Psychopathology in multiple sclerosis: diagnosis, prevalence and treatment

Ida S. Haussleiter, Martin Brüne and Georg Juckel

Therapeutic Advances in
Neurological Disorders

(2009) 2(1) 13–29

DOI: 10.1177/
1756285608100325

© The Author(s), 2009.

Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system. Demyelination of nerve fibres not only affects the motor and sensory systems functionally, but may also cause psychopathological signs and symptoms. In addition to the psychiatric manifestations of MS, many patients have reactive psychological problems that are often hard to distinguish from the ‘organic’ causation of psychopathology. In any event, psychiatric comorbidity in MS deserves greater clinical attention than has been previously paid, because the presence of psychopathology may have deleterious effects on the disease process and impair coping with disability.

Keywords: multiple sclerosis, psychiatric comorbidity, coping, outcome

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, causing motor and sensory impairment by progressive demyelination. It affects about 2.5 million people worldwide and is the most common cause of neurologic disability in young and middle-aged adults. MS is twice as common in women than in men. The onset of the disease usually occurs between 20 and 50 years of age with a peak at about 30 years of age. It has been recognized across all ethnicities. The occurrence of MS decreases proportionally with the distance from the poles, thus it is more common in Caucasians compared to native African and Asian populations [Ebers, 2008].

In contrast to a wealth of research into the neurological manifestations of MS, there is a paucity of studies on psychiatric disorders or comorbidity in those patients. This is surprising given that psychopathological signs and symptoms have been well known since MS has first been systematically described by Charcot. He already observed a marked enfeeblement of the memory combined with pathological laughing and weeping, euphoria, mania, hallucinations and depression [Charcot, 1877].

The relationship of psychological and psychiatric disorders with MS is complex and the extent to

which they might be reactive to countless psychosocial factors or even be symptoms resulting from the neuropathological process itself remains unclear. Certainly they aggravate physical symptoms like fatigue, leading to disability, suffering and significant disruption of family, work and social life, thus increasing the huge burden of the chronic inflammatory disease. The neuropsychiatric abnormalities in MS can broadly be divided into two categories: disorders of mood, affect and behaviour and abnormalities affecting cognition [Ghaffar and Feinstein, 2007]. The leading group of psychiatric abnormalities embodies the mood and affective disorders, whose symptoms in MS patients are like those observed in the general population suffering from these disturbances [Feinstein, 2004; Minden and Schiffer, 1990]. The mood and affective disorders can be divided into four broad categories including major depression, bipolar affective disorder, euphoria, and pseudobulbar affect. Behavioural changes such as confabulations, paranoid ideas, irritability, pathologically increased libido, and alcohol and substance abuse have been reported sporadically in MS patients with extensive brain lesions, requiring specialized psychiatric management [McDonald and Compston, 2006].

Diaz-Olavarrieta evaluated 44 stable MS patients between relapses and found neuropsychiatric

Correspondence to:

Ida S. Haussleiter
Department of Psychiatry,
LWL-University Hospital
Bochum, Bochum,
Germany.
ida.haussleiter@wkp-lwl.org

Martin Brüne
Georg Juckel
Department of Psychiatry,
LWL-University Hospital
Bochum, Bochum,
Germany

symptoms in 95% of them, the most common being depression (79%), agitation (40%), anxiety (37%), irritability (35%), apathy (20%), euphoria (13%), disinhibition (13%), hallucinations (10%), aberrant motor behaviour (9%), and delusions (7%) [Diaz-Olavarrieta *et al.* 1999]. In this article, we seek to provide an overview of the most recent research on psychiatric symptoms and comorbid disorders associated with MS. Tables 1 to 3 summarise the morphological correlates of psychiatric MS symptoms, the prevalence of psychiatric disorders in MS and the general population, and the correlation of psychiatric symptoms with MS features.

Depression and suicide

Almost one in two MS patients will experience clinically significant depression in their lifetime

(overall lifetime frequency of 25–50%), which equals approximately three times the prevalence rate in the general population [Siebert and Abernethy, 2005; Feinstein, 2004; Minden and Schiffer, 1990]. It represents a potent risk factor for disease morbidity with depressed persons having a twice as high mortality rate in comparison to nondepressed persons [Cuijpers and Smit, 2002].

The rate of depression and other psychiatric disorders is greater in MS than in other chronic medical [Patten *et al.* 2003] or neurological [Cummings *et al.* 2006] diseases. In most studies reporting a higher incidence and prevalence for depressive symptoms in MS compared with other neurological illnesses, the clinicians diagnosing depression were not blind to the patient's conditions or the hypotheses at issue [Schiffer, 1990].

Table 1. Morphological correlates of psychiatric MS symptoms.

Morphology	MRI	Ref
Depression	<ul style="list-style-type: none"> – left arcuate fasciculus, medial orbito-frontal regions and limbic perfusion – left suprainular white matter – greater volume left medial inferior prefrontal lesions – frontal atrophy – right frontal lesion load, volume of right hemisphere and temporal brain – cortical-subcortical disconnection in limbic system projections areas – right frontal lesion load and temporal brain volume – frontal and parietal white matter destructive lesions 	Feinstein <i>et al.</i> (2004) Feinstein <i>et al.</i> (2004) Feinstein <i>et al.</i> (2004) Zorzon <i>et al.</i> (2001) Zorzon <i>et al.</i> (2001) Zorzon <i>et al.</i> (2001) Bakshi <i>et al.</i> (2000) Zorzon <i>et al.</i> (2001) Bakshi <i>et al.</i> (2000) Zorzon <i>et al.</i> (2001)
Anxiety	No association	Tellez <i>et al.</i> (2006)
Fatigue	No association	Young <i>et al.</i> (1997)
Bipolar	<ul style="list-style-type: none"> – ubiquitous white matter changes – plaques in bilateral temporal horn areas 	Feinstein <i>et al.</i> (1992)
Euphoria	<ul style="list-style-type: none"> – reduced global grey matter volume 	Sanfilippo <i>et al.</i> (2006)
Psychosis	<ul style="list-style-type: none"> – lesions in temporal areas – plaques temporal horns bilaterally – predominance of lesions in the temporal lobes – generally larger lesions, higher total lesion score – greater pathology in the temporal-parietal region 	Feinstein <i>et al.</i> (1992) Amato <i>et al.</i> (2006c) Feinstein <i>et al.</i> (1992) Feinstein (2004) Foong and Ron (2003), Feinstein <i>et al.</i> (1992) Ron and Logsdail (1989) Panitch <i>et al.</i> (2006)
PBA	<ul style="list-style-type: none"> – frontal, parietal and brainstem regions 	Ghaffar <i>et al.</i> (2008)
Cognitive imp.	<ul style="list-style-type: none"> – basal ganglia – subcortical grey matter (caudate, putamen, globus pallidus, thalamus) 	Hildebrandt <i>et al.</i> (2006)
	<ul style="list-style-type: none"> – total lesion burden and regional lesion volume – cerebral atrophy – ventricular enlargement – severe atrophy of the corpus callosum – white and grey matter volume 	Hildebrandt <i>et al.</i> (2006) Bermel and Bakshi, (2006) Bermel and Bakshi, (2006) Pantano <i>et al.</i> (2006) Huber <i>et al.</i> (1992) Sanfilippo <i>et al.</i> (2006)
Dementia	<ul style="list-style-type: none"> – brain atrophy, ventricle enlargement, neocortical volume 	Benedict and Bobholz (2007)

Moreover, most of the prevalence studies have taken samples from patients attending an MS clinic, thus patients coping well in the community might be under-represented. Another issue concerns the wide variety of measures used to diagnose and quantify the severity of depression. There is no consensus among researchers as to the clinical 'gold standard' for diagnosing depression in patients with MS. Additionally, with the use of behavioural rating scales designed for a general psychiatric setting, the somatic symptoms of MS, such as fatigue, may lead to inflated estimates of depression [Siegert and Abernethy, 2005].

Jefferies considered an advanced stage as well as shorter disease duration to be associated with a greater probability of significant depressive symptoms [Jefferies, 2006]. Foong and Ron [2003] agree on the association with progressive neurological disability but do not see a close relationship neither to the degree of physical impairment nor to the disease duration. While some authors describe depression in relapsing-remitting MS as more common during relapses than in remission phases [McCabe, 2005], others do not connect depressive symptoms and pattern of illness

progression [Jefferies, 2006]. The pathogenesis of depression in MS is most likely multifactorial, including psychological, social, neurobiological, immunologic, and genetic factors [Gold and Irwin, 2006]. Depression may simply be primarily reactive in nature, a response to facing a chronic illness characterized by an uncertain prognosis and without any cure, but it may also be related to disease-specific processes such as CNS damage or changes in immune parameters.

A pronounced breakdown of the blood-brain barrier, entry of inflammatory cells into the CNS and local production of cytokines within the brain are at the core of presumed pathogenesis: the effect of cytokines on the brain itself may be important as well for behavioural symptoms because of their contribution to neuronal and oligodendroglial damage [Gold and Irwin, 2006]. Some cytokines, such as interferon (IFN)- α and interleukin (IL)-1, may affect serotonergic and noradrenergic transmission in the CNS. Others seem to activate the neuroendocrine system [Dunn *et al.* 2005]. A correlation was found between depression and brain inflammatory markers, evidenced by enhanced MRI lesions and CSF pleocytosis

Table 2. Prevalence of psychiatric disorders in MS and general population.

