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.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 neuropsychiatric syndromes of MS was conducted in Medline, PsycINFO and Scopus databases.

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 underrecognised 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 Those symptoms which may more accurately indicate a comorbid depressive episode include a pernicious 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).

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,15–19 while others have demonstrated an association between MDD and MS duration20 and disease progression.21–22 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.23 24 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.25

Aetiological factors implicated with comorbid MDD include hypothalamic-pituitary-adrenal axis dysfunction, medications used in the treatment of
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 associated with increased numbers of gadolinium-enhancing lesions. Twenty-five percent of individuals regarding the risk of interferon-induced 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 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.31–38 For instance, increased numbers of brain lesions have been demonstrated in the frontal,31–34 right parietal and right temporal lobes31–38 in individuals with comorbid MDD. It has thus been suggested that lesions in brain regions that are projections of the basolimbic system produce a disruption of limbic-cortical pathways and increase the risk of MDD in individuals with MS.3 Moreover, 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.39–42

Reduced total grey matter,43 frontal lobe42–44 and hippocampal volume39–41 have been found in individuals with MS and comorbid MDD, consistent with findings in individuals with depression without comorbid MS.6 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.66

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.47–50 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.14 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.51–53 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,17 the tricyclic antidepressant (TCA) desipramine54 and cognitive behavioural therapy (CBT).55–56 An appropriate first-line pharmacological strategy for MDD is the utilisation of SSRIs, given their relatively good tolerability and relatively benign side effect profile.17,18 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,47 and potentially reducing the production of new enhancing lesions,59 while also increasing cAMP production initiating a reduction of inflammation and demyelination.60 Mirtazapine, due to its low propensity for sexual overfamiliarity, psychomotor agitation, disinhibition, insomnia and impulsivity.5

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);61 and bupropion (for depression and reduced risk of sexual dysfunction).62 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 (EAEnote) (the most frequently used animal model of MS) and reducing demyelination, microglia activation and leucocyte infiltration in the spinal cord of mice.63 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.64 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.65 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,66 optimising disease-modifying agents should also be considered as a viable initial treatment option.67 Finally, agents demonstrated to have an effect on intractable fatigue may be associated with a potential mood enhancing qualities including amantadine, pemoline, modafinil and armodafanil.68–68

**BIPOLAR AFFECTIVE DISORDER**

The prevalence of BPAD in MS is approximately twice that in the general population,69 with rates of 0.3%–2.4% found,70 although rates as high as 10% have been reported.71,72 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.73 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.74,75 Other agents have also been implicated in causing episodes of (hypo)mania including baclofen, dantrolene, tizanidine and psychoactive substances.76 Drug-induced manic symptoms appear generally to be dose dependent, occur early in treatment and are usually responsive to treatment.77,78 Manic symptoms (non-medication induced) may precede other neurological signs but more commonly become evident approximately 1 year after diagnosis,79 and include increased energy, pressured or rapid speech, overfamiliarity, psychomotor agitation, disinhibition, insomnia and impulsivity.80

