

## REVIEW

## Neuropsychiatric syndromes of multiple sclerosis

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**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.<sup>1</sup> 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%).<sup>2,3</sup> 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 neuropsychiatric 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.<sup>4</sup> Almost 50% of all patients with MS will experience a clinically significant depressive episode following the onset of MS during their lifetime.<sup>5,6</sup> Such episodes are often under-recognised and undertreated.<sup>1,7,8</sup> 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.<sup>6</sup> Those 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).<sup>9</sup>

Suicide is a significant cause of mortality with a 3% rate of completed suicide in individuals with MS,<sup>10</sup> 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.<sup>4,11–13</sup> 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.<sup>14</sup> 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.<sup>9,14</sup>

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,<sup>15–19</sup> while others have demonstrated an association between MDD and MS duration<sup>20</sup> and disease progression.<sup>21,22</sup> 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.<sup>23,24</sup> 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.<sup>10</sup>

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

Neuropsychiatric disorder	Principal presenting symptoms	Treatment
<b>Depression</b>	<ul style="list-style-type: none"> <li>▶ Pervasive low mood</li> <li>▶ Diurnal mood variation</li> <li>▶ Fatigue</li> <li>▶ Functional change</li> <li>▶ Pessimism/negative thinking patterns</li> <li>▶ Suicidal ideation</li> </ul> Iatrogenic depressive symptoms secondary to use of corticosteroids, baclofen, dantrolene and tizanidine	SSRIs are first line (fluoxetine, sertraline) TCAs—desipramine SNRIs especially if comorbid pain (venlafaxine, duloxetine) Mirtazapine (less sexual dysfunction) Psychotherapy—CBT, supportive, mindfulness, IPT, exercise and relaxation techniques Lithium augmentation (diuresis and polyuria may be issues) ECT for treatment-resistant cases but may increase risk of MS relapse
<b>Bipolar disorder</b>	<ul style="list-style-type: none"> <li>▶ Elated mood</li> <li>▶ Increased energy</li> <li>▶ Talkativeness</li> <li>▶ Overfamiliarity</li> <li>▶ Psychomotor agitation</li> <li>▶ Disinhibition</li> <li>▶ Impulsivity</li> <li>▶ Insomnia</li> </ul>	Lithium (risk of diuresis) Sodium valproate mania with psychotic symptoms—risperidone, quetiapine, olanzapine, ziprasidone If steroid-induced mania, consider lithium, phenytoin, olanzapine and/or reduced dose of steroids
<b>Psychosis</b>	<ul style="list-style-type: none"> <li>▶ Hallucinations and delusions</li> <li>▶ Irritability and agitation</li> <li>▶ Sleep disturbance and grandiosity</li> <li>▶ Blunted affect, flight of ideas, depression, reduced self-care and pressured speech</li> <li>▶ More complex delusions occasionally (erotomaniac, nihilistic and misidentification)</li> </ul>	Atypical antipsychotics <ul style="list-style-type: none"> <li>▶ Risperidone</li> <li>▶ Clozapine</li> <li>▶ Aripiprazole</li> <li>▶ Quetiapine</li> <li>▶ Ziprasidone</li> </ul> Typical antipsychotics (ie, chlorpromazine may worsen balance) Benzodiazepines (may help sedation but may worsen cognitive impairment)
<b>Anxiety disorders</b>	<ul style="list-style-type: none"> <li>▶ GAD</li> <li>▶ Panic disorder</li> <li>▶ OCD</li> <li>▶ Social anxiety disorder</li> <li>▶ Simple phobia (self-injection anxiety)</li> </ul> Anxiety symptoms associated with underlying condition	SSRIs are first-line agents Other options include <ul style="list-style-type: none"> <li>▶ Venlafaxine</li> <li>▶ Buspirone</li> <li>▶ Pregabalin</li> <li>▶ Gabapentin</li> <li>▶ Beta-blockers</li> <li>▶ Benzodiazepines (short-term only)</li> </ul>
<b>Substance misuse</b>	<ul style="list-style-type: none"> <li>▶ Increased depression</li> <li>▶ Increased suicidal ideation</li> <li>▶ Exacerbate cognitive deficits</li> <li>▶ Coordination difficulties</li> <li>▶ Interact with MS treatments</li> <li>▶ Heightened codependence on carer or family</li> </ul> Symptoms in line with underlying condition	Counselling services appropriate for the substance of misuse Consider anticraving agents such as acamprostate
<b>Pseudobulbar affect and euphoria</b>	<ul style="list-style-type: none"> <li>▶ Incongruent emotional expression in response to a non-specific stimulus</li> <li>▶ Emotions (laughing/crying) disproportionate to the underlying emotional experience</li> <li>▶ Absence of voluntary control of facial expression</li> </ul>	TCAs (amitriptyline, desipramine, nortriptyline) SSRIs Levodopa Amantadine Dextromethorphan and quinidine