	Multiple sclerosis [%]	Reference	General population [%]	Reference
Depression	22.8	Patten <i>et al.</i> (2003)	16.2	Kessler <i>et al.</i> (2003)
Suicidal intent	28.6	Feinstein (2002)	3.8	Sadovnick (1991)
Anxiety	36	Korostil and Feinstein, (2007)	5.1	Aarsland and Figved, (2007)
Fatigue	75	Tellez <i>et al.</i> (2006)	23.7	Price <i>et al.</i> (1992)
Bipolar	0.3	Schiffer <i>et al.</i> (1986)	0.2	Perälä <i>et al.</i> (2007)
Euphoria	25	Rabins (1990)	/	
Psychosis	2-3	Reiss <i>et al.</i> (2006)	0.5-1	Reiss <i>et al.</i> (2006)
PBA	10	Feinstein <i>et al.</i> (1997)	/	
Cognitive Impairment	40-65	McIntosh-Michaelis <i>et al.</i> (1991), Rao <i>et al.</i> (1991), Bobholz and Rao, (2003), Lebrun (2001)	3.2	Ritchie <i>et al.</i> (2001)

Table 3. Correlation of psychiatric symptoms with MS features.

Association $\uparrow\downarrow \iff$	MS duration	MS course	Physical disability (EDSS)
Depression	$\downarrow$ (6), $\iff$ (38)	$\uparrow$ (37), $\iff$ (38)	$\uparrow$ (6), $\iff$ (38)
Anxiety	$\iff$ (49)		$\iff$ (49), $\downarrow$ (79)
Fatigue	$\iff$ (13, 139)	$\iff$ (13)	$\iff$ (44,87)
PBA	$\uparrow$ (21)		$\uparrow$ (21)
Cogn. Imp.	$\iff$ (25,26)	$\iff$ (25,26)	$\iff$ (25,26), $\uparrow$ (46)
$\uparrow$ Positive correlation between the two variables, $\downarrow$ Negative correlation between the two variables, $\iff$ No correlation between the two variables			

[Fassbender *et al.* 1998]. Additionally, perceived psychosocial stressors seem to have some influence [Aikens *et al.* 1997] and there is a suggestion that immune abnormalities, in association with dysfunction of the hypothalamic–pituitary–adrenal axis, may be the mechanism underlying the high lifetime risk for depression [Fassbender *et al.* 1998; Wei and Lightman, 1997].

In animal models, induction of proinflammatory cytokines yielded behaviour changes characterized by decreased appetite, weight loss, sleep disturbances, retardation of motor activity, reduced interest in physical and social environment, and loss of libido [Kelley *et al.* 2003]. In healthy humans an induced cytokine production was also transiently accompanied with depressed mood, anxiety, and memory impairments [Reichenberg *et al.* 2001]. Thus, the sickness-behaviour model may apply to depressive symptoms in MS [Gold and Irwin, 2006]. In experimental autoimmune encephalomyelitis (EAE), the animal model of MS, behavioural alterations occurred after immunization but before the onset of neurological signs of disease. Hence, such symptoms as anorexia, weight loss and reduced social exploration may reflect motivational defects rather than impairments in motor function. In accordance with a cytokine-mediated pathogenesis of these symptoms, the onset of sickness behaviour coincided with inflammatory cell infiltration of the brain as well as cytokine synthesis in brain tissue and anti-inflammatory treatment ameliorated the behavioural effects [Pollak *et al.* 2003].

MS patients with higher depression scores had significantly increased white blood cell counts in the CSF, clear MRI evidence for CNS inflammation, activation of the hypothalamic-pituitary-adrenal (HPA) axis [Fassbender *et al.* 1998], and increased serum levels of specific cytokines [Kahl *et al.* 2002]. The amelioration of depression after psychotherapy or medication was paralleled by decreased cytokine production and less enhanced MRI lesions [Puri *et al.* 2001]. Hence, aggressive management of depressive disorders in patients or individuals at risk for disease may improve disease outcome or prevent disease development [Gold and Irwin, 2006]. Drug-induced depression could be a differential diagnosis of low mood in MS, since steroids, baclofen, dantrolene and tizanidine used for symptomatic treatment could all cause depression on their own.

With the advent of IFN beta as a treatment for MS, concern arose regarding the potential for this drug to cause or exacerbate depression [Feinstein, 2004]. However, with the high prevalence rates for depression in MS noted above, it is difficult to draw any meaningful conclusions from anecdotal accounts or individual case reports [Siegert and Abernethy, 2005]. The anecdotal evidence of increased depression during IFN treatment is better explained by prior history of depression [Feinstein *et al.* 2002].

In the CHAMPS study (controlled high-risk subjects avonex MS prevention study), a higher rate of depression (20%) was found in the treated patients than in the placebo arm (13%) [Jacobs *et al.* 2000]. However, these results should be interpreted cautiously since a close correspondence between decreased use of active coping strategies over time and increased mood disturbances had been observed previously [Arnett and Randolph, 2006]. Furthermore, another multicentre trial, the PRISMS study (Prevention of Relapses and disability by Interferon beta 1-a Subcutaneously in MS), did not reveal any differences in the levels of depression among the active treatment and placebo group [Patten and Metz, 2001]. Thus, there is no firm evidence so far that IFN treatment may induce depression in MS patients. Instead, the presence of baseline depressive symptoms seemed to predict the presence of depression at follow-up [Porcel *et al.* 2006; Patten and Metz, 2001]. Patten *et al.* [2003] also reported that rates of depression are the same for patients treated with IFN and for patients treated with glatiramer acetate in clinical settings.

A few studies reported flu-like symptoms such as fever, malaise, headache and myalgia as most common side-effects of treatments with IFN- β . These symptoms typically occur a few weeks after the start but tend to attenuate as treatment continues. However, neuropsychiatric symptoms including anxiety, dysphoria, anhedonia, fatigue, anorexia, and slowing cognitive and psychomotor functions generally occur after several months and persist until the treatment is terminated or supplemented. These late onset symptoms may, therefore, be an epiphenomenon to the induction of endogenous cytokines [Gold and Irwin, 2006]. In summary, screening for depression and monitoring of mood should be a feature of the medical management of all patients with MS, regardless of IFN reception.

Coping and social support seem to mediate the relationship between depression and MS [McCabe, 2005], but psychosocial factors alone cannot account for the higher frequency of the affective disorder seen in MS compared with other chronic progressive diseases [Patten *et al.* 2003]. Nevertheless, patients with active coping strategies are able to deal with problems rather than avoiding them, and those with a good level of support tend to have lower levels of depression [Chwastiak *et al.* 2002]. The research findings on coping with MS closely resemble those on coping with stress – that is, positive adjustment is typically associated with problem focused coping and higher symptom levels are associated with emotion-focused coping or escape avoidance [Folkman and Moskowitz, 2004]. Furthermore, social support had a beneficial effect on adjustment [Williams *et al.* 2004]. Treating depression actually results in improvements on a number of aspects of social support and there is evidence that depression itself may actually cause reduced social support [Mohr *et al.* 2004]. Other psychosocial variables affecting mood in MS include illness intrusiveness, uncertainty, hope and spirituality [McNulty *et al.* 2004].

Clinical symptoms of depression like anxiety, irritability, anger and somatic disturbances are more frequently reported in MS patients than apathy and withdrawal [Sá, 2007]. Pervasive mood change, diurnal mood variation, suicidal ideation, functional change not related to or out of proportion to physical disability, and pessimistic or negative patterns of thinking may be helpful diagnostic indicators of depression in MS since many of the somatic depressive symptoms also occur in chronic MS without depression [Jefferies, 2006]. Scores for all items in the Beck Depression Inventory and 12 of the 17 items in the Hamilton Rating Scale for Depression decreased significantly with treatment, suggesting that these items are correctly tapping depression in MS [Moran and Mohr, 2005].

The Goldman Consensus Group noted in 2005 that depression in patients with MS was linked with poorer cognitive functioning, more time off work, and a lower quality of life than MS without depression. They also cited evidence suggesting that MS patients with depression were less likely to adhere to their medication regimens [Goldman Consensus Group, 2005]. Depression adversely affects quality of life in MS patients [Jonsson *et al.* 1996], which is

linked to poorer treatment compliance, therefore affecting long-term outcome [Mohr *et al.* 1997], and is finally reported to be the most powerful determinant of suicidal intent in these patients [Feinstein, 2002]. Despite this evidence that depression is a major complication of MS, this condition remains underdiagnosed and undertreated in most patients [Feinstein, 2002].

Organic correlates of depressive symptoms in MS patients

There is no clear link between brain abnormalities identified by magnetic resonance imaging (MRI) and depression, but several studies report a variety of association. Regarding specific brain regions, an asymmetry was found with lesion predominance in the left hemisphere. Here depressive symptoms were associated with lesions in the arcuate fasciculus, medial orbitofrontal regions and limbic perfusion [Feinstein *et al.* 2004] and in the right hemisphere with frontal lesion load and temporal brain volume [Zorzon *et al.* 2001]. Some authors report lesions in the left suprainular white matter [Feinstein *et al.* 2004], and others claim black holes in superior frontal and parietal regions to predict depression [Bakshi *et al.* 2000]. Feinstein *et al.* used brain MRI to compare 21 MS patients with major depression and 19 carefully matched nondepressed MS patients. They rigorously excluded any patient with a premorbid history of psychiatric disorder. They found more hyperintense lesions in the left anterior medial frontal regions and greater atrophy of left anterior frontal regions in depressed patients [Feinstein *et al.* 2004]. Some reports indicate that a cortical–subcortical disconnection in the projection areas of the limbic system as well as more frontal atrophy may be responsible for symptoms of depression in MS [Zorzon *et al.* 2001]. Diagnosis and severity of depression were correlated with right frontal lesion load and with right temporal lobe volume in 95 MS patients. The severity of symptoms correlated significantly with total temporal volume as well as right hemisphere volume [Zorzon *et al.* 2001]. However, the statistical significance of these correlations was modest. Even though the site and extend of MS lesions seems to be associated with certain depressive features, it is fair to say that no clear anatomic pattern has been established so far [Gold and Irwin, 2006]. Nevertheless, MS patients with brain lesions are not only significantly more depressed than those with lesions only in the spinal cord but the

depression was also positively correlated with the extent of neurological impairment [Rabins *et al.* 1986].