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,81 within which certain haplotypes are over-represented in patients with MS.82 Other aetiological factors include psychological and adjustment processes associated with underlying personality.
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<tr>
<td>Reischies et al (1988)</td>
<td>46</td>
<td>Neurologist ratings (depression=11%, euphoria=11%, irritability=22%, impaired judgement=9%, reduced drive=2%, lability of affect=11%)</td>
<td>–</td>
<td>0.35 T Magnetom, 10 mm slices Radiological evaluation of lesions</td>
<td>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)</td>
<td>–</td>
<td>The presence 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.</td>
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<td>Möller et al (1994)</td>
<td>19</td>
<td>6</td>
<td>–</td>
<td>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</td>
<td>Fatigue Severity Scale HDRS MADRS</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>Tsolaki et al (1994)</td>
<td>22</td>
<td>Mean HDRS=1.8 (SD=6) and not significantly greater than controls</td>
<td>15</td>
<td>0.5 T GE Scanner, 5 mm slices Radiological evaluation of lesions and measurement of CC</td>
<td>HDRS (several cognitive scales)</td>
<td>Mean KDSS score=3.3</td>
<td>No correlation between HDRS and lesion load or volume of the CC</td>
</tr>
<tr>
<td>Sabatini et al (1996)</td>
<td>10</td>
<td>(All RR)</td>
<td>10 (All RR)</td>
<td>1.5 T Siemens Magnetom Scanner, 6 mm slices with 0.3 mm gap. Radiological evaluation of lesions. SPECT</td>
<td>BDI HDRS SAS</td>
<td>–</td>
<td>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.</td>
</tr>
<tr>
<td>Fasbender et al (1998)</td>
<td>23</td>
<td>(All RR)</td>
<td>4/23 individuals fulfilled DSM-IIIR criteria for major depression</td>
<td>1.5 T superconducting unit, Siemens Scanner, enhanced with gadolinium-pentetic acid. Radiological evaluation of lesions</td>
<td>HAS HDRS</td>
<td>Mean EDDS=3.5</td>
<td>Individuals with gadolinium-enhancing lesions had higher scores of depression and anxiety.</td>
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<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%, delusions=7%)</td>
<td>25 (84% had no symptoms based on the NPI)</td>
<td>Gadolinium-enhanced MR images Radiological evaluation of lesions</td>
<td>MMSE NPI</td>
<td>Mean EDDS=3.3</td>
<td>Only euphoria and hallucinations correlated with the severity of demyelination.</td>
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<tr>
<td>Bakshi et al (2000)</td>
<td>29</td>
<td>(RR=23, SP=6)</td>
<td>19 (RR=10, SP=9)</td>
<td>1.5 T Philips Gyroscan Scanner, 5 mm slices, radiological evaluation of lesions and atrophy</td>
<td>BDI HDRS</td>
<td>Mean EDDS=4.3 for depressed group and 2.9 for non-depressed group</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>
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<tr>
<th>Study group</th>
<th>MS or comorbid psychiatric disorder</th>
<th>Healthy controls</th>
<th>Disability status</th>
<th>MRI</th>
<th>Psychometric instruments</th>
<th>Findings</th>
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<tr>
<td>Berg et al. (2000)</td>
<td>1.5 T Siemens Magnetom Vision or 1.5 T Gyroscan. 5 mm slices. Manual tracing of lesions. Radiological evaluation of lesions</td>
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<td>Ms + comorbid psychiatric disorder</td>
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<td>Healthy controls</td>
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<td>Zorzon et al. (2001)</td>
<td>1.5 T Philips, Gyroscan Scanner. 5 mm slices. Semiautomated measurements of lesion load and regional brain volumes. DTI analysis, FA and MD maps attained.</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>
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<td>Feinstein et al. (2004)</td>
<td>1.5 T Sigma Systems, GE Scanner. 3 mm slices. Manual tracing of lesions and semiautomated brain region extraction. DTI analysis, FA and MD maps attained.</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 group.</td>
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<td>Pujol et al. (2000)</td>
<td>1.5 T Sigma Systems, GE Sanner. 5 mm slices. Manual tracing of lesions and coronal T2 weighted inversion recovery sequence.</td>
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<td>BDIFatigue Severity ScaleGHQHDRSMADRS</td>
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<td>Median EDSS=6 for depressed group and 5 for non-depressed group. Higher lesion load in right temporal lobe in depressed group and right frontal lobe in non-depressed group. Lesion load correlated with BDI, HDRS and MADRS scores in the right temporal lobe.</td>
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<td>MSG+MDD group. MS+MDD group.</td>
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<td>1.5 T Sigma Systems, GE Scanner. 5 mm slices. Manual tracing of lesions and coronal T2 weighted inversion recovery sequence.</td>
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<td>Median EDSS=3.3</td>
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<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 group.</td>
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<td>Median EDSS=6 for depressed group and 5 for non-depressed group. Higher lesion load in right temporal lobe in depressed group and right frontal lobe in non-depressed group. Lesion load correlated with BDI, HDRS and MADRS scores in the right temporal lobe.</td>
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<td>Study group</td>
<td>Patient group</td>
<td>MS</td>
<td>MS+comorbid psychiatric disorder</td>
<td>Healthy controls</td>
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<tr>
<td>Papadopoulou et al (2013)</td>
<td>91</td>
<td>91</td>
<td>Of 89 tested, mean CES-D=13.6, SD=10.5</td>
<td>–</td>
<td>1.5 T Avanto, Siemens Scanner, 1.5mm slices. Radiological evaluation of lesions and semi-automated mechanism for lesion volume used</td>
<td>CES-D (several cognitive scales)</td>
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<td>Gobbi et al (2014)</td>
<td>54</td>
<td>69</td>
<td>90</td>
<td>3 T scanner</td>
<td>Automatic segmentation technique for evaluation of lesions VBM</td>
<td>MADRS</td>
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<tr>
<td>Goldi et al (2014)</td>
<td>83 (CES-D&lt;20) (women)</td>
<td>26 (CES-D&gt;20) (women)</td>
<td>–</td>
<td>3 T scanner, 1 mm slices, a number of scanners used SIENA X programme generated hippocampal volumes Shape analysis with surface mesh modelling</td>
<td>CES-D</td>
<td>Mean EDSS 3.36 in depressed group and 3.08 in non-depressed group</td>
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<tr>
<td>Kern et al (2015)</td>
<td>27 RR</td>
<td>20</td>
<td>4/27 RR had severe depressive symptoms</td>
<td>3 T Scanner</td>
<td>Trackvis Deterministic fibre tracking</td>
<td>EDSS</td>
</tr>
<tr>
<td>Shen et al (2014)</td>
<td>15 RR</td>
<td>15</td>
<td>9/15 depressive symptoms</td>
<td>3 T Scanner</td>
<td>TBSS</td>
<td>EDSS</td>
</tr>
<tr>
<td>Hanken et al (2015)</td>
<td>49 RR</td>
<td>14</td>
<td>37/49 cognitive fatigue patients with depressive symptoms</td>
<td>3 T Scanner</td>
<td>NeuroQlab3.531 Fibre tracking</td>
<td>EDSS</td>
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<td>Nigro et al. (2015)</td>
<td>22</td>
<td>20</td>
<td>16</td>
<td>3 T Scanner</td>
<td>EDSS</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>Nigro et al. (2015)</td>
<td>61</td>
<td>RR</td>
<td>16/61</td>
<td>1.5 T Scanner</td>
<td>EDSS</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).†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.).44 BDI, Beck Depression Inventory; CBF, cerebral blood flow; CC, corpus callosum; CES-D, Center for Epidemiological Studies Depression Scale; CID, 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; KDDSS, 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 risk of suicide, and may represent a viable therapeutic option, not withstanding 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.

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

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<td>Ron and Logsdail (1989)</td>
<td>116</td>
<td>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)</td>
<td>40 HC 48 PO (11=arthritis condition, 37=neurological condition with no brain involvement) (depression=5, adjustment D/O=3)</td>
<td>0.5 T superconducting system, 10 mm slices with 2 mm gap, radiological evaluation of lesions</td>
<td>BDI CIS SSSI MMSE</td>
<td>Elation correlated with widespread MRI abnormalities Pathology in temporo-parietal region correlated with flattened affect, delusions and thought disorder</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 EDSS=4.9</td>
</tr>
<tr>
<td>Feinstein et al (1992)</td>
<td>3/35 (RR=12, CP=7, CIL=16)</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 EDSS=3.5</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 Radiological evaluation of lesions</td>
<td>MMSE NPI</td>
<td>Mean EDSS=3.3</td>
</tr>
<tr>
<td>Benedict et al (2004)</td>
<td>37 (RR=30, SP=7)</td>
<td>31/37 had NPI administered</td>
<td>—</td>
<td>1.5 T Philips Gyroscan, 5 mm slices</td>
<td>NPI</td>
<td>Mean EDSS=2.5</td>
</tr>
<tr>
<td>Ghaffar et al (2008)</td>
<td>14 (RR=7, SP=5, PP=2)</td>
<td>14 PBA (RR=3, SP=7, PP=4)</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 EDSS in PBA=6.0 and in MS alone=4.6 (p=0.08)</td>
</tr>
</tbody>
</table>

**Study group**: healthy controls; **MS patients**: NPI, Neuropsychiatric Inventory; **MRI analysis**: 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.

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

- **Study group**: healthy controls; **MS patients**: NPI, Neuropsychiatric Inventory; **MRI analysis**: 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.

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on balance, coordination, incontinence and fatigue. Corticosteroid-induced mania can be managed with lithium, olanzapine and phenytoin,9 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,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 marginally 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 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 erotomaniac delusion.89 The clinical presentation of symptoms has been purported to be related to MS neuropathology in periventricular 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 circumstances and medicinal cannabis used for individuals with MS alone.22 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 alleviation of psychosis, is suggested with trials indicating clinical benefit from a variety of psychotropic agents including risperidone,91 ziprasidone,92 clozapine,93 aripiprazole,94 quetiapine95 and olanzapine.61 although clozapine is predominantly prescribed for treatment-resistant psychosis due to its association with agranulocytosis.41 An additional rationale for treatment with risperidone and quetiapine relates to their demonstrated disease-modifying characteristics in EAE mice models.65 96 There are also limited case report data demonstrating an amelioration of psychotic symptoms with disease-modifying agents.2

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.77 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.22 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.22 28 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.29 The coexistence of depressive and anxiety symptoms has been found to be associated with increased rates of physical symptomatology, social dysfunction and suicidal ideation.104

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.101 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.102

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.44 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.61 Non-pharmacological strategies including stress management and CBT should also be considered for the management of anxiety disorders in patients with MS.103 An additional benefit of treating anxiety in patients with MS may relate to a consequent reduction in the development of new MRI brain lesions,103 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.29 In addition to the known physical manifestations of alcohol abuse or dependence, other deleterious consequences may include increased depressive symptomatology,106 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 symptoms 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 significant beneficial effects,107 cannabis use was detected in 33% of individuals with MS in one study.106 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.22 108 109
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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.110 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.76 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.7

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.22 111 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.112 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.113 114

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.113 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.114 115 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,113 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).113 116 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.117 118 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,119 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.120 Prevalence rates of up to 25% have been noted.121 The presence of euphoria in MS has been associated with disease progression,122 and extensive neuropathological lesions, particularly in the frontal lobe,77 123 although there is a paucity of MRI studies to date examining this phenomenon (table 3).77

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.7 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).124

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,22 or ‘post-traumatic growth,’ where individuals experience positive psychological changes in response to a challenging situation,125 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; SO’D: 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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