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,<sup>22</sup> a finding frequently replicated in MDD alone.<sup>25</sup> Furthermore, failure of cortisol suppression has been associated with increased numbers of gadolinium-enhancing lesions.<sup>26</sup> 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.<sup>11</sup> 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.<sup>23 27</sup>

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.<sup>28</sup> However, subsequent studies have failed to confirm an association.<sup>29–31</sup> 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.<sup>2</sup> 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.<sup>32</sup>

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.<sup>33–38</sup> For instance, increased numbers of brain lesions have been demonstrated in the frontal,<sup>33–36</sup> right parietal and right temporal lobes<sup>37, 38</sup> 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 MS.<sup>37</sup> 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.<sup>34, 39–42</sup>

Reduced total grey matter,<sup>35</sup> frontal lobe<sup>42–44</sup> and hippocampal volume<sup>39, 40</sup> have been found in individuals with MS and comorbid MDD, consistent with findings in individuals with depression without comorbid MS.<sup>45</sup> 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.<sup>46</sup>

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.<sup>47–50</sup> 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 a lifetime diagnosis of MDD had never received either a psychological or pharmacotherapeutic intervention.<sup>14</sup> Because of the comorbidity of depressive symptoms and active symptoms of MS, caution is required with the interpretation of psychometric instruments for the measurement of MDD. However, a number of user-friendly screening tools including the Beck Fast Screen for Depression in Medically Ill Patients, the Hospital Anxiety and Depression Scale and the Beck Depression Inventory have been validated for use in MS patients with MDD.<sup>51–53</sup> There is a paucity of well-designed randomised controlled trials (RCT) examining pharmacotherapeutic and/or psychotherapeutic options for MDD in individuals with MS. However, a number of clinical strategies have demonstrated a clinical benefit in this cohort, including most notably the selective serotonin reuptake inhibitor (SSRI) sertraline,<sup>17</sup> the tricyclic antidepressant (TCA) desipramine<sup>54</sup> and cognitive behavioural therapy (CBT).<sup>55, 56</sup> An appropriate first-line pharmacological strategy for MDD is the utilisation of SSRIs, given their relatively good tolerability and relatively benign side effect profile.<sup>17, 57</sup> Another putative benefit relates to evidence that SSRIs can reduce axonal degradation via induction of glycogenolysis in astrocytes, thereby increasing the energy source to neurons,<sup>58</sup> and potentially reducing the production of new enhancing lesions,<sup>59</sup> while also increasing cAMP production initiating a reduction of inflammation and demyelination.<sup>60</sup> Mirtazapine, due to its low propensity for sexual dysfunction and inhibition of cerebral proinflammatory cytokine

production, is a viable alternative to SSRIs, although caution is required due to its sedative and weight increasing effects.<sup>35</sup>

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);<sup>61</sup> and bupropion (for depression and reduced risk of sexual dysfunction).<sup>61</sup> 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.<sup>62</sup> 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.<sup>63</sup> 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.<sup>64</sup> 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,<sup>65</sup> optimising disease-modifying agents should also be considered as a viable initial treatment option.<sup>2</sup> Finally, agents demonstrated to have an effect on intractable fatigue may be associated with a potential mood enhancing qualities including amantadine, pemoline, modafinil and armodafinil.<sup>66–68</sup>