Suicidal ideation is common in MS with male gender, young age at onset, history of depression, social isolation, and substance misuse as particular risk factors [Jefferies, 2006]. MS patients have a lifetime prevalence of suicidal intent of 28.6% [Feinstein, 2002] and reported rates of suicides reaching values 7.5 times greater than in normal age-matched populations [Sadovnick *et al.* 1991] and in patients with other neurological disorders [Stenager *et al.* 1992]. In a follow-up study over 16 years, suicide accounted for 15% of all ascertained deaths in patients with MS [Sadovnick *et al.* 1991]. Since 83% of MS patients with suicidal ideation have a history of depression [Feinstein, 2002], an association between depression and suicide in MS is likely to exist, even though there is so far no study proving this link [Jefferies, 2006]. Of particular concern is the fact that two-thirds of patients with current major depression were not receiving antidepressants and one third of suicidal patients had not received any psychological assistance [Feinstein, 2002].

Stress, anxiety and fatigue

Stress is considered as some kind of change in an individual's life, requiring readjustments that surpass the ability of coping and leading to psychological or biological harm. Charcot already assumed that grief or anger might have a role in the occurrence of neurological diseases like MS [Charcot, 1877]. An association between stress and MS relapses seems theoretically unexpected on physiological grounds since stress stimulates the HPA axis resulting in increased levels of circulating endogenous cortisol, which controls inflammation and thus should biologically abort eventual relapses. Hypothetically, acute stress (like major stressful life events) could induce higher cortisol levels than chronic stress (family and work stress) and have a major impact in reducing the risk of MS relapses. Thus, stress may either have an immune-suppressive or increasing effect depending on its intensity and duration [Martinelli, 2000], mediated by a glucocorticoid resistance with downregulation of receptors on immune cells secondary to chronic stress. Recently, consensus statements about the importance of stress regulation in MS were published, claiming the association between stressful life-events and MS relapses inconclusive,

the cytokine response to psychological and physical stressors weakened, the HPA reactivity varied by disease subgroup and stage, and an autonomous nerve dysfunction correlated with inflammatory activity and disease progression [Heesen *et al.* 2007].

The lifetime prevalence of any anxiety disorder observed in MS was about 35.7%, with panic disorder, obsessive-compulsive disorder, and generalized anxiety disorder the most common diagnosis obtained [Korostil and Feinstein, 2007]. Female gender, a comorbid diagnosis of depression, and restricted social support were considered as risk factors, but the diagnosis of anxiety disorders had been overlooked and therefore not been treated in most subjects [Korostil and Feinstein, 2007]. Particular high rates of anxiety were found in newly diagnosed MS patients (34%) and in their partners (40%) compared with controls [Janssens *et al.* 2003]. Anxiety may also be disclosed by acute relapses of MS since patients experience these as unexpected disrupting events in daily life and as a remembrance of their chronic disease. Like depression, anxiety seems to be associated with disease activity but not with its duration or severity [Janssens *et al.* 2006]. A study conducted in Norway revealed a significant association of fatigue, pain, lower Expanded Disability Status Scale score, and younger age at onset with symptoms of anxiety. The proportion of reported treatment in this study was 15.9% and 11.1% for depression and anxiety, respectively, and 18.2% of untreated patients with symptoms expressed the need for treatment [Beiske *et al.* 2008].

All studies researching the level of anxiety in MS observed patients attending clinics who may have had higher levels of symptoms than a community-based sample. Moreover, even among those patients, there is no detailed information regarding the specific subtypes of anxiety disorder present [Siegert and Abernethy, 2005]. After the introduction of self-injectable immunomodulatory drugs, the condition of self-injection anxiety emerged and led to anxiety in MS, presumably affecting 50% of all patients [Mohr *et al.* 2002]. The assumption that anxiety emerges as a reactive phenomenon to a variety of situations is strengthened by the lack of association between anxiety and MRI abnormalities or clinical variables [Zorzon *et al.* 2001]. A baseline screening for anxiety at diagnosis of MS could be used to

predict the levels of anxiety and distress in the period of follow-up.

Fatigue is a persistent somatic symptom reported by almost 75% of MS patients [Freal *et al.* 1984] and identified as most interfering with daily activities. It may occur in any stage of MS and seems independent from disability or ambulation [Tellez *et al.* 2006]. It is tempting to ascribe the presence of depression to fatigue and vice-versa, but still the relationship between these two symptoms is not entirely clarified [Mohr *et al.* 2003]. Moreover, several studies observed fatigue to be a common and troubling symptom in MS patients but found no correlation with depression (BDI) or disability (EDSS) [Vercoulen *et al.* 1996; Krupp *et al.* 1988], thus emphasizing the importance of viewing fatigue as a discrete symptom of MS that is not accounted for by depression. Ford *et al.* [1998] recently found a strong relationship by scoring separately for mental, physical and total fatigue. They discovered that depression was more strongly related to mental rather than physical fatigue, which could be explained by a cytokine-mediated pathogenesis [Ford *et al.* 1998]. Cytokines typically associated with sickness behaviour have been found to be associated with MS fatigue as well [Gold and Irwin, 2006].

Another study showed that depression and fatigue were independent predictors of quality of life. When both were present, treating the depression seemed to reduce fatigue. It is still not known whether fatigue occurs as a direct result of brain lesions or as a psychological reaction [Janardhan and Bakshi, 2002].

Bipolar disorder and euphoria sclerotica

The literature about bipolar disorder in patients with MS is scarce, and the relationship between both conditions seems complex. So far, there are no studies adequately explaining the reason for a doubled rate of bipolar disorder in MS compared with the general population or providing treatment guidelines [Sanfilipo *et al.* 2006]. Like depression, mania may occur as part of the physical disorder or secondary to drug treatments. Baclofen, dantrolene, tizanidine and illicit drugs are all culprits to induce hypomaniac moods in MS patients [Jefferies, 2006], and in up to a third of patients given steroids mild-to-moderate degrees of mania may occur. Caution should be taken in patients having a family or premorbid

history of affective disorder or alcoholism. Hysterical pictures are classically associated with the search of secondary gain and may be a major handicap in patients with minimal physical disability [McDonald and Compston, 2006]. Both MS and mania are associated with white-matter changes on MRI, although the pathogenesis is likely to be different [Young *et al.* 1997]. There is MRI evidence suggesting that patients showing mania with psychotic symptoms have plaques predominantly distributed in the bilateral temporal horn areas [Feinstein *et al.* 1992].

Euphoria refers to an overly optimistic state of mental and physical wellbeing in the presence of significant neurological disability [Ghaffar and Feinstein, 2007]. In 1926, Cottrell and Wilson reported euphoria in over two-thirds of their sample of people with 'disseminated sclerosis' [Cottrell and Wilson, 1926], but few studies since have reported such high rates. Rabins [1990] summarized a median rate of 25%. Over the past century, euphoria was long regarded as the psychopathological trait of MS. Along with disinhibition, it likely represents a personality change and occurs in later stages of the disease [Benedict and Bobholz, 2007]. It correlates with an EDSS score in the upper range [Rabins, 1990], worsening cognition and cerebral atrophy as the disease progresses [Benedict and Bobholz, 2007]. Euphoria bears some similarity to hypomania in terms of elevated affect but lacks the associated overactivity. Anatomically, it seems to be associated with reduced global grey matter volume [Sanfilipo *et al.* 2006].

Psychosis

Co-occurrence of psychosis and MS is uncommon and most reports are single case studies [Jefferies, 2006]. Psychosis was observed in MS as often as in the general population, but a recent study reported rates of 2–3% compared with 0.5–1% in the general population [Reiss *et al.* 2006]. Brief psychotic episodes – mainly comprising religious or persecutory delusions and hallucinations – may occur as manifestation as well as a remission-followed onset relapse in MS. Psychosis in MS distinctly differs from schizophrenia as it has a later age at onset, quicker resolution, fewer relapses, better response to treatment and a better prognosis [Feinstein *et al.* 1992]. But given the current media descriptions of symptom relief of MS by the use of cannabis, an increase of drug-induced

psychosis is likely. Among previously healthy persons with an acute psychotic disorder, even the slightest neurological abnormality justifies a cranial MRI examination [Jongen, 2006]. The scarce database on psychosis in MS suggests an involvement of lesions in temporal areas [Amato *et al.* 2006b; Feinstein *et al.* 1992]. It may be related to a predominance of lesions in the temporal lobes [Feinstein, 2004; Foong and Ron, 2003] and with larger lesions in general. MS patients with psychosis had a higher total lesion score and significantly differed from patients with MS alone in bilateral plaques involving the temporal horns [Feinstein *et al.* 1992]. In all cases, neurological symptoms preceded the onset of psychosis. The psychotic group also had a later age of onset of psychosis than psychotic patients without brain disease. These results point to an aetiological association between the pathological process of MS and psychosis [Feinstein *et al.* 1992]. In another study, flattened affect, delusions and thought disorder was associated with greater pathology in the temporo-parietal region in a sample of 116 MS patients compared with a control group with physical disabilities [Ron and Logsdail, 1989].

Pseudobulbar affect

Pseudobulbar affect (PBA) is also referred to as pathological laughing and crying, emotional incontinence and involuntary emotional expression disorder (IEED) [Arciniegas, 2005]. The syndromic behaviour occurs in the absence of specific stimuli, an association between affective change and observed expression, voluntary control of facial expression, and in the absence of a corresponding change in mood exceeding the laughing or crying. Uncontrollable crying seems to be more common than laughing. This disorder has been described in 10% of the MS patients and seems to be associated with dysfunction of the prefrontal cortex. There seems to be no difference between genders, but longstanding disease, cognitive impairment and progressive, severe disability were linked with pathological laughing-and-crying syndrome. Lesions involving a widely dispersed neural network including frontal, parietal and brainstem regions have recently been implicated [Ghaffar *et al.* 2008; Panitch *et al.* 2006].

Cognitive impairment

MS-associated cognitive impairment was first described over a century ago. However, with the

advent of standardized neuropsychological testing and quantitative brain imaging, the frequency, quality and correlates of cognitive impairment are better understood. Since the demyelinating action of MS predominantly affects the white matter, cognitive dysfunction associated with the disease was sometimes also termed as 'subcortical dementia'.

Recent studies establish the prevalence rates of cognitive dysfunction in MS in the range 40–65% [Bobholz and Rao, 2003; McIntosh-Michaelis *et al.* 1991; Rao *et al.* 1991]. Impairment develops in established cases, although it can be present early in the disease course, but the profile of deficits clearly broadens with progressing disease [Bobholz and Rao, 2003]. Although some authors claim no close association with physical disability, disease duration or disease course [McIntosh-Michaelis *et al.* 1991; Rao *et al.* 1991], others observed it to be more frequent and severe in progressive forms and correlating with the rate of physical disability [Calabrese, 2006]. In general, relapsing–remitting patients suffer less from cognitive impairment than those with chronic progressive illness and among those secondary progressive patients favour a worse picture [Amato *et al.* 2006c], but even in benign MS without physical disability, cognitive impairment was found in 44% [Benedict *et al.* 2005]. Cognitive impairment in MS is often a hidden condition and again there is interdependency with depression since it may worsen cognitive functioning just as cognitive dysfunction may induce depression [Sá, 2007], but recent studies were not able to find a correlation between both disorders [Siegert and Abernethy, 2005]. The lack of any association seems rather surprising given the mounting evidence for the neuropsychological deficits accompanying depression [Shenal *et al.* 2003]. If physically healthy people with depression are prone to cognitive dysfunction it seems paradoxical that this is not the case for depressed people with MS. In summary, earlier research studies consistently failed to find any clear relation between depression and cognitive impairment in MS. However, some recent work suggests that effortful rather than automatic information processing is most likely compromised in depressed MS patients. Hence, performance may be quite normal on routine tasks but impaired on those tasks that place demand upon attentional resources, such as information processing speed, working memory, and executive functioning

[Arnett and Randolph, 2006]. Psychotropic medication does not seem to affect the performance of patients in memory testing [Rao *et al.* 1991].

A general consensus is emerging on the nature of cognitive dysfunction [Griffiths *et al.* 2005]. Common symptoms may be forgetfulness, slowness of thought processes, emotional or personality changes, and impaired ability to manipulate information [Jefferies, 2006]. Impaired attention and slowness of information processing are hallmarks of such subcortical dementia. Deficits in working, semantic and episodic memory have been reported and replicated, while procedural and implicit memory appears to be less affected [Bobholz *et al.* 2006; Henry and Beatty, 2006]. Executive dysfunction, including deficits in concept formation, abstract reasoning and verbal fluency are also found [Benedict *et al.* 2006]. Verbal and nonverbal memories are adversely affected and the mechanism involves failure at both the acquisition and retrieval stages. Deficits are more apparent on tests of recall than recognition [Feinstein, 1999].

The Mini-Mental State Examination has been shown to be unhelpful in screening for cognitive impairment in MS [Franklin *et al.* 1988]. Recently an expert panel proposed a 90-min cognitive battery – the Minimal Assessment of Cognitive Dysfunction in MS (MACFIMS) – for clinical monitoring and research, which comprises seven tests covering five cognitive domains commonly impaired in MS, namely processing speed, memory, executive function, visual-spatial processing and word retrieval [Huijbregts *et al.* 2006].

The volume of MRI hypodensities in the basal ganglia correlated with cognitive impairment [Hildebrandt *et al.* 2006] and other sequences emphasize correlations, albeit modest, with total lesion burden and regional lesion volume [Bermel and Bakshi, 2006]. Some results suggest that severe atrophy of the corpus callosum reflects global disease and provides a relatively focal morphological marker of severe cognitive impairment in MS [Huber *et al.* 1992]. In contrast with the confusing picture in depression, the degree and pattern of cognitive dysfunction is highly correlated with the amount and location of white-matter disease within the cerebral hemispheres [Rao *et al.* 1991]. White matter volume was the best predictor of mental processing speed and working memory, whereas grey matter

volume predicted verbal memory, euphoria and disinhibition [Sanfilipo *et al.* 2006]. Another study reported a correlation of hypodensities in subcortical grey matter (caudate, putamen, globus pallidus, thalamus), possibly representing iron deposition [Hildebrandt *et al.* 2006]. Markers of cerebral atrophy have emerged as more important correlates of cognitive decline than lesion volume [Bermel and Bakshi, 2006], and ventricular enlargement, being one index of brain atrophy, was associated with abnormalities on various cognitive tests [Bermel and Bakshi, 2006; Pantano *et al.* 2006].

Moreover, functional MRI studies have demonstrated the brain's ability to compensate, in part, for damage associated with the disease. Thus, MS patients recruit additional brain regions or exhibit greater activation within the same regions as those used by healthy controls during cognitive activation tasks [Sweet *et al.* 2006]. These increased activations may lessen as task difficulty increases or disease progresses beyond a certain threshold. [Amato *et al.* 2006a]. Therefore, the 'functional reserve' is limited and decreases with evolving disease. Should the disease burden be too severe; however, compensatory mechanisms fail and cognitive deficits increase accordingly [Ghaffar and Feinstein, 2007].

Dementia is rare in MS, although it is known to occur in 10–25% of patients. In addition to the cognitive impairments evident in MS dementia, changes in personality and social behaviour also occur. Some patients develop euphoria and marked deficiency in social empathy, conditions that, in combination with executive dysfunction, cause considerable hardship for patients and caregivers [Benedict and Bobholz, 2007]. These neuropsychiatric manifestations of MS dementia are correlated with magnetic resonance imaging indicators of brain atrophy, including ventricle enlargement, neocortical volume and normalized whole brain volume [Benedict and Bobholz, 2007].

Treatment

Clinicians need to understand the factors that influence the development of psychiatric disorders in MS, the relationship between disease-modifying therapies and psychiatric distress, and the issues surrounding the treatment of psychiatric conditions in this chronic inflammatory disease. Treatment of psychopathology

associated with MS or psychiatric comorbidity is usually performed according to the general guidelines for mental disorders, thus ignoring the comorbid chronic inflammatory condition. In other words, no specific information is available so far as to whether or not psychotropic drugs have anti-inflammatory effects. Recently, there was some evidence in the literature suggesting that antidepressants could reduce the release of proinflammatory cytokines and other immunological factors, although their precise neuroimmune mechanisms are little known and remain uncertain [Sutcgil *et al.* 2007; Leonard, 2001]. Mirtazapine as an antidepressant was shown to inhibit cerebral proinflammatory cytokines production [Zhu *et al.* 2008], whereas other results provided evidence for anti-inflammatory properties of levetiracetam [Haghikia *et al.* 2008]. Atypical antipsychotics with dopamine D₂ receptor antagonism as well as aripiprazole have recently been reported to have significantly inhibitory effects on IFN-induced microglial activation *in vitro*, which is not only directly toxic to neurons but also has an inhibitory effect on neuro- and oligodendrogenesis [Bian *et al.* 2008; Kato *et al.* 2008]. Whether or not anti-inflammatory 'side-effects' of a treatment with psychotropic drugs could prove especially beneficial in MS patients remains to be investigated.

Even though depression is one of the strongest predictors of reduced quality of life, it is often not detected nor treated in MS [Patten *et al.* 2003], although as a rule the symptoms respond well to standard treatment [Minden, 2000]. The treatment of depression and mood changes is generally based on various psychological interventions and antidepressants [Thomas *et al.* 2007]. Based on empirical data, the Goldman Consensus Group found cognitive behavioural therapy and antidepressants equally effective for MS depressed patients and the use of individually adapted, combined modalities was recommended [Goldman Consensus Group, 2005]. A meta-analysis concluded that patients responded well to treatment with either antidepressants (desipramine) or psychotherapy, which should emphasize coping skills rather than an insight-oriented therapy [Mohr and Goodkin, 1999]. It was also speculated that depression in MS might be particularly responsive to treatment, arguing that most MS patients lack any extensive history of depression and rarely have comorbid psychiatric diagnoses [Mohr and Goodkin, 1999].

Antidepressant drugs used in MS include selective serotonin reuptake inhibitors (SSRIs, such as fluoxetine or sertraline), tricyclic antidepressants (TCAs), monoamine oxidase (MAO) inhibitors, reversible MAO-A inhibitors, and serotonin noradrenaline reuptake inhibitors (SNRIs) [Crayton and Rossman, 2006; Henze *et al.* 2006], with a predominance of the first two groups. TCAs, like desipramine, seem to be more effective than placebo, but some patients experience dose-limiting anticholinergic side-effects, which may especially complicate the underlying neurological disease [Feinstein, 2004]. Due to their less troubling side-effects, SSRI seem to be the treatment of choice for depression in MS. Treatment with 100 mg sertraline daily for 3 months showed distinct improvement without any undesirable side-effects in 10 patients [Scott *et al.* 1995]. There is no evidence that any one SSRI is superior in the treatment of depression in MS, but fluoxetine may be helpful for some of the neurological symptoms as well as fatigue. In patients who do not respond to antidepressants, lithium augmentation may prove effective. There has been one double-blind placebo-controlled trial of antidepressant medication for depression in MS, in which patients with psychotherapy combined with desipramine *vs* placebo were compared and the participants on desipramine showed a statistically significant improvement in mood compared with those in the placebo group [Schiffer, 1986].

According to the Cochrane review, psychotherapy may be of help in depression, and sound evidence exists for cognitive behavioural therapy (CBT) [Thomas *et al.* 2007]. The latter is an effective treatment [Larcombe and Wilson, 1984], rivalling standard dosing of sertraline in patients with depression [Ghaffar and Feinstein, 2007]. Individual or group psychotherapy can be particularly helpful for less severe depression, and in more severe cases it can be a useful adjunct to antidepressants [Larcombe and Wilson, 1984]. Electroconvulsive therapy (ECT) may be used to treat severe drug-refractory depression, but there appears to be a risk of triggering a relapse of MS, and the presence of active brain lesions on MRI before treatment is a potential risk factor for neurological relapse following ECT [Mattingly *et al.* 1992]. In summary, despite the recommendations for an individualized therapeutic regime in depressed MS patients [Goldman Consensus Group, 2005], algorithms for this particular population still have to be tested.

Anxiety and stress in MS are usually treated with the same techniques used in the general population; that is, psychotherapy, cognitive behavioural therapy (CBT), and anxiolytic drugs [Sá, 2007]. For self-injection, anxiety specific forms of CBT have been described [Mohr *et al.* 2002]. Whereas SSRIs have been shown not to be useful in the treatment of chronic fatigue syndrome, reversible inhibitors of MAO-A (RIMAs) are helpful in treating some aspects of fatigue syndromes and CBT is beneficial [Siegert and Abernethy, 2005; Vercoulen *et al.* 1996a, 1996b]. Whether this approach is also as useful in MS is presently unknown. Currently-available treatments include graded exercise training, energy management strategies, cooling therapies and in-patient rehabilitation as non-pharmacological approaches [Storr *et al.* 2006] and both cognitive behavior therapy (CBT) and relaxation training (RT) appear to be clinically effective treatments for fatigue in MS patients. Even 6 months after treatment, both treatment groups reported levels of fatigue equivalent to those of the healthy comparison group [van Kessel *et al.* 2008]. Generally, treating depression in MS patients does seem to produce improvements in self-reports of fatigue. However, this evidence is based upon one uncontrolled study of patients who received either CBT or supportive group therapy or sertraline [Mohr *et al.* 2003]. Further specific pharmacological options comprise amantadine, modafinil, pemoline and fampridine, which demonstrated an effect in randomized, placebo-controlled trials. Amantadine has monoaminergic, cholinergic and glutaminergic effects on the CNS and is most widely used with modestly effectiveness to treat fatigue [Taus *et al.* 2003]. Modafinil has α 1-adrenergic properties and has been studied in two trials with controversial results [Stankoff *et al.* 2005; Rammohan *et al.* 2002]. However, a substantial placebo effect of this substance on outcomes such as fatigue, excessive sleepiness and depression in patients with multiple sclerosis has been shown without any benefit greater than placebo [Kumar, 2008]. The CNS stimulant pemoline exerts dopaminergic effects and showed a positive trend in MS patients with fatigue although the published placebo-controlled randomized clinical trials had limitations due to size, treatment periods and design [Schwid and Murray, 2005]. Furthermore its potential liver toxicity limits the use of pemoline in chronic MS patients. One small randomized clinical trial

showed a slight but significant reduction of fatigue in MS patients when treated with the potassium-channel blocker fampridine [Romani *et al.* 2004].

Bipolar affective disorders in MS are usually treated with lithium or anticonvulsants [Ameis and Feinsein, 2006], but so far there is no data about the effect of conventionally used mood stabilizers like carbamazepine or valproate in MS. Lithium carbonate is effective in manic episodes, but there are no controlled trials of its use to treat manic symptoms in MS. Sodium valproate is also effective and can be used in those unable to tolerate lithium, although again there are no trials of its use in people with manic symptoms and MS [Jefferies, 2006].

Psychosis in MS is usually treated with typical and atypical antipsychotics [Ameis and Feinsein, 2006]. There are no studies of treatment of the psychosis associated with MS. While some authors suggest clozapine as treatment of choice [Chong and Ko, 1997], other authors suggest ziprasidone, one of the newer antipsychotic agents [Davids *et al.* 2004]. As in any other case of psychosis, atypical antipsychotics such as risperidone or clozapine should be the treatment of choice, as they have fewer side-effects than the older, typical antipsychotics and benzodiazepines may be used for sedation.

Pathological laughing and crying in MS may be controlled with TCAs, SSRIs and dopaminergic agents [Ameis and Feinsein, 2006]. Treatments with amantadine, levodopa and amitriptyline all enhance cerebral dopamine transmission and may, therefore, improve the laughing-and-crying syndrome [Schiffer *et al.* 1985; Udaoka *et al.* 1984]. Antidepressants and L-dopa have been traditionally used [Panitch *et al.* 2006], and a recent study also showed efficacy in a combination of dextromethorphan and quinidine to improve the symptoms and, therefore, QoL in MS patients [Patten *et al.* 2005]. Fluoxetine may also be of benefit and have fewer side-effects [Seliger *et al.* 1992].

No specific treatment seems to be effective in cognitive impairment, but given its devastating effects, appropriate strategies to ameliorate cognitive deficits could improve everyday functioning in MS [O'Brien *et al.* 2008], thus greatly reducing the negative impact of the disease on the lives of people with MS [Lebrun, 2001].

Some authors claim a potential improvement with disease-modifying drugs [Lublin and Reingold, 1996], but there is a considerable lack of well-designed studies for effective treatment. Acetylcholinesterase inhibitors used in Alzheimer's disease, such as donepezil, seemed to have marginal benefit on a single cognitive domain [Krupp *et al.* 2004]. Regarding immunomodulating drugs, individuals with MS who were given IFN-1b demonstrated significant improvements on measures of complex attention, concentration and visual learning and recall after 1 year compared with untreated controls [Barak and Achiron, 2002]. Current research is progressing on the cognitive effects of anti-inflammatory and immunosuppressive agents such as the combination of cyclophosphamide and methylprednisolone, which significantly improved measures of global cognitive efficiency, learning, organizational and planning abilities [Zéphir *et al.* 2005]. On the contrary, nonpharmacological interventions, such as cognitive rehabilitation, have not consistently demonstrated similar efficacy in the treatment of cognitive disorders in MS [Pinkston *et al.* 2007]. O'Brien *et al.* reviewed 16 studies of cognitive rehabilitation specific to persons with MS, most of them focusing on the remediation of learning and memory, which are among the most common cognitive impairments seen in MS patients [Amato *et al.* 2006c]. The few existing cognitive rehabilitation programs have been aimed at improving attentional deficits [Plohmann *et al.* 1998], communication skills and memory functioning within MS [Allen *et al.* 1998]. Furthermore, strategies such as cognitive structuring, substitution strategies, use of compensatory devices and mnemonic approaches should be included. O'Brien *et al.* underscored the need for cognitive rehabilitation interventions for persons with MS and found evidence that a domain-specific approach may not necessarily generalize to other functional domains and research should therefore also focus on interventions that are more functional and contextual in nature and directly address generalization during treatment [2008].

Conclusions

Psychiatric disorders occur frequently in MS either as a symptom of first onset or during the course of the chronic inflammatory disease. Despite numerous investigations, the pathogenesis of these disturbances remains unclear and they have yet to be identified as illness indicator,

comorbid condition or both. The rapidly developing neuroimaging techniques considerably advance our understanding of the neuropsychiatry of MS and we have greater insight into prevalence, pathophysiology and ecological validity of the many psychometric findings associated with this disease, but the association with anatomical correlates in neuroimaging still needs to be proven.

Notwithstanding the known existence of psychopathological findings in MS patients, the considerable impact on their quality of life and adherence to therapy and, therefore, their influence on the general outcome of the chronic inflammatory disease, most of the affected patients are still insufficiently treated. Despite the overwhelming presence of neurological MS symptoms, close attention should be paid to the early diagnosis and sufficient treatment of the psychiatric aspects. Considering the insufficient number of controlled trials and tested algorithms for the particular population of psychiatrically affected MS patients, the current treatment should be based on general psychiatric treatment guidelines.

On the other hand, psychiatrists should include MS in their differential diagnosis and initiate the appropriate workup to identify the illness. General medical conditions should always be eliminated before diagnosing a primary psychiatric condition, especially in a patient with late-onset or atypical features, peripheral physical findings, a lack of response to standard treatments and cognitive changes.

Conflict of interest statement

None declared.

References

- Aarsland, D. and Figved, N. (2007) Are anxiety disorders undertreated in patients with multiple sclerosis?, *Nat Clin Pract Neurol* 3: 372–373.
- Aikens, J.E., Fischer, J.S., Namey, M. and Rudick, R.A. (1997) A replicated prospective investigation of life stress, coping, and depressive symptoms in multiple sclerosis, *J Behav Med* 5: 433–445.
- Allen, D.D., Goldstein, G., Heyman, R.A. and Rondinelli, T. (1998) Teaching memory strategies to persons with multiple sclerosis, *J Rehabil Res Dev* 35: 405–410.

- Amato, M.P., Portaccio, E. and Zipoli, V. (2006a) Are there protective treatments for cognitive decline in MS?, *J Neurol Sci* 245: 183–186.
- Amato, M.P., Zipoli, V., Goretti, B., Portaccio, E., De Caro, M.F., Ricchiuti, L. *et al.* (2006b) Benign multiple sclerosis: cognitive, psychological and social aspects in a clinical cohort, *J Neurol* 253: 1054–1059.
- Amato, M.P., Zipoli, V. and Portaccio, E. (2006c) Multiple sclerosis-related cognitive changes: a review of cross-sectional and longitudinal studies, *J Neurol Sci* 245: 41–46.
- Ameis, S.H. and Feinsein, A. (2006) Treatment of neuropsychiatric conditions associated with multiple sclerosis, *Expert Rev Neurother* 6: 1555–1567.
- Arciniegas, D.B. (2005) A clinical overview of pseudobulbar affect, *Am J Geriatr Pharmacother* 3 (Suppl. A): 4–8; quiz 16–17.
- Arnett, P.A. and Randolph, J.J. (2006) Longitudinal course of depression symptoms in multiple sclerosis, *J Neurol Neurosurg Psychiatry* 77: 606–610.
- Bakshi, R., Czarnecki, D., Shaikh, Z.A., Priore, R.L., Janardhan, V., Kaliszky, Z. *et al.* (2000) Brain MRI lesions and atrophy are related to depression in multiple sclerosis, *Neuroreport* 11: 1153–1158.
- Barak, Y. and Achiron, A. (2002) Effect of interferon-beta-1b on cognitive functions in multiple sclerosis, *Eur Neurol* 47: 11–14.
- Beiske, A.G., Svensson, E., Sandanger, I., Czujko, B., Pedersen, E.D., Aarseth, J.H. *et al.* (2008) Depression and anxiety amongst multiple sclerosis patients, *Eur J Neurol* 15: 239–245.
- Benedict, R.H. and Bobholz, J.H. (2007) Multiple sclerosis, *Semin Neurol* 27: 78–85.
- Benedict, R.H., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N. *et al.* (2006) Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS), *J Int Neuropsychol Soc* 12: 549–558.
- Benedict, R.H., Zivadinov, R., Carone, D.A., Weinstock-Guttman, B., Gaines, J., Maggiore, C. *et al.* (2005) Regional lobar atrophy predicts memory impairment in multiple sclerosis, *AJNR Am J Neuroradiol* 26: 1824–1831.
- Bermel, R.A. and Bakshi, R. (2006) The measurement and clinical relevance of brain atrophy in multiple sclerosis, *Lancet Neurol* 5: 158–170.
- Bian, Q., Kato, T., Monji, A., Hashioka, S., Mizoguchi, Y., Horikawa, H. *et al.* (2008) The effect of atypical antipsychotics, perospirone, ziprasidone and quetiapine on microglial activation induced by interferon-gamma, *Prog Neuropsychopharmacol Biol Psychiatry* 32: 42–48.
- Bobholz, J.A. and Rao, S.M. (2003) Cognitive dysfunction in multiple sclerosis: a review of recent developments, *Curr Opin Neurol* 16: 283–288.
- Bobholz, J.A., Rao, S.M., Lobeck, L., Elsinger, C., Gleason, A., Kanz, J. *et al.* (2006) fMRI study of episodic memory in relapsing-remitting MS: correlation with T2 lesion volume, *Neurology* 67: 1640–1645.
- Calabrese, P. (2006) Neuropsychology of multiple sclerosis. An overview, *J Neurol* 253(Suppl. 1): 10–15.
- Charcot, J.M. (1877) *Lectures on the Diseases of the Nervous System*. La Salpêtrière: London.
- Chong, S. and Ko, S. (1997) Clozapine treatment of psychosis associated with multiple sclerosis, *Can J Psychiat* 42: 90–91.
- Chwastiak, L., Ehde, D.M., Gibbons, L.E., Sullivan, M., Bowen, J.D. and Kraft, G.H. (2002) Depressive symptoms and severity of illness in multiple sclerosis: epidemiologic study of a large community sample, *Am J Psychiatry* 159: 1862–1868.
- Cottrell, S.S. and Wilson, S.A.K. (1926) The affective symptomatology of disseminated sclerosis, *J Neurol Psychopathol* 7: 1–30.
- Crayton, H.J. and Rossman, H.S. (2006) Managing the symptoms of multiple sclerosis: a multimodal approach, *Clin Ther* 28: 445–460.
- Cuijpers, P. and Smit, F. (2002) Excess mortality in depression: a meta-analysis of community studies, *J Affect Disord* 72: 227–236.
- Cummings, J.L., Arciniegas, D.B., Brooks, B.R., Herndon, R.M., Lauterbach, E.C., Pioro, E.P. *et al.* (2006) Defining and diagnosing involuntary emotional expression disorder, *CNS Spectr* 11: 1–7.
- Davids, E., Hartwig, U. and Gastpar, M. (2004) Antipsychotic treatment of psychosis associated with multiple sclerosis, *Prog Neuropsychopharmacol Biol Psychiatry* 28: 743–744.
- Diaz-Olavarrieta, C., Cummings, J.L., Velazquez, J. and Garcia de la Cadena, C. (1999) Neuropsychiatric manifestations of multiple sclerosis, *J Neuropsychiatry Clin Neurosci* 11: 51–57.
- Dunn, A.J., Swiergiel, A.H. and de Beaurepaire, R. (2005) Cytokines as mediators of depression: what can we learn from animal studies?, *Neurosci Biobehav Rev* 29: 891–909.
- Ebers, G.C. (2008) Environmental factors and multiple sclerosis, *Lancet Neurol* 7: 268–277.
- Fassbender, K., Schmidt, R., Moßner, R., Kischka, U., Kuhnen, J., Schwartz, A. *et al.* (1998) Mood disorders and dysfunction of the hypothalamic-pituitary-adrenal axis in multiple sclerosis, *Arch Neurol* 55: 66–72.
- Feinstein, A. (1999) *The Clinical Neuropsychiatry of Multiple Sclerosis*. Cambridge University Press: Cambridge.
- Feinstein, A. (2002) An examination of suicidal intent in patients with multiple sclerosis, *Neurology* 59: 674–678.

- Feinstein, A. (2004) The neuropsychiatry of multiple sclerosis, *Can J Psychiatry* 49: 157–163.
- Feinstein, A., du Boulay, G. and Ron, M.A. (1992) Psychotic illness in multiple sclerosis. A clinical and magnetic resonance imaging study, *Br J Psychiatry* 161: 680–685.
- Feinstein, A., Feinstein, K.J., Gray, T. and O'Connor, P. (1997) The prevalence and neuro-behavioral correlates of pathological laughter and crying in multiple sclerosis, *Arch Neurol* 54: 1116–1121.
- Feinstein, A., O'Connor, P. and Feinstein, K. (2002) Multiple sclerosis, interferon beta-1b and depression. A prospective investigation, *J Neurol* 249: 815–820.
- Feinstein, A., Roy, P., Lobaugh, N., Feinstein, K., O'Connor, P. and Black, S. (2004) Structural brain abnormalities in multiple sclerosis patients with major depression, *Neurology* 62: 586–590.
- Folkman, S. and Moskowitz, J.T. (2004) Coping: pitfalls and promise, *Annu Rev Psychol* 55: 745–774.
- Foong, J. and Ron, M.A. (2003) 'Neuropsychiatry: cognition and mood disorders'. In McDonald, W.I. and Noseworthy, J.H. (eds) *Multiple Sclerosis 2*. Butterworth-Heinemann Publishers: Philadelphia, 115–124.
- Ford, H., Trigwell, P. and Johnson, M. (1998) The nature of fatigue in multiple sclerosis, *J Psychosom Res* 45: 33–38.
- Franklin, G.M., Heaton, R.K., Nelson, L.M., Filley, C.M. and Seibert, C. (1988) Correlation of neuropsychological and MRI findings in chronic/progressive multiple sclerosis, *Neurology* 38: 1826–1829.
- Freal, J.E., Kraft, G.H. and Coryell, J.K. (1984) Symptomatic fatigue in multiple sclerosis, *Arch Phys Med Rehabil* 65: 135–138.
- Ghaffar, O., Chamelian, L. and Feinstein, A. (2008) Neuroanatomy of pseudobulbar affect: a quantitative MRI study in multiple sclerosis, *J Neurol* 255: 406–412.
- Ghaffar, O. and Feinstein, A. (2007) The neuropsychiatry of multiple sclerosis: a review of recent developments, *Curr Opin Psychiatry* 20: 278–285.
- Gold, S.M. and Irwin, M.R. (2006) Depression and immunity: inflammation and depressive symptoms in multiple sclerosis, *Neurol Clin* 24: 507–519.
- Golden Consensus Group (2005) The Goldman Consensus statement on depression in multiple sclerosis, *Mult Scler* 11: 328–337.
- Griffiths, S.Y., Yamamoto, A., Boudreau, V.G., Ross, L.K., Kozora, E. and Thornton, A.E. (2005) Memory interference in multiple sclerosis, *J Int Neuropsychol Soc* 11: 737–746.
- Haghikia, A., Ladage, K., Hinkerohe, D., Vollmar, P., Heupel, K., Dermietzel, R. et al. (2008) Implications of antiinflammatory properties of the anticonvulsant drug levetiracetam in astrocytes, *J Neurosci Res* 86: 1781–1788.
- Heesen, C., Mohr, D.C., Huitinga, I., ThenBergh, F., Gaab, J., Otte, C. et al. (2007) Stress regulation in multiple sclerosis – current issues and concepts, *Mult Scler* 13: 143–148.
- Henry, J.D. and Beatty, W.W. (2006) Verbal fluency deficits in multiple sclerosis, *Neuropsychologia* 44: 1166–1174.
- Henze, T., Rieckmann, P. and Toyka, K.V. (2006) Symptomatic treatment of multiple sclerosis multiple sclerosis therapy consensus group (MSTCG) of the German multiple sclerosis society, *Eur Neurol* 56: 78–105.
- Hildebrandt, H., Hahn, H.K., Kraus, J.A., Schulte-Herbrüggen, A., Schwarze, B. and Schwendemann, G. (2006) Memory performance in multiple sclerosis patients correlates with central brain atrophy, *Mult Scler* 12: 428–436.
- Huber, S.J., Bornstein, R.A., Rammohan, K.W., Christy, J.A., Chakeres, D.W. and McGhee, R.B. (1992) Magnetic resonance imaging correlates of neuropsychological impairment in multiple sclerosis, *J Neuropsychiatry Clin Neurosci* 4: 152–158.
- Huijbregts, S.C., Kalkers, N.F., de Sonnevile, L.M., de Groot, V. and Polman, C.H. (2006) Cognitive impairment and decline in different MS subtypes, *J Neurol Sci* 245: 187–194.
- Jacobs, L.D., Beck, R.W., Simon, J.H., Kinkel, R.P., Brownschidle, C.M., Murray, T.J. et al. (2000) Intramuscular interferon-beta-1 therapy initiated during a first demyelinating event in multiple sclerosis, *N Engl J Med* 343: 898–904.
- Janardhan, V. and Bakshi, R. (2002) Quality of life in patients with multiple sclerosis: the impact of fatigue and depression, *J Neurol Sci* 205: 51–58.
- Janssens, A.C.J.W., Buljevac, D., van Doorn, P.A., van der Meche, F.G.A., Polman, C.H., Passchier, J. et al. (2006) Prediction of anxiety and distress following diagnosis of multiple sclerosis: a two-year longitudinal study, *Mult Scler* 12: 794–801.
- Janssens, A.C.J.W., van Doorn, P.A., de Boer, J.B., van der Meche, F.G.A., Passchier, J. and Hintzen, R.Q. (2003) Impact of recently diagnosed multiple sclerosis on quality of life, anxiety, depression and distress of patients and partners, *Acta Neurol Scand* 108: 389–395.
- Jefferies, K. (2006) The neuropsychiatry of multiple sclerosis, *Advan Psychiatr Treat* 12: 214–220.
- Jongen, P.J. (2006) Psychiatric onset of multiple sclerosis, *J Neurol Sci* 245: 59–62.
- Jonsson, A., Dock, J. and Ravnborg, M.H. (1996) Quality of life as a measure of rehabilitation outcome in patients with multiple sclerosis, *Acta Neurol Scand* 93: 229–235.

- Kahl, K.G., Kruse, N., Faller, H., Weiss, H. and Rieckmann, P. (2002) Expression of tumor necrosis factor- α and interferon- γ mRNA in blood cells correlates with depression scores during an acute attack in patients with multiple sclerosis, *Psychoneuroendocrinology* 27: 671–681.
- Kato, T., Mizoguchi, Y., Monji, A., Horikawa, H., Suzuki, S.O., Seki, Y. *et al.* (2008) Inhibitory effects of aripiprazole on interferon- γ -induced microglial activation via intracellular Ca(2+) regulation *in vitro*, *J Neurochem* 106: 815–825.
- Kelley, K.W., Bluthé, R.M., Dantzer, R., Zhou, J.H., Shen, W.H., Johnson, R.W. *et al.* (2003) Cytokine-induced sickness behavior, *Brain Behav Immun* 17(Suppl. 1): S112–118.
- Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R. *et al.* (2003) The survey replication epidemiology of major depressive disorder results from the National Comorbidity Survey Replication, *JAMA* 289: 3095–3105.
- Korostil, M. and Feinstein, A. (2007) Anxiety disorders and their clinical correlates in multiple sclerosis patients, *Mult Scler* 13: 67–72.
- Krupp, L.B., Alvarez, L.A., LaRocca, N.G. and Scheinberg, L.C. (1988) Fatigue in multiple sclerosis, *Arch Neurol* 45: 435–437.
- Krupp, L.B., Christodoulou, C., Melville, P., Scherl, W.F., MacAllister, W.S. and Elkins, L.E. (2004) Donepezil improved memory in multiple sclerosis in a randomized clinical trial, *Neurology* 63: 1579–1585.
- Kumar, R. (2008) Approved and investigational uses of modafinil: an evidence-based review, *Drugs* 68: 1803–1839.
- Larcombe, N.A. and Wilson, P.H. (1984) An evaluation of cognitive – behaviour therapy for depression in patients with multiple sclerosis, *Br J Psychiatry* 145: 366–371.
- Lebrun, C. (2001) Therapeutic indications in symptomatic cognitive and psychopathological disorders in multiple sclerosis, *Rev Neurol (Paris)* 157: 1085–1090.
- Leonard, B.E. (2001) The immune system, depression and the action of antidepressants, *Prog Neuropsychopharmacol Biol Psychiatry* 25: 767–780.
- Lublin, F.D. and Reingold, S.C. (1996) Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis, *Neurology* 46: 907–911.
- Martinelli, V. (2000) Trauma, stress and multiple sclerosis, *Neurol Sci* 21: S849–S852.
- Mattingly, G., Baker, K., Zorumski, C.F. and Figiel, G.S. (1992) Multiple sclerosis and ECT: possible value of gadolinium-enhanced magnetic resonance scans for identifying high-risk patients, *J Neuropsychiatry Clin Neurosci* 4: 145–151.
- McCabe, M.P. (2005) Mood and self-esteem of persons with multiple sclerosis following an exacerbation, *J Psychosom Res* 59: 161–166.
- McDonald, I. and Compston, A. (2006) ‘The symptoms and signs of multiple sclerosis’, in Compston, A. *et al.* (eds) *McAlpine’s Multiple Sclerosis*, 4th edition. Churchill Livingstone: Philadelphia, 321–322.
- McIntosh-Michaelis, S.A., Roberts, M.H., Wilkinson, S.M., Diamond, I.D., McLellan, D.L., Martin, J.P. *et al.* (1991) The prevalence of cognitive impairment in a community survey of multiple sclerosis, *Br J Clin Psychol* 30: 333–348.
- McNulty, K., Livneh, H. and Wilson, L.M. (2004) Perceived uncertainty, spiritual well-being and psychosocial adaptation in individuals with multiple sclerosis, *Rehabil Psychol* 9: 91–99.
- Minden, S.L. and Schiffer, R.B. (1990) Affective disorders in multiple sclerosis: Review and recommendations for clinical research, *Arch Neurol* 47: 98–104.
- Minden, S.L. (2000) Mood disorders in multiple sclerosis: diagnosis and treatment, *J Neurovirol* 6(Suppl. 2): S160–S167.
- Mohr, D.C., Classen, C. and Barrera Jr.M. (2004) The relationship between social support, depression and treatment for depression in people with multiple sclerosis, *Psychol Med* 34: 533–541.
- Mohr, D.C., Cox, D., Epstein, L. and Boudewyn, A. (2002) Teaching patients to self- inject: pilot study of a treatment for injection anxiety and phobia in multiple sclerosis patients prescribed injectable medications, *J Behav Ther Exp Psychiatry* 33: 39–47.
- Mohr, D.C., Goodkin, D.E., Likosky, W., Gatto, N., Baumann, K.A. and Rudick, R.A. (1997) Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis, *Arch Neurol* 54: 531–533.
- Mohr, D.C. and Goodkin, D.E. (1999) Treatment of depression in multiple sclerosis, *Clin Psychol Sci Pract* 6: 1–9.
- Mohr, D.C., Hart, S.L. and Goldberg, A. (2003) Effects of treatment for depression on fatigue in multiple sclerosis, *Psychosom Med* 65: 542–547.
- Moran, P.J. and Mohr, D.C. (2005) The validity of Beck Depression Inventory and Hamilton Rating Scale for Depression items in the assessment of depression among patients with multiple sclerosis, *J Behav Med* 28: 35–41.
- O’Brien, A.R., Chiaravalloti, N., Goverover, Y. and Deluca, J. (2008) Evidenced-based cognitive rehabilitation for persons with multiple sclerosis: a review of the literature, *Arch Phys Med Rehabil* 89: 761–769.
- Panitch, H.S., Thisted, R.A., Smith, R.A., Wynn, D.R., Wymer, J.P., Achiron, A. *et al.* (2006)

- Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis, *Ann Neurol* 59: 780–787.
- Pantano, P., Mainero, C. and Caramia, F. (2006) Functional brain reorganization in multiple sclerosis: evidence from fMRI studies, *J Neuroimaging* 16: 104–114.
- Patten, S.B., Beck, C.A., Williams, J.V., Barbui, C. and Metz, L.M. (2003) Major depression in multiple sclerosis: a population-based perspective, *Neurology* 61: 1524–1527.
- Patten, S.B. and Metz, L.M. (2001) InterferonB-1a and depression in relapsing-remitting multiple sclerosis: an analysis of depression data from the PRISMS clinical trial, *Mult Scler* 7: 243–248.
- Patten, S.B., Svenson, L.W. and Metz, L.M. (2005) Psychotic disorders in MS: population-based evidence of an association, *Neurology* 65: 1123–1125.
- Perälä, J., Suvisaari, J., Saarni, S.I., Kuoppasalmi, K., Isometsä, E., Pirkola, S. *et al.* (2007) Lifetime prevalence of psychotic and bipolar I disorders in a general population, *Arch Gen Psychiatry* 64: 19–28.
- Pinkston, J.B., Kablinger, A. and Alekseeva, N. (2007) Multiple sclerosis and behavior, *Int Rev Neurobiol* 79: 323–339.
- Plohmman, A.M., Kappos, L., Ammann, W., Thordai, A., Wittwer, A., Huber, S. *et al.* (1998) Computer assisted retraining of attentional impairments in patients with multiple sclerosis, *J Neurol Neurosurg Psychiatry* 64: 455–462.
- Pollak, Y., Ovadia, H., Orion, E. and Yirmiya, R. (2003) The EAE-associated behavioral syndrome: II. Modulation by anti-inflammatory treatments, *J Neuroimmunol* 137: 100–108.
- Porcel, J., Rio, J., Sanchez-Betancourt, A., Arevalo, M.J., Tintore, M., Tellez, N. *et al.* (2006) Long-term emotional state of multiple sclerosis patients treated with interferon beta, *Mult Scler* 12: 802–807.
- Price, R.K., North, C.S., Wessely, S. and Fraser, V.J. (1992) Estimating the prevalence of chronic fatigue syndrome and associated symptoms in the community, *Public Health Rep* 107: 514–522.
- Puri, B.K., Bydder, G.M., Chaudhuri, K.R., Al Saffar, B.Y., Curati, W.L., White, S.J. *et al.* (2001) MRI changes in multiple sclerosis following treatment with lofepramine and L-phenylalanine, *Neuroreport* 12: 1821–1824.
- Rabins, P.V., Brooks, B.R., O'Donell, P., Pearlson, G.D., Moberg, P., Jubelt, B. *et al.* (1986) Structural brain correlates of emotional disorder in multiple sclerosis, *Brain* 109: 585–597.
- Rabins, P.V. (1990) 'Euphoria in multiple sclerosis'. In Rao, S.M. (ed.) *Neurobehavioural Aspects of Multiple Sclerosis*. Oxford University Press: New York, 180–185.
- Rammohan, K.W., Rosenberg, J.H., Lynn, D.J., Blumenfeld, A.M., Pollak, C.P. and Nagaraja, H.N. (2002) Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study, *J Neurol Neurosurg Psychiatry* 72: 179–183.
- Rao, S.M., Leo, G.J., Bernadin, L. and Unverzagt, F. (1991) Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns and prediction, *Neurology* 41: 685–691.
- Reichenberg, A., Yirmiya, R., Schuld, A., Kraus, T., Haack, M., Morag, A. *et al.* (2001) Cytokine-associated emotional and cognitive disturbances in humans, *Arch Gen Psychiatry* 58: 445–452.
- Reiss, J.P., Sam, D. and Sareen, J. (2006) Psychosis in multiple sclerosis associated with left temporal lobe lesions on serial MRI scans, *J Clin Neurosci* 13: 282–284.
- Ritchie, K., Artero, S. and Touchon, J. (2001) Classification criteria for mild cognitive impairment: a population-based validation study, *Neurology* 56: 37–42.
- Romani, A., Bergamaschi, R., Candeloro, E., Alfonsi, E., Callieco, R. and Cosi, V. (2004) Fatigue in multiple sclerosis: multidimensional assessment and response to symptomatic treatment, *Mult Scler* 10: 462–468.
- Ron, M.A. and Logsdail, S.J. (1989) Psychiatric morbidity in multiple sclerosis: a clinical and MRI study, *Psychol Med* 19: 887–895.
- Sá, M.J. (2008) Psychological aspects of multiple sclerosis, *Clin Neurol Neurosurg* 110: 868–877.
- Sadovnick, A.D., Eisen, K., Ebers, G.C. and Paty, D.W. (1991) Cause of death in patients attending multiple sclerosis clinics, *Neurology* 41: 1193–1196.
- Sanfilipo, M.P., Benedict, R.H., Weinstock-Guttman, B. and Bakshi, R. (2006) Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis, *Neurology* 66: 685–692.
- Schiffer, R.B. (1990) 'Disturbances of affect'. In Rao, S.M. (ed.) *Neurobehavioral Aspects of Multiple Sclerosis*. Oxford University Press: New York, 186–195.
- Schiffer, R.B., Herndon, R.M. and Rudick, R.A. (1985) Treatment of pathologic laughing and weeping with amitriptyline, *N Engl J Med* 312: 1480–1482.
- Schiffer, R.B., Wineman, M. and Weitkamp, L.R. (1986) Association between bipolar affective disorder and multiple sclerosis, *Am J Psychiatry* 143: 94–105.
- Schwid, S.R. and Murray, J.T. (2005) Treating fatigue in patients with MS: one step forward, one step back, *Neurology* 64: 1111–1112.
- Scott, T.F., Nussbaum, P., McConnell, H. and Brill, P. (1995) Measurement of treatment response to sertraline in depressed multiple sclerosis patients using the Carroll scale, *Neurol Res* 17: 421–422.

- Seliger, G.M., Hornstein, A., Flax, J., Herbert, J. and Schroeder, K. (1992) Fluoxetine improves emotional incontinence, *Brain Inj* 6: 267–270.
- Shackleton, B., Harrison, K. and Taylor, C. (2008) Dementia 2: early diagnosis and initial nursing care, *Nurs Times* 104: 26–27.
- Shenal, B.V., Harrison, D.W. and Demaree, H.A. (2003) The neuropsychology of depression: a literature review and preliminary model, *Neuropsychol Rev* 13: 33–42.
- Siebert, R.J. and Abernethy, D.A. (2005) Depression in multiple sclerosis: a review, *J Neurol Neurosurg Psychiatry* 76: 469–475.
- Stankoff, B., Waubant, E., Confavreux, C., Edan, G., Debouverie, M., Rumbach, L. *et al.* (2005) Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study, *Neurology* 64: 1139–1143.
- Stenager, E.N., Stenager, E., Koch-Henriksen, N., Brønnum-Hansen, H., Hyllested, K., Jensen, K. *et al.* (1992) Suicide and multiple sclerosis: an epidemiological investigation, *J Neurol Neurosurg Psychiatry* 55: 542–545.
- Storr, L.K., Sorensen, P.S. and Ravnborg, M. (2006) The efficacy of multidisciplinary rehabilitation in stable multiple sclerosis patients, *Mult Scler* 12: 235–242.
- Sutçigil, L., Oktenli, C., Musabak, U., Bozkurt, A., Cansever, A., Uzun, O. *et al.* (2007) Pro- and anti-inflammatory cytokine balance in major depression: effect of sertraline therapy, *Clin Dev Immunol* 2007: 76396.
- Sweet, L.H., Rao, S.M., Primeau, M., Durgerian, S. and Cohen, R.A. (2006) Functional magnetic resonance imaging response to increased verbal working memory demands among patients with multiple sclerosis, *Hum Brain Map* 27: 28–36.
- Taus, C., Giuliani, G., Pucci, E., D'Amico, R. and Solari, A. (2003) Amantadine for fatigue in multiple sclerosis, *Cochrane Database Syst Rev* 2003: CD002818.
- Tellez, N., Rio, J., Tintore, M., Nos, C., Galan, I. and Montalban, X. (2006) Fatigue in multiple sclerosis persists over time: a longitudinal study, *J Neurol* 253: 1466–1470.
- Thomas, P.W., Thomas, S., Hillier, C., Galvin, K., Baker, R. and The Cochrane Collaboration (2007) Psychological interventions for multiple sclerosis (review) *The Cochrane Library*. Vol 1. John Wiley & Sons: Chichester, 1–51.
- Udaka, F., Yamao, S., Nagata, H., Nakamura, S. and Kameyama, M. (1984) Pathologic laughing and crying treated with levodopa, *Arch Neurol* 41: 1095–1096.
- van Kessel, K., Moss-Morris, R., Willoughby, E., Chalder, T., Johnson, M.H. and Robinson, E. (2008) A randomized controlled trial of cognitive behavior therapy for multiple sclerosis fatigue, *Psychosom Med* 70: 205–213.
- Vercoulen, J.H.M.M., Hommes, O.R., Swanink, C.M.A., Jongen, P.J., Fennis, J.F., Galama, J.M. *et al.* (1996) The measurement of fatigue in patients with multiple sclerosis: a multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects, *Arch Clin Neurol* 53: 642–649.
- Wei, T. and Lightman, S.L. (1997) The neuroendocrine axis in patients with multiple sclerosis, *Brain* 120: 1067–1076.
- Williams, R.M., Turner, A.P., Hatzakis, M., Chu, S., