peter A Calabresi,4 Mohammed AS Ahmed,5 Adam Kaplin,6 Brian Hallahan2

ABSTRACT

Neuropsychiatric signs and symptoms occur frequently in individuals with multiple sclerosis (MS), either as the initial presenting complaint prior to a definitive neurological diagnosis or more commonly with disease progression. However, the pathogenesis of these comorbid conditions remains unclear and it remains difficult to accurately elucidate if neuropsychiatric symptoms or conditions are indicators of MS illness severity. Furthermore, both the disease process and the treatments of MS can adversely impact an individual’s mental health. In this review, we discuss the common neuropsychiatric syndromes that occur in MS and describe the clinical symptoms, aetiology, neuroimaging findings and management strategies for these conditions.

INTRODUCTION

Neuropsychiatric abnormalities are diverse, are reported in up to 60% of patients with multiple sclerosis (MS) and are among the main contributors to the morbidity and mortality associated with MS.1 Although psychiatric abnormalities generally present subsequent to neurological diagnosis, the first clinical presentation of MS has been reported to include concomitant psychiatric and neurological symptoms (2.3%) or consist of solely psychiatric symptoms (0.2%–2%).2,3 Neuropsychiatric conditions encountered include disorders of affect and behaviour, and psychotic and anxiety disorders. Although psychiatric comorbidity can be difficult to diagnose, it is generally responsive to treatment, conferring benefits in functional status, quality of life and overall disease burden. In this review, we discuss the common neuropsychiatric syndromes (psychiatric disorders occurring in the context of the neurological disorder MS) that occur in MS and describe the clinical symptoms, aetiology, neuroimaging findings and management strategies for these conditions. A comprehensive bibliographic search of articles examining neuropsychiatri syndromes (major depressive disorder (MDD), bipolar affective disorder (BPAD), psychosis, anxiety disorders, psychoactive substance misuse, pseudobulbar affect (PBA), euphoria) that occur in MS from the Medline, PsycINFO and Scopus databases was conducted.

MAJOR DEPRESSIVE DISORDER

MDD is the most common psychiatric disorder associated with MS, with an estimated annual prevalence rate of 15% and rates of up to 25% reported in people aged 18–45 years, which is approximately five times the rate observed in the general population.4 Almost 50% of all patients with MS will experience a clinically significant depressive episode following the onset of MS during their lifetime.5–6 Such episodes are often under-recognised and undertreated.7–8 One reason for this lack of detection of MDD is that typical biological symptoms including fatigue, anorexia, poor concentration, memory deficits and insomnia can be present in the absence of MDD in individuals with active MS. Furthermore, typical depressive symptoms including apathy, social withdrawal, feelings of worthlessness, guilt and poor self-esteem are less common than symptoms of frustration or irritability in individuals with MS and comorbid MDD.9 These symptoms which may more accurately indicate a comorbid depressive episode include a pervasive low mood, anhedonia, diurnal mood variation, suicidal ideation, pessimistic or negative patterns of thinking and impaired functionality unrelated to or out of proportion to one’s physical disability (table 1).9

Suicide is a significant cause of mortality with a 3% rate of completed suicide in individuals with MS,10 which is approximately 7.5 times higher than that of the general population and significantly higher than that reported in individuals experiencing other neurological or chronic medical disease disorders.4,11–13 The presence of suicidal ideation with intent has been reported to be as high as 29%, with depressive symptoms proposed as the most important factor associated with suicidal ideation.14 Additional risk factors for parasuicide include male gender, young age at onset of illness, the initial 5 years following diagnosis, current or previous history of depression or deliberate self-harm, social isolation, recent functional deterioration and illicit substance misuse.9,14

The association of MS with MDD including the impact of MS disease activity, severity and duration remains complicated with some studies reporting no relationship between MDD and these indices of MS illness,15–17 while others have demonstrated an association between MDD and MS duration18 and disease progression.19,20 This association is complex, with depressive episodes proposed as a possible consequence of the MS neuropathological process itself and/or reaction to the associated psychosocial stress of being diagnosed with MS.20,21 A genetic predisposition for MDD in individuals with MS is unlikely, as increased incidence rates of depression among first-degree relatives of depressed patients with MS have not been reported.22 Aetiological factors implicated with comorbid MDD include hypothalamic-pituitary-adrenal axis dysfunction, medications used in the treatment of


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**Table 1** Presenting symptoms and management options for neuropsychiatric disorders in individuals with MS

<table>
<thead>
<tr>
<th>Neuropsychiatric disorder</th>
<th>Principal presenting symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Pervasive low mood</td>
<td>SSRIs are first line (fluoxetine, sertraline)</td>
</tr>
<tr>
<td></td>
<td>Diurnal mood variation</td>
<td>TCAs—desipramine</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>SNRIs especially if comorbid pain (venlafaxine, duloxetine)</td>
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<tr>
<td></td>
<td>Functional change</td>
<td>Mirtazapine (less sexual dysfunction)</td>
</tr>
<tr>
<td></td>
<td>Pessimism/negative thinking patterns</td>
<td>Psychotherapy—CBT, supportive, mindfulness, IPT, exercise and relaxation techniques</td>
</tr>
<tr>
<td></td>
<td>Suicidal ideation</td>
<td>Lithium augmentation (diuresis and polyuria may be issues)</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic depressive symptoms secondary to use of corticosteroids, baclofen, dantrolene and tizanidine</td>
<td>ECT for treatment-resistant cases but may increase risk of MS relapse</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Elated mood</td>
<td>Lithium (risk of diuresis)</td>
</tr>
<tr>
<td></td>
<td>Increased energy</td>
<td>Sodium valproate</td>
</tr>
<tr>
<td></td>
<td>Talkativeness</td>
<td>Mania with psychotic symptoms—risperidone, quetiapine, olanzapine, ziprasidone</td>
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<tr>
<td></td>
<td>Overfamiliarity</td>
<td>If steroid-induced mania, consider lithium, phenytoin, olanzapine and/or reduced dose of steroids</td>
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<td></td>
<td>Psychomotor agitation</td>
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<td></td>
<td>Disinhibition</td>
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<td></td>
<td>Impulsivity</td>
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<tr>
<td></td>
<td>Insomnia</td>
<td></td>
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<tr>
<td>Psychosis</td>
<td>Hallucinations and delusions</td>
<td>Atypical antipsychotics</td>
</tr>
<tr>
<td></td>
<td>Irritability and agitation</td>
<td>Risperidone</td>
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<td></td>
<td>Sleep disturbance and grandiosity</td>
<td>Clozapine</td>
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<td></td>
<td>Blunted affect, flight of ideas, depression, reduced self-care and pressured speech</td>
<td>Aripiprazole</td>
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<td></td>
<td>More complex delusions occasionnally (erotomanic, nihilistic and misidentification)</td>
<td>Quetiapine</td>
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<td></td>
<td></td>
<td>Ziprasidone</td>
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<td></td>
<td></td>
<td>Typical antipsychotics (ie, chlorpromazine may worsen balance)</td>
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<td></td>
<td></td>
<td>Benzodiazepines (may help sedation but may worsen cognitive impairment)</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>GAD</td>
<td>SSRIs are first-line agents</td>
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<td></td>
<td>Panic disorder</td>
<td>Other options include</td>
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<tr>
<td></td>
<td>OCD</td>
<td>Venlafaxine</td>
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<td></td>
<td>Social anxiety disorder</td>
<td>Buspirone</td>
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<tr>
<td></td>
<td>Simple phobia (self-injection anxiety)</td>
<td>Pregabalin</td>
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<td></td>
<td>Anxiety symptoms associated with underlying condition</td>
<td>Gabapentin</td>
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<td></td>
<td></td>
<td>Beta-blockers</td>
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<td></td>
<td></td>
<td>Benzodiazepines (short-term only)</td>
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<tr>
<td>Substance misuse</td>
<td>Increased depression</td>
<td>Counselling services appropriate for the substance of misuse</td>
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<td></td>
<td>Increased suicidal ideation</td>
<td>Consider anticraving agents such as acamprosate</td>
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<td></td>
<td>Exacerbate cognitive deficits</td>
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<td></td>
<td>Coordination difficulties</td>
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<td></td>
<td>Interact with MS treatments</td>
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<td></td>
<td>Heightened codependence on carer or family</td>
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<tr>
<td></td>
<td>Symptoms in line with underlying condition</td>
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<tr>
<td>Pseudobulbar affect and euphoria</td>
<td>Incongruent emotional expression in response to a non-specific stimulus</td>
<td>TCAs (amitriptyline, desipramine, nortriptyline)</td>
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<tr>
<td></td>
<td>Emotions (laughing/crying) disproportionate to the underlying emotional experience</td>
<td>SSRIs</td>
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<td></td>
<td>Absence of voluntary control of facial expression</td>
<td>Levodopa</td>
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<td></td>
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<td>Amantadine</td>
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<td>Dextromethorphan and quinidine</td>
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</tbody>
</table>

**B-FS**, Beck Fast Screen for Depression in Medically Ill Patients; CBT, cognitive behavioural therapy; CNS-LS, Center for Neurologic Study-Lability Scale; GAD, generalized anxiety disorder; HADS, Hospital Anxiety and Depression Scale; IPT, interpersonal therapy; MS, multiple sclerosis; NARI, noradrenaline reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; NMDA, N-Methyl-D-aspartate; SNRI, serotonin noradrenergic reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

MS and regional brain pathology. Fifty per cent of individuals with MS and comorbid MDD have been found to have reduced suppression of cortisol when administered the dexamethasone suppression test, a finding frequently replicated in MDD alone. Furthermore, failure of cortisol suppression has been associated with increased numbers of gadolinium-enhancing lesions. Psychosocial stressors implicated in MDD include lower socioeconomic status, limited social support, inadequate coping and adjustment mechanisms, unpredictable disease course, loss of recreational activities, severe physical disability and perceived physical incapacity. Moreover, hopelessness together with uncertainty around prognosis has been demonstrated to lead to irritability and frustration and has been associated with depressive symptoms and suicidal ideation.

Following the introduction of interferon beta as a disease-modifying therapy (DMT) in the early 1990s, concern was raised in relation to a putative association between such treatments and the development of depressive symptoms and suicidal ideation. However, subsequent studies have failed to confirm an association. Nevertheless, common clinical practice post beta-interferon treatment frequently comprises psychoeducation of individuals regarding the risk of interferon-induced depressive symptoms, with the use of prophylactic treatment to be considered in high-risk individuals. Corticosteroids in particular, but also other treatments used in the symptomatic management of MS including baclofen, dantrolene and tizanidine, have been associated with an increased risk of MDD both with their use and their abrupt discontinuation.
In relation to brain pathology in MS and its aetiological association with MDD, MRI studies to date have reported variable findings (table 2). A potential association between a greater lesion load in brain regions associated with depressive pathology (frontal and temporal lobes and limbic system) has been demonstrated in a number of studies. For instance, increased numbers of brain lesions have been demonstrated in the frontal, right parietal and right temporal lobes in individuals with comorbid MDD. It has thus been suggested that lesions in brain regions that are projections of the basal-limbic system produce a disruption of limbic-cortical pathways and increase the risk of MDD in individuals with M. However, conversely a number of more recent studies have failed to replicate such an association between lesion load in any brain region and the presence of comorbid MDD.

Reduced total grey matter, frontal lobe and hippocampal volume have been found in individuals with MS and comorbid MDD, consistent with findings in individuals with depression without comorbid MS. A negative association has also recently been demonstrated between depressive symptoms and cortical surface area in frontal and parietal regions, similar to that noted in MDD without MS.

MRI techniques evaluating white matter in individuals with MS and comorbid MDD including diffusion tensor imaging, analysed using Tract-Based Spatial Statistics and most recently connectome analysis, have demonstrated abnormalities in white matter connectivity and regional integration in several brain regions (eg, the frontal lobes and limbic regions) including the hippocampus and amygdala and subcortical regions. Based on the above neuroimaging findings, one could postulate that individuals with MS who develop MDD already have a structural susceptibility to MDD. However, given the variability of findings to date, further studies are required to more clearly elucidate the association between abnormal brain pathology and the presence of MDD in individuals with MS.

Depressive symptoms frequently go undetected or unrecognised in individuals with MS, with reports that two-thirds of individuals with active symptoms and one-third of individuals with MS experience a corticosteroid-induced manic episode or to antidepressant-induced (hypo)manic states. Drug-induced manic symptoms appear generally to be dose dependent, occur early in treatment and are usually responsive to treatment. Manic symptoms (non-medication induced) may precede other neurological signs but more commonly become evident approximately 1 year after diagnosis, and include increased energy, pressured or rapid speech, flight of ideas, increased risk-taking, impaired judgement, overfamiliarity, psychomotor agitation, disinhibition, insomnia and impulsivity.

BIPOLAR AFFECTIVE DISORDER

The prevalence of BPAD in MS is approximately twice that in the general population, with rates of 0.3%–2.4% found, although rates as high as 10% have been reported. A 2014 study of patients with MS noted an OR of 15.9 for the presence of any mood disorder and 44.4 for bipolar spectrum disorders. This increased rate is not solely attributable to the effects of steroid treatment although up to one-third of individuals experience a corticosteroid-induced manic episode or to antidepressant-induced (hypo)manic states. Other agents have also been implicated in causing episodes of (hypo)mania including baclofen, dantrolene, tizanidine and psychoactive substances. Drug-induced manic symptoms appear generally to be dose dependent, occur early in treatment and are usually responsive to treatment. Manic symptoms (non-medication induced) may precede other neurological signs but more commonly become evident approximately 1 year after diagnosis, and include increased energy, pressured or rapid speech, overfamiliarity, psychomotor agitation, disinhibition, insomnia and impulsivity.

Unlike MDD, a genetic contribution to BPAD is probable, given reports of familial clustering of both diagnoses. Furthermore, one of the genetic loci (6q 21–22 region) identified as an aetiological factor in BPAD is located within or close to the histocompatibility human leucocyte antigen system, within which certain haplotypes are over-represented in patients with MS. Other aetiological factors include psychological and adjustment processes associated with underlying personality production, is a viable alternative to SSRIs, although caution is required due to its sedative and weight increasing effects.

Other pharmacotherapeutic options, although potentially associated with a greater risk of adverse effects, include low-dose TCAs (for both depression and the symptomatic relief of pain or bladder dysfunction); selective serotonin and noradrenergic reuptake inhibitors (SNRIs) (for depression and comorbid pain); and bupropion (for depression and reduced risk of sexual dysfunction). Lithium is often used in treatment-resistant MDD; however, caution is required in individuals with MS as diuresis secondary to treatment may exacerbate bladder dysfunction. An additional reason to consider lithium treatment in MS relates to studies on animal models with evidence of lithium abolishing experimental autoimmune encephalomyelitis (EAE) (the most frequently used animal model of MS) and reducing demyelination, microglia activation and leucocyte infiltration in the spinal cord of mice. Electro-convulsive therapy (ECT) used for intractable depressive episodes in a recent review was found to be a safe and efficacious treatment, associated with minimal neurological deterioration. Thus, given both the limited evidence for efficacy and significant adverse effects associated with a range of other pharmacological agents, where active enhancing lesions are not present, ECT represents a viable therapeutic option for intractable depressive episodes.

Engagement in exercise has also been to have an antidepressant effect, although limited supporting evidence is available to date. As neuropsychiatric symptoms have been reported to fluctuate depending on current neurological status, with associations between resolution of disease activity and resolution of psychiatric symptoms, optimising disease-modifying agents should also be considered as a viable initial treatment option. Finally, agents demonstrated to have an effect on intractable fatigue may be associated with a potential mood enhancing qualities including amantadine, pemoline, modafinil and armodafanid.
### Table 2 Structural MRI findings in MS and comorbid major depressive disorder

<table>
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<tr>
<th>Patient group</th>
<th>MS</th>
<th>MRI findings</th>
<th>Disability status</th>
<th>Findings</th>
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<tbody>
<tr>
<td><strong>Reischies et al (1988)</strong></td>
<td>46</td>
<td><em>Neurologist ratings</em> (depression=11%, euphoria=11%, irritability=22%, impaired judgement=9%, reduced drive=2%, liability of affect=11%)</td>
<td>No standard instruments, 7-point scale for each of five symptoms of depression, euphoria, irritability, impaired judgement, reduced drive, with liability of mood scored for extent of occurrence of depressed mood and euphoria simultaneously</td>
<td>The presence of lesions in the frontal lobes were related to higher total scores of psychopathology. Periventricular lesions associated with liability of affect, disorders of judgement, depression and euphoria</td>
</tr>
<tr>
<td><strong>Möller et al (1994)</strong></td>
<td>19</td>
<td><em>Radiological evaluation of lesions</em></td>
<td>Mean EDDS depressed group=3.2 and in non-depressed group=3.1</td>
<td>No association between scores of depression and lesion load, gadolinium-enhanced lesions or VBR</td>
</tr>
<tr>
<td><strong>Tsolaki et al (1994)</strong></td>
<td>22</td>
<td><em>Radiological evaluation of lesions</em></td>
<td>HDRS (several cognitive scales)</td>
<td>No correlation between HDRS and lesion load or volume of the CC</td>
</tr>
<tr>
<td><strong>Sabatini et al (1996)</strong></td>
<td>10</td>
<td><em>Radiological evaluation of lesions</em></td>
<td>BDI HDRS SAS</td>
<td>No difference in number, size, location of area of demyelinating lesions SPECT demonstrated higher CBF in left limbic cortex and lower CBF in right limbic cortex in depressed group</td>
</tr>
<tr>
<td><strong>Fassbender et al (1998)</strong></td>
<td>23</td>
<td><em>SPECT</em></td>
<td>HAS HDRS</td>
<td>Individuals with gadolinium-enhancing lesions had higher scores of depression and anxiety</td>
</tr>
<tr>
<td><strong>Díaz-Olavarrieta et al (1999)</strong></td>
<td>44</td>
<td><em>Radiological evaluation of lesions</em></td>
<td>MMSE NPI</td>
<td>Only euphoria and hallucinations correlated with the severity of demyelination</td>
</tr>
<tr>
<td><strong>Bakshi et al (2000)</strong></td>
<td>29</td>
<td><em>Radiological evaluation of lesions</em></td>
<td>BDI HDRS</td>
<td>Higher lesion load in superior frontal and superior parietal lobes in depressed group. Lateral and third ventricular enlargement and frontal atrophy noted in depressed group</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Study group</th>
<th>Patient group</th>
<th>MS</th>
<th>MS+comorbid psychiatric disorder</th>
<th>Healthy controls</th>
<th>MRI Scanner, slices (mm), method</th>
<th>Psychometric instruments</th>
<th>Disability status</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berg et al (2000)</td>
<td></td>
<td>47</td>
<td>(RR=20, SP=23, PP=4)</td>
<td>31</td>
<td>1.5 T Siemens Magnetom Vision or 1.5 T Gyroscan 15 Philips Scanner, 5 mm slices, radiological evaluation of lesions</td>
<td>BDI, HDRS, MADRS</td>
<td>Median EDSS=6 for depressed group and 5 for non-depressed group</td>
<td>Higher lesion load in right temporal lobe in depressed patients with a trend towards an increased lesion load in the right parietal lobe, right frontal lobe and cerebellum. Lesion load correlated with BDI, HDRS and MADRS scores in the right temporal lobe</td>
</tr>
<tr>
<td>Pujol et al (2000)</td>
<td></td>
<td>45</td>
<td>(predominantly RR, but exact figures not given)†</td>
<td>9</td>
<td>1.5 T Siemens Magnetom Vision or 1.5 T Gyroscan 15 Philips Scanner, 5 mm slices, radiological evaluation of lesions</td>
<td>BDI</td>
<td>Mean EDSS=3.3</td>
<td>Lesions in the left arcuate fasciculus were significantly related to affective symptoms, somatic complaints and BDI scores</td>
</tr>
<tr>
<td>Zorzan et al (2001)</td>
<td></td>
<td>77</td>
<td>(predominantly RR, but exact figures not given)†</td>
<td>18</td>
<td>1.5 T Siemens Magnetom Vision or 1.5 T Gyroscan 15 Philips Scanner, 5 mm slices, radiological evaluation of lesions</td>
<td>BDI</td>
<td>Median EDSS=2.0</td>
<td>Greater depression scores in patients with mainly cerebral involvement than those with spinal cord lesion localization. The severity of depressive symptoms was weakly correlated with right frontal lesion load and right temporal lobe volume</td>
</tr>
<tr>
<td>Benesova et al (2003)</td>
<td></td>
<td>10</td>
<td></td>
<td>10</td>
<td>1.5 T Siemens Magnetom Vision or 1.5 T Gyroscan 15 Philips Scanner, 5 mm slices, radiological evaluation of lesions</td>
<td>HDRS, MADRS, SDS</td>
<td>Mean EDSS=2.5</td>
<td>Increased lesion load area in right frontal lobe in MS+MDD group. Highest number of lesions was observed in the right frontal lobe in MS+MDD group</td>
</tr>
<tr>
<td>Feinstein et al (2004)</td>
<td></td>
<td>19</td>
<td>(RR=7, SP=10, PP=2)</td>
<td>21</td>
<td>1.5 T Siemens Magnetom Vision or 1.5 T Gyroscan 15 Philips Scanner, 5 mm slices, radiological evaluation of lesions</td>
<td>BDI</td>
<td>Mean EDSS=4.7 in depressed group and 4.6 in non-depressed group</td>
<td>Less GM volume and more CSF volume in left anterior temporal region. Greater T2 weighted lesion volume and extensive T1 weighted lesion volume in left medial inferior prefrontal cortex</td>
</tr>
<tr>
<td>Feinstein et al (2010)</td>
<td></td>
<td>32</td>
<td>(BDI&lt;19) (13 taking antidepressants) (RR=26; SP=4; PP=2)</td>
<td>30</td>
<td>1.5 T Siemens Magnetom Vision or 1.5 T Gyroscan 15 Philips Scanner, 5 mm slices, radiological evaluation of lesions</td>
<td>BDI</td>
<td>Mean EDSS=3.5 in depressed group and 2.5 in non-depressed group</td>
<td>Individuals with depression had reduced white matter volume in the left superior frontal lobe and greater lesion volume in the right medial inferior frontal lobe. Higher MD in the grey matter of the left anterior temporal lobe and in lesions in the right inferior frontal region. Reduced FA in the white matter of the left anterior temporal lobe</td>
</tr>
<tr>
<td>Gold et al (2010)</td>
<td></td>
<td>21</td>
<td>(BDI&lt;13) (All RR)</td>
<td>8</td>
<td>3 T Siemens Scanner, 1 mm slices. Automated measurement of brain volume and manual tracing of lesions. Segmentation of hippocampus</td>
<td>BAI, BDI</td>
<td>Mean EDSS=2.5</td>
<td>No difference in brain atrophy or lesion volume between depressed and non-depressed groups. Both MS groups demonstrated smaller hippocampal volume compared with controls. The depressed group had smaller dentate gyrus volume compared with non-depressed MS individuals and dentate gyrus was inversely correlated with depression as measured by the BDI (r=−0.38, p=0.04)</td>
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Table 2 Continued

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Healthy controls</th>
<th>MRI Scanners, slices (mm), method</th>
<th>Psychometric instruments</th>
<th>Disability status</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>Papadopoulou et al (2013)</td>
<td>91</td>
<td>1.5 T Avanto, Siemens Scanner, 1.5 mm slices; Radiological evaluation of lesions and semiautomated mechanism for lesion volume used</td>
<td>CES-D (several cognitive scales)</td>
<td>Median EDSS=3.6</td>
<td>No association with lesion load or volume (WM or cortical lesions) and depression scores</td>
</tr>
<tr>
<td>Gobbi et al (2014)</td>
<td>54</td>
<td>3 T scanner, Automatic segmentation technique for evaluation of lesions</td>
<td>MADRS</td>
<td>Median EDSS in depressed group=2.5, and 2 in non-depressed group</td>
<td>No difference in lesion frequency or location between the MS groups No difference in WM atrophy between the MS groups Atrophy of the left middle frontal gyrus and right inferior frontal gyrus was selectively related to depression</td>
</tr>
<tr>
<td>Goldi et al (2014)</td>
<td>83 (CES-D&lt;20) (women)</td>
<td>26 (CES-D&gt;20) (women)</td>
<td>CES-D</td>
<td>Mean EDSS 3.36 in depressed group and 3.08 in non-depressed group</td>
<td>No difference in lesion load between the two groups: Smaller right hippocampal volume in depressed group (p=0.04), but no difference in left hippocampal or total hippocampal volume. Areas of hippocampal volume reduction included the CA2-3 region and posterior subiculum Right hippocampal shape (reduced thickness) associated with depressive symptoms (affective but not vegetative symptoms)</td>
</tr>
<tr>
<td>Kern et al (2015)</td>
<td>27 RR</td>
<td>4/27 RR had severe depressive symptoms</td>
<td>EDSS</td>
<td>Mean EDSS 2.5</td>
<td>Depressive symptoms associated with smaller volumes in hippocampal subregions CA2, CA3, and dentate gyrus Depressive symptoms associated with lower scores in spatial memory and attention/executive function Hippocampal and thalamic atrophy in RRMS group Reduced white matter FA in cingulum, fornix and uncinate fasciculus</td>
</tr>
<tr>
<td>Shen et al (2014)</td>
<td>15 RR</td>
<td>9/15 depressive symptoms</td>
<td>EDSS</td>
<td>Mean EDSS 1.73</td>
<td>HAMD scores positively correlated with FA values in left hypothalamus, right posterior middle cingulate gyrus and hippocampus, right precentral gyrus and posterior cingulate WM Depressive symptoms negatively associated with demyelinating lesions in limbic system and frontal lobe</td>
</tr>
<tr>
<td>Hanken et al (2015)</td>
<td>49 RR</td>
<td>37/49 cognitive fatigue patients with depressive symptoms</td>
<td>EDSS</td>
<td>Mean EDSS (3.2 CF/4.1 CNP)</td>
<td>Interaction effects between BDI scores and WM between prefrontal cortex and pons</td>
</tr>
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Table 2  Continued

<table>
<thead>
<tr>
<th>Study group</th>
<th>MS</th>
<th>MS + comorbid psychiatric disorder</th>
<th>Healthy controls</th>
<th>MRI, Scanner, slices (mm), method</th>
<th>Psychometric instruments</th>
<th>Disability status</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nigro et al (2015)</td>
<td>22</td>
<td>20</td>
<td>16</td>
<td>3T Scanner, LST lesion segmentation toolbox, Brain connectivity toolbox</td>
<td>EDSS, BD-II</td>
<td>Mean EDSS (2.3 non-MDD, 2.8 MDD)</td>
<td>Increased nodal path length in right hippocampus and amygdala in patients with MD in MS. Increased shortest distance between right hippocampus and right amygdala and dorsolateral and ventrolateral prefrontal cortex, orbitofrontal cortex, and sensorimotor cortices and supplementary motor area.</td>
</tr>
<tr>
<td>Nygaard et al (2015)</td>
<td>61 RR</td>
<td>16/61</td>
<td>61</td>
<td>1.5T Scanner, Cortical thickness, surface area and volume</td>
<td>EDSS, BDI</td>
<td>Mean 1.9</td>
<td>Depressive symptoms related to reduced surface area in frontal pole, pars orbitalis, orbital frontal, rostral and caudal middle frontal, and pre-central and post-central regions bilaterally, and left hemisphere included middle temporal, fusiform and parahippocampal regions. Volume reductions were associated with similar regions associated to surface area findings and extended to right supramarginal and superior temporal regions and inferior temporal of left hemisphere.</td>
</tr>
</tbody>
</table>

*Study includes the individuals investigated in Pujol et al (1997).129*

1A 2-year follow-up study on same cohort of patients demonstrated no difference in lesion load between the groups, but noted increased brain atrophy in left frontal lobe in the depressed cohort (Zorzon et al).44

BDI, Beck Depression Inventory; CBF, cerebral blood flow; CC, corpus callosum; CES-D, Center for Epidemiological Studies Depression Scale; CL, clinically isolated lesions; CP, chronic progressive; CIS, Clinical Interview Schedule; DSM, Diagnostic Statistics Manual; DTI, diffusion tensor imaging; EDSS, Expanded Disability Scale; FA, fractional anisotropy; FIM, Functional Independence Measure; HADS, Hospital Anxiety and Depression Scale; HRS, Hamilton Depression Rating Scale; KSS, Kurtzke Disability Status Scale; MADRS, Montgomery and Asberg Depression Scale; MMSE, Mini-Mental State Examination; MD, mean diffusivity; MS, multiple sclerosis; NPI, Neuropsychiatric Inventory; PD, physically disabled; PSE, Present State Examination; RR, relapse remitting; SAS, Zung Self-rated Anxiety Scale; SCL, symptom check-list; SDS, Zung Self-rated Depression Scale; SPECT, single-photon emission CT; SSSI, Social Stress and Support Interview; VBM, voxel-based morphometry; VBR, ventricular brain ratio.

traits and coping mechanisms. To date, there have been few MRI studies examining individuals with MS and BPAD (table 3), with the limited evidence suggesting that manic episodes are more likely in patients with higher brain lesion volumes.

There is also a lack of published data in relation to specific management strategies for BPAD in patients with MS. The same pharmacotherapeutic agents used in those individuals without a comorbid diagnosis of MS are often used, although caution is required due to the increased potential for adverse effects. As described above, lithium, in addition to its mood-stabilising qualities, is also associated with potential global atrophy; however, these correlations were non-significant when cognitive function was controlled for.

**Table 3** Structural MRI findings in MS and other comorbid neuropsychiatric conditions

<table>
<thead>
<tr>
<th>Study group</th>
<th>Patient group</th>
<th>MS</th>
<th>MS+comorbid psychiatric disorder</th>
<th>Healthy controls</th>
<th>MRI Scanner, slices (mm), method</th>
<th>Psychometric instruments</th>
<th>Disability status</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ron and Logsdail (1989)</td>
<td>116</td>
<td>50/116 (adjustment: D/O=22, depression=5, delusional disorder=5)</td>
<td>40 HC</td>
<td>0.5 T superconducting system Scanner, 10 mm slices with 2 mm gap, radiological evaluation of lesions</td>
<td>BDI, CIS, SSSI, MMSE</td>
<td>—</td>
<td>Elation correlated with widespread MRI abnormalities</td>
<td></td>
</tr>
<tr>
<td>Feinstein et al (1992)</td>
<td>10</td>
<td>10 (mania with psychosis)</td>
<td>—</td>
<td>0.5 T Picker Scanner, 5 mm slices, radiological evaluation of lesions</td>
<td>PSE, SCL</td>
<td>Mean</td>
<td>EDSS=4.9</td>
<td></td>
</tr>
<tr>
<td>Feinstein et al (1992)</td>
<td>19</td>
<td>3/35 individuals had comorbid psychiatric disorders (1=psychosis, 2=euphoria)</td>
<td>30</td>
<td>0.5 T Picker Scanner, 5 mm slices, radiological evaluation of lesions</td>
<td>CIS, HADS, SSSI</td>
<td>Mean</td>
<td>EDSS=3.5</td>
<td></td>
</tr>
<tr>
<td>Diaz-Olavarrieta et al (1999)</td>
<td>44</td>
<td>42/45 had symptoms on NPI (dysphoria=79%, agitation=40%, anxiety=37%, apathy=20%, euphoria=13%, irritability=13%, hallucinations=10%)</td>
<td>25 (84% had no symptoms based on the NPI)</td>
<td>Gadolinium-enhanced MR images</td>
<td>MMSE, NPI</td>
<td>Mean</td>
<td>EDSS=3.3</td>
<td></td>
</tr>
<tr>
<td>Benedict et al (2004)</td>
<td>37</td>
<td>31/37 had NPI administered</td>
<td>—</td>
<td>1.5 T Philips Gyroscan Scanner, 5 mm slices</td>
<td>NPI</td>
<td>Mean</td>
<td>EDSS=2.5</td>
<td></td>
</tr>
<tr>
<td>Ghaffar et al (2008)</td>
<td>14</td>
<td>14</td>
<td>—</td>
<td>1.5 T Sigma Systems, GE Scanner, 1.2–1.4 mm slices, lesion analysis, measurement of GM, WM, CSF</td>
<td>—</td>
<td>Mean</td>
<td>EDSS in PD=6.0 and in MS alone=4.6 (p=0.08)</td>
<td></td>
</tr>
</tbody>
</table>

BDI, Beck Depression Inventory; CIS, Clinical Interview Schedule; CP, chronic progressive; CSF, cerebrospinal fluid; D/O, disorder; EDSS, Expanded Disability Scale; GM, grey matter; HADS, Hospital Anxiety and Depression Scale; HC, healthy controls; HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery and Asberg Depression Scale; MMSE, Mini-Mental State Examination; MS, multiple sclerosis; NPI, Neuropsychiatric Inventory; PBA, pseudobulbar affect; PSE, Present State Examination; RR, relapse remitting; SAS, Zung Self-rated Anxiety Scale; SDS, Zung Self-rated Depression Scale; SSSI, Social Stress and Support Interview; WM, white matter.
on balance, coordination, incontinence and fatigue. Corticoste-
roid-induced mania can be managed with lithium, olanzapine
and phenytoin,9 without the requirement for steroid disconti-
nuation (see table 1).

PSYCHOSIS
The rate of psychosis in MS has been reported at 2%–4%, a
rate approximately three times that found in the general popu-
lation,86 with over 90% of individuals having symptoms of MS
prior to the onset of psychosis.87 This increased rate of psychosis
may not include an increased risk of a diagnosis of schizophrenia
with a recent nationwide Swedish cohort study, noting a margin-
ally decreased risk of schizophrenia in individuals with MS.88
Symptoms of psychosis reflect the underlying pathology of the
psychotic disorder, and thus a non-affective psychotic disorder
such as schizophrenia may typically be associated with persecu-
dory delusions and auditory hallucinations, whereas an affective
psychotic disorder such as mania with psychosis or a steroid-in-
duced psychosis may be associated with grandiose or erotomani-
cal delusion.89 The clinical presentation of symptoms has been
purported to be related to MS neuropathology in periventric-
ular white matter, and temporal and fronto-temporal regions.86
However, to date, there is a paucity of both MRI (table 2) or
neuropathology studies examining this. Other aetiological
factors include an inflammatory process, with some although
limited data indicating that patients with schizophrenia alone
have similar profiles of cytokine levels,90 psychosocial circum-
stances and medicinal cannabis used for individuals with MS
alone.91 There is limited evidence for genetic factors playing a
significant role in the development of psychotic illness.89

The treatment of psychosis is similar in individuals with MS
to those without comorbid MS. However, caution is required in
relation to the choice of psychotropic agent prescribed due
to the potential for exacerbating adverse effects, especially
extra-pyramidal side effects (EPSE). Consequently, the use
of low-dose atypical (second-generation) antipsychotic agents,
given their lower propensity for EPSE for the control or alle-
viation of psychosis, is suggested with trials indicating clin-
cal benefit from a variety of psychotropic agents including
risperidone,91 ziprasidone,92 clozapine,93 aripiprazole,94 queti-
apine95 and olanzapine.61 although clozapine is predominantly
prescribed for treatment-resistant psychosis due to its association
with agranulocytosis.61 An additional rationale for treatment
with risperidone and quetiapine relates to their demonstrated
disease-modifying characteristics in EAE mice models.88 93 96 There
are also limited case report data demonstrating an amelioration
of psychotic symptoms with disease-modifying agents.7

The choice of antipsychotic agent should consider the individ-
ual’s clinical characteristics (MS and psychosis) and the poten-
tial adverse effects they may suffer secondary to the use of the
psychotropic agent employed.

ANXIETY DISORDERS
Much less research has been undertaken in relation to comorbid
anxiety disorders. The lifetime prevalence of anxiety disorders
has been quoted to be as high as 36%, with generalised anxiety
disorder (19%), panic disorder (10%), obsessive-compulsive
disorder (9%) and social anxiety disorder (8%) the most common
disorders reported.77 A number of risk factors for anxiety disor-
ders have been identified that potentially relate to MS, including
being newly diagnosed with MS, increased MS disease activity,
experiencing pain, fatigue or sleep disturbance.22 Additional risk
factors noted include female gender, social isolation, a previous

PSYCHOACTIVE SUBSTANCE MISUSE
Patients with MS have been reported to have a 13.6% lifetime pre-
valence of alcohol abuse or dependence.99 In addition to the known
physical manifestations of alcohol abuse or dependence, other dele-
terious consequences may include increased depressive symptom-
atology,100 suicidal ideation27 and coordination difficulties.22 Brief
screening tools such as the CAGE questionnaire or the Alcohol
Use Disorders Identification Test may be beneficial for clinicians
to adopt into routine clinical practice to help identify if alcohol
misuse is present. Psychoactive substance misuse or dependence
has also been noted to be present at increased rates in individuals
with MS, with rates for psychoactive substance or alcohol misuse
in the previous month of 19% noted.105 However, data pertaining
to rates of individual psychoactive substance misuse in individuals
with MS have not been reported to our knowledge. Higher rates of
alcohol or psychoactive substance (excluding cannabis) use were
found among younger sufferers, those still employed and patients
who had less severe MS symptoms.105

Cannabis use has been reported to alleviate neurological symp-
toms including spasticity, pain, tremor, insomnia and bladder
dysfunction, and its use has been associated with individuals
with greater physical disability and dependency.106 Although
clinical trials of cannabis have failed to consistently detect signif-
ificant beneficial effects,107 cannabis use was detected in 33% of
individuals with MS in one study.106 Certain synthetic cannabi-
noid oral compounds (Sativex and Nabilone) are licensed for the
 treatment of MS-related spasticity and neuropathic pain in some
European countries. Cannabis use is however associated with a
number of adverse effects including worsening cognitive
function (eg, memory disturbance, poor concentration) and
increasing or exacerbating depression and psychosis.22 108 109
PBA AND EUPHORIA

PBA, also known as ‘pathological laughing and crying,’ ‘emotional incontinence,’ ‘pathological emotionalism’ or ‘involuntary emotional expression disorder,’ occurs in approximately 10% of individuals with MS, to varying degrees of severity, with uncontrollable (pathological) crying more common than uncontrollable laughing. PBA presents more commonly in chronic disease sufferers and often in the progressive stages of MS. It is distinguishable from an affective disorder by the disassociation evident between affect and the underlying mood, resulting in incongruent emotional expression disproportionate to the underlying emotional experience and without both the expected biological symptoms of a mood disorder and the required time duration. The uncontrollable reaction occurs in response to non-specific stimuli, in the absence of a corresponding change in mood or loss of voluntary control of facial expression.

PBA has traditionally been considered a disconnection syndrome resulting in the loss of cortical or brainstem inhibition of a putative centre for laughing and crying, possibly due to lesions in the cerebro-ponto-cerebellar pathways which are involved in appropriate adjustment to social and cognitive contexts. Furthermore, a widespread increased pattern of lesions including the brainstem, and inferior frontal and parietal lobes, areas acknowledged to be involved in unconscious involvement of emotional expression, has been noted in one small (n=14) MRI study. It has also been postulated that the monoaminergic neurotransmitter systems may be implicated, as dramatic improvements have been noted after treatments with agents acting primarily on these systems, such as SSRIs and dextromethorphan.

Rating scales to detect and measure severity of PBA are available and include the self-report Center for Neurologic Study-Lability Scale. Treatment should be considered if the syndrome is associated with a high degree of social or occupational disability. A combination of dextromethorphan and quinidine with effects on serotonin and on sigma-1 receptors, glutamate and hepatic metabolism blockade (quinidine) to increase bioavailability has demonstrated significant benefits for reducing emotional intensity and responses, and is licensed by both the Food and Drug Administration in the United States of America and the European Medicines Agency. Clinical benefits have been associated with SSRIs (fluoxetine, fluvoxamine, citalopram and sertraline) at low therapeutic doses with rapid improvement in symptoms including within the first week of treatment, and are probably the first-line treatment. Other antidepressants associated with efficacy in the treatment of PBA include SNRIs, mirtazapine, reboxetine (a noradrenaline reuptake inhibitor) and TCAs (amitriptyline, desipramine and nortriptyline). Additional agents including levodopa and amantadine (enhanced cerebral dopamine transmission), a combination of dextromethorphan and quinidine, and the mood stabiliser lamotrigine have also been associated with some clinical benefits in PBA. Care is required with the administration of these treatments given the large array of adverse effects that may occur, as detailed above.

Twenty percent of patients with MS have been reported to suffer with emotional lability, defined as an excessive but generally brief emotional response to a minor stimulus, and management is similar to that used for PBA.

The presence of euphoria in MS (also known as ‘euphoria sclerotica’) is a well-established phenomenon and indicates a subjective state of physical well-being with a lack of concern at one’s associated physical disability. Prevalence rates of up to 25% have been noted. The presence of euphoria in MS has been associated with disease progression, and extensive neuropsychopathological lesions, particularly in the frontal lobe, although there is a paucity of MRI studies to date examining this phenomenon (table 3).

Euphoria can present in a similar fashion to hypomania or mania; however, euphoria is not associated with overactivity, speech disturbance or psychotic symptoms. It is strongly associated with cognitive impairment and is often untreated due to the lack of subjective distress. More substantial personality changes including irritability, emotional lability and apathy can also be found in this cohort and are associated with extensive neuroanatomical abnormalities, with both the localization and extentiveness of these lesions determining the characteristics of personality change (table 2).

REFERENCES


Neuropsychiatric signs and symptoms occur frequently in individuals with MS, either as the initial presenting complaint prior to a definitive neurological diagnosis or more commonly with disease progression. However, the pathogenesis of these comorbid conditions remains unclear, and it remains difficult to accurately elucidate if neuropsychiatric symptoms or conditions are indicators of MS illness severity. Furthermore, both the disease process and treatments of MS can adversely impact on individuals’ mental health. It should also be noted that a significant proportion of MS sufferers do not exhibit neuropsychiatric sequelae. This may be related in part to the ‘theory of resilience,’ where an individual develops an ability to maintain psychological well-being and ability to function in the face of adversity, or ‘post-traumatic growth,’ where individuals experience positive psychological changes in response to a challenging situation, although of course many very resilient individuals with MS exhibit significant neuropsychiatric sequelae. Optimum treatment of neuropsychiatric symptoms usually requires an interdisciplinary approach, with input from both neurological and psychiatric services. Management strategies include the optimisation of disease-modifying agents, reducing doses of iatrogenic agents where possible, initiating psychotropic agents that are least likely to exacerbate physical symptoms and the addition of appropriate psychotherapeutic interventions.

Contributors RM: study design, methodology, write-up; SD: study design, write-up; TC: study design, review of article; CMcD: study design, review of article; BH: study design, write-up, review of article.

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