## BIPOLAR AFFECTIVE DISORDER

The prevalence of BPAD in MS is approximately twice that in the general population,<sup>69</sup> with rates of 0.3%–2.4% found,<sup>1, 70</sup> although rates as high as 10% have been reported.<sup>71, 72</sup> 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.<sup>73</sup> 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.<sup>74, 75</sup> Other agents have also been implicated in causing episodes of (hypo)mania including baclofen, dantrolene, tizanidine and psychoactive substances.<sup>9</sup> Drug-induced manic symptoms appear generally to be dose dependent, occur early in treatment and are usually responsive to treatment.<sup>76</sup> Manic symptoms (non-medication induced) may precede other neurological signs but more commonly become evident approximately 1 year after diagnosis,<sup>77</sup> and include increased energy, pressured or rapid speech, overfamiliarity, psychomotor agitation, disinhibition, insomnia and impulsivity.<sup>78</sup>

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,<sup>79</sup> within which certain haplotypes are over-represented in patients with MS.<sup>80</sup> Other aetiological factors include psychological and adjustment processes associated with underlying personality

**Table 2** Structural MRI findings in MS and comorbid major depressive disorder

Study group	Patient group		Healthy controls	MRI Scanner, slices (mm), method	Psychometric instruments	Disability status	Findings
	MS	MS+comorbid psychiatric disorder					
Reischies <i>et al</i> (1998) <sup>126</sup>	46	Neurologist ratings (depression=11%, euphoria=11%, irritability=22%, impaired judgement=9%, reduced drive=2%, lability of affect=11%)	–	0.35 T Magnetom, 10 mm slices Radiological evaluation of lesions	No standard instruments, 7-point scale for each of five symptoms (depression, euphoria, irritability, impaired judgement, reduced drive, with lability of mood scored for extent of occurrence of depressed mood and euphoria simultaneously)	–	The presences of lesions in the frontal lobes were related to higher total scores of psychopathology. Periventricular lesions associated with lability of affect, disorders of judgement, depression and euphoria
Möller <i>et al</i> (1994) <sup>15</sup>	19	6	–	0.5 T Scanner (make not given), 5 mm slices, enhanced with gadolinium-pentetic acid. Radiological evaluation of lesions, video display ball and track cursor method used for VBR and CC measurements	Fatigue Severity Scale HDRS MADRS	Mean EDSS depressed group=3.2 and in non-depressed group=3.1	No association between scores of depression and lesion load, gadolinium-enhanced lesions or VBR
Tsolaki <i>et al</i> (1994) <sup>127</sup>	22	Mean HDRS=11.8 (SD=6) and not significantly greater than controls	15	0.5 T GE Scanner, 5 mm slices Radiological evaluation of lesions and measurement of CC	HDRS (several cognitive scales)	Mean KDS score=3.3	No correlation between HDRS and lesion load or volume of the CC
Sabatini <i>et al</i> (1996) <sup>128</sup>	10 (All RR)	10 (All RR)	–	1.5 T Siemens Magnetom Scanner, 6 mm slices with 0.3 mm gap. Radiological evaluation of lesions. SPECT	BDI HDRS SAS	–	No difference in number, size, location or area of demyelinating lesions SPECT demonstrated higher CBF in left limbic cortex and lower CBF in right limbic cortex in depressed group
Fassbender <i>et al</i> (1998) <sup>36</sup>	23 (All RR)	4/23 individuals fulfilled DSM-III-R criteria for major depression	17	1.5 T superconducting unit, Siemens Scanner, enhanced with gadolinium-pentetic acid. Radiological evaluation of lesions	HAS HDRS	Mean EDSS=3.5	Individuals with gadolinium-enhancing lesions had higher scores of depression and anxiety
Diaz-Olavarrieta <i>et al</i> (1999) <sup>124</sup>	44	42/45 had symptoms on NPI (dysphoria=79%, agitation=40%, anxiety=37%, apathy=20%, euphoria=13%, irritability=13%, hallucinations=10%, delusions=7%)	25 (84% had no symptoms based on the NPI)	Gadolinium-enhanced MR images Radiological evaluation of lesions	MMSE NPI	Mean EDSS=3.3	Only euphoria and hallucinations correlated with the severity of demyelination
Bakshi <i>et al</i> (2000) <sup>36</sup>	29 (RR=23, SP=6)	19 (RR=10, SP=9)	–	1.5 T Philips Gyroscan Scanner, 5 mm slices, radiological evaluation of lesions and atrophy	BDI HDRS	Mean EDSS=4.3 for depressed group and 2.9 for non-depressed group	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

Continued

Table 2 Continued

Study group	Patient group		MRI Scanner, slices (mm), method	Psychometric instruments	Disability status	Findings
	MS	MS+comorbid psychiatric disorder				
Berg <i>et al</i> (2000) <sup>37</sup>	47 (RR=20, SP=23, PP=4)	31 (RR=17, SP=10, PP=4)	1.5 T Siemens Magnetom Vision or 1.5 T Gyroscan 15 Philips Scanner, 5 mm slices, radiological evaluation of lesions	BDI Fatigue Severity Scale GHQ HDRS MADRS	Median EDSS=6 for depressed group and 5 for non-depressed group	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
Pujol <i>et al</i> (2000) <sup>29</sup>	45*	9	1.5 T Sigma Systems, GE Scanner, 5 mm slices with a 2.5 mm gap, evaluation of myelin loss through coronal inversion recovery sequence Tissue segmentation	BDI	Mean EDSS=3.3	Lesions in the left arcuate fasciculus were significantly related to affective symptoms, somatic complaints and BDI scores
Zorzon <i>et al</i> (2001) <sup>34</sup>	77 (predominantly RR, but exact figures not given)†	18	1.5 T Philips, Gyroscan Scanner, 5 mm slices, semiautomated measurements of lesion load and regional brain volumes	FIM HAI HDRS MMSE	Median EDSS=2.0	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
Benesova <i>et al</i> (2003) <sup>33</sup>	10	10	1.5 T Scanner Radiological evaluation of lesions	HDRS MADRS SDS	Mean EDSS=2.5	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
Feinstein <i>et al</i> (2004) <sup>35</sup>	19 (RR=7, SP=10, PP=2)	21 (RR=8, SP=12, PP=1)	1.5 T Sigma Systems, GE Scanner, 3 mm slices, Semiautomated measurements of lesion load and regional brain volumes	BDI HDRS	Mean EDSS 4.7 in depressed group and 4.6 in non-depressed group)	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
Feinstein <i>et al</i> (2010) <sup>43</sup>	32 (BDI<19) (13 taking antidepressants) (RR=26, SP=4, PP=2)	30 (BDI>19) (20 taking antidepressants) (RR=23, SP=7)	1.5 T Sigma Systems Scanner, 1.2–1.4 mm slices, manual tracing of lesions and semiautomated brain region extraction DTI analysis, FA and MD maps attained	BDI	Mean EDSS in depressed group=3.5 and 2.5 in non-depressed group	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
Gold <i>et al</i> (2010) <sup>39</sup>	21 (BDI<13) (All RR)	8 (BDI>13) (All RR)	3 T Siemens Scanner, 1 mm slices. Automated measurement of brain volume and manual tracing of lesions. Segmentation of hippocampus	BAI BDI	Mean EDSS=2.5	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)

Continued

Table 2 Continued

Study group	Patient group		MRI Scanner, slices (mm), method	Psychometric instruments	Disability status	Findings
	MS	MS+comorbid psychiatric disorder				
Papadopolou <i>et al</i> (2013) <sup>41</sup>	91	Of 89 tested, mean CES-D=13.6, SD=10.5	1.5 TAvanto, Siemens Scanner, 1.5mm slices. Radiological evaluation of lesions and semiautomated mechanism for lesion volume used	CES-D (several cognitive scales)	Median EDSS=3.6	No association with lesion load or volume (WM or cortical lesions) and depression scores
Gobbi <i>et al</i> (2014) <sup>42</sup>	54	69	3 T scanner Automatic segmentation technique for evaluation of lesions VBM	MADRS	Median EDSS in depressed group=2.5, and 2 in non-depressed group	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
Gold <i>et al</i> (2014) <sup>40</sup>	83 (CES-D<20) (women)	26 (CES-D>20) (women)	3 T Scanner, 1 mm slices, a number of scanners used SIENA X programme generated hippocampal volumes Shape analysis with surface mesh modelling	CES-D	Mean EDSS 3.36 in depressed group and 3.08 in non-depressed group	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)
Kern <i>et al</i> (2015) <sup>130</sup>	27 RR	4/27 RR had severe depressive symptoms	3 T Scanner Trackvis Deterministic fibre tracking	EDSS BDI-II	Mean EDSS 2.5	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
Shen <i>et al</i> (2014) <sup>47</sup>	15 RR	9/15 depressive symptoms	3 T Scanner TBSS	EDSS HAM-D	Mean EDSS 1.73	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
Hanken <i>et al</i> (2015) <sup>49</sup>	49 RR	37/49 cognitive fatigue patients with depressive symptoms	3 T Scanner NeuroLab3.531 Fibre tracking	EDSS BDI	Mean EDSS (3.2 CF/4.1 CNF)	Interaction effects between BDI scores and WM between prefrontal cortex and pons

Continued

Table 2 Continued

Study group	Patient group			MRI Scanner, slices (mm), method	Psychometric instruments	Disability status	Findings
	MS	MS+comorbid psychiatric disorder	Healthy controls				
Nigro <i>et al</i> (2015) <sup>50</sup>	22	20	16	3 T Scanner LST lesion segmentation toolbox Brain connectivity toolbox	EDSS BDI-II	Mean EDSS (2.3 non-MDD, 2.8 MDD)	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
Nygaard <i>et al</i> (2015) <sup>46</sup>	61 RR	16/61	61	1.5 T Scanner Cortical thickness, surface area and volume	EDSS BDI	Mean 1.9	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

\* Study includes the individuals investigated in Pujol *et al* (1997).<sup>729</sup>

† A 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*).<sup>44</sup>  
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; HAS, Hamilton Anxiety Scale; HC, healthy controls; HDRS, Hamilton Depression Rating Scale; KDS, Kurtzke Disability Status 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.

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

Study group	Patient group			MRI Scanner, slices (mm), method	Psychometric instruments	Disability status	Findings
	MS	MS+comorbid psychiatric disorder	Healthy controls				
Ron and Logsdail (1989) <sup>83</sup>	116	50/116 (adjustment D/O=22, depression=12 bipolar D/O=5, delusional D/O=4, atypical psychosis=3, anxiety D/O=2, organic disorder=1)	40 HC 48 PD (11=arthritic condition, 37=neurological condition with no brain involvement) (depression=5, adjustment D/O=3)	0.5 T superconducting system Scanner, 10 mm slices with 2 mm gap, radiological evaluation of lesions	BDI CIS SSSI MMSE	—	Elation correlated with widespread MRI abnormalities Pathology in temporo-parietal region correlated with flattened affect, delusions and thought disorder
Feinstein <i>et al</i> (1992) <sup>84</sup>	10	10 (mania with psychosis)	—	0.5 T Picker Scanner, 5 mm slices, radiological evaluation of lesions	PSE SCL	Mean EDSS=4.9	Trends reported for greater total lesions in left trigone and areas surrounding the third ventricle in group with psychosis The psychosis group had a higher total lesion score and greater lesions in periventricular areas, predominantly around the temporal horn Neurological symptoms preceded onset of psychosis No significant correlations were found between individual psychotic symptoms and site of MRI lesions
Feinstein <i>et al</i> (1992) <sup>131</sup>	19 (RR=12, CP=7) CIL=16	3/35 individuals had comorbid psychiatric disorders (1=psychosis, 2=euphoria)	30	0.5 T Picker Scanner, 5 mm slices Radiological evaluation of lesions	CIS HADS SSSI	Mean EDSS=3.5	No significant findings with quantitative lesion score and psychiatric status
Diaz-Olavarrieta <i>et al</i> (1999) <sup>124</sup>	44	42/45 had symptoms on NPI (dysphoria=79%, agitation=40%, anxiety=37%, apathy=20%, euphoria=13%, irritability=13%, hallucinations=10%)	25 (84% had no symptoms based on the NPI)	Gadolinium-enhanced MR images Radiological evaluation of lesions	MMSE NPI	Mean EDSS=3.3	Only euphoria and hallucinations correlated with the severity of demyelination
Benedict <i>et al</i> (2004) <sup>123</sup>	37 (RR=30, SP=7)	31/37 had NPI administered	—	1.5 T Philips Gyroscan Scanner, 5 mm slices	NPI	Mean EDSS=2.5	Euphoria, depression and agitation were correlated with lesion volume, and euphoria was correlated with global brain atrophy; however, these correlations were non-significant when cognitive function was controlled for
Ghaffar <i>et al</i> (2008) <sup>112</sup>	14 (RR=7, SP=5, PP=2)	14 PBA (RR=3, SP=7, PP=4)	—	1.5 T Sigma Systems, GE Scanner, 1.2–1.4 mm slices, lesion analysis, measurement of GM, WM, CSF	—	Mean EDSS in PBA=6.0 and in MS alone=4.6 (p=0.08)	Increased brain lesions in the brainstem, left inferior parietal lobe, and left and right medial and inferior frontal lobes No difference in brain atrophy between the groups

BDI, Beck Depression Inventory; CIL, clinically isolated lesions; 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.

traits and coping mechanisms.<sup>81 82</sup> 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.<sup>83 84</sup>

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 well-recognised mood-stabilising qualities, is also associated with potential disease-modifying effects in MS,<sup>62</sup> and is associated with a reduced risk of suicide,<sup>85</sup> and may represent a viable therapeutic option, notwithstanding its association with polyuria in patients with MS-associated bladder dysfunction. Caution in the use of antipsychotics is required due to their potential adverse effects



on balance, coordination, incontinence and fatigue. Corticosteroid-induced mania can be managed with lithium, olanzapine and phenytoin,<sup>9</sup> without the requirement for steroid discontinuation (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 population,<sup>86</sup> with over 90% of individuals having symptoms of MS prior to the onset of psychosis.<sup>87</sup> 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 marginally decreased risk of schizophrenia in individuals with MS.<sup>88</sup> 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 persecutory delusions and auditory hallucinations, whereas an affective psychotic disorder such as mania with psychosis or a steroid-induced psychosis may be associated with grandiose or erotomanic delusion.<sup>89</sup> The clinical presentation of symptoms has been purported to be related to MS neuropathology in periventricular white matter, and temporal and fronto-temporal regions.<sup>86</sup> 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,<sup>90</sup> psychosocial circumstances and medicinal cannabis used for individuals with MS alone.<sup>22</sup> There is limited evidence for genetic factors playing a significant role in the development of psychotic illness.<sup>89</sup>

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 alleviation of psychosis, is suggested with trials indicating clinical benefit from a variety of psychotropic agents including risperidone,<sup>91</sup> ziprasidone,<sup>92</sup> clozapine,<sup>93</sup> aripiprazole,<sup>94</sup> quetiapine<sup>61</sup> and olanzapine,<sup>61</sup> although clozapine is predominantly prescribed for treatment-resistant psychosis due to its association with agranulocytosis.<sup>61</sup> An additional rationale for treatment with risperidone and quetiapine relates to their demonstrated disease-modifying characteristics in EAE mice models.<sup>95,96</sup> There are also limited case report data demonstrating an amelioration of psychotic symptoms with disease-modifying agents.<sup>2</sup>

The choice of antipsychotic agent should consider the individual's clinical characteristics (MS and psychosis) and the potential 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.<sup>97</sup> A number of risk factors for anxiety disorders have been identified that potentially relate to MS, including being newly diagnosed with MS, increased MS disease activity, experiencing pain, fatigue or sleep disturbance.<sup>22</sup> Additional risk factors noted include female gender, social isolation, a previous

history of suicidal ideation, a past or present diagnosis of MDD and alcohol or psychoactive substance misuse.<sup>22,98</sup> Anxiety symptoms can present with clinical characteristics similar to those found during a relapse of MS and can often be related to the underlying disease process itself.<sup>99</sup> The coexistence of depressive and anxiety symptoms has been found to be associated with increased rates of physical symptomatology, social dysfunction and suicidal ideation.<sup>100</sup>

In recent years, since the development of self-injectable DMTs, a phenomenon known as 'self-injection anxiety' has emerged. This anxiety can affect up to 50% of patients, and similar to simple (specific) phobias, this condition is responsive to CBT.<sup>101</sup> Caution is required in relation to diagnosis of 'self-injection anxiety' when patients receive treatment with glatiramer acetate, given its demonstrated adverse effect profile including anxiety, dyspnoea, palpitations and tachycardia.<sup>102</sup>

There are no published RCTs specifically addressing the pharmacological treatment of anxiety disorders in MS. However, as with MDD, SSRIs should be considered first line, with venlafaxine, buspirone, pregabalin, gabapentin and beta-blockers as further options in treatment-resistant cases.<sup>61</sup> Benzodiazepine use should be restricted to relief of acute and severe anxiety. Caution with their use is required due to their adverse effect profile of sedation and mild cognitive impairment and should not be prescribed for more than a 4-week period to avoid dependence.<sup>61</sup> Non-pharmacological strategies including stress management and CBT should also be considered for the management of anxiety disorders in patients with MS.<sup>103</sup> An additional benefit of treating anxiety in patients with MS may relate to a consequent reduction in the development of new MRI brain lesions,<sup>103</sup> although this association requires replication.

## PSYCHOACTIVE SUBSTANCE MISUSE

Patients with MS have been reported to have a 13.6% lifetime prevalence of alcohol abuse or dependence.<sup>99</sup> In addition to the known physical manifestations of alcohol abuse or dependence, other deleterious consequences may include increased depressive symptomatology,<sup>104</sup> suicidal ideation<sup>27</sup> and coordination difficulties.<sup>22</sup> 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.<sup>105</sup> 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.<sup>105</sup>

Cannabis use has been reported to alleviate neurological symptoms including spasticity, pain, tremor, insomnia and bladder dysfunction, and its use has been associated with individuals with greater physical disability and dependency.<sup>106</sup> Although clinical trials of cannabis have failed to consistently detect significant beneficial effects,<sup>107</sup> cannabis use was detected in 33% of individuals with MS in one study.<sup>106</sup> Certain synthetic cannabinoid 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.<sup>22,108,109</sup>

## 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.<sup>110</sup> 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.<sup>76</sup> 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.<sup>9</sup>

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.<sup>22 111</sup> 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.<sup>112</sup> 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.<sup>113 114</sup>

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.<sup>113</sup> 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.<sup>114 115</sup> 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,<sup>113</sup> 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).<sup>113 116</sup> 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.<sup>117 118</sup> Care is required with the administration of these treatments given the large array of adverse effects that may occur, as detailed above.

Twenty per cent 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,<sup>119</sup> 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.<sup>120</sup> Prevalence rates of up to 2.5% have been noted.<sup>121</sup> The presence of euphoria in MS

has been associated with disease progression,<sup>122</sup> and extensive neuropathological lesions, particularly in the frontal lobe,<sup>77 123</sup> although there is a paucity of MRI studies to date examining this phenomenon (table 3).<sup>77</sup>

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.<sup>61</sup> 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 extensiveness of these lesions determining the characteristics of personality change (table 2).<sup>124</sup>

## SUMMARY

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 individual’s 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,<sup>22</sup> or ‘post-traumatic growth,’ where individuals experience positive psychological changes in response to a challenging situation,<sup>125</sup> 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.

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## Neuropsychiatric syndromes of multiple sclerosis

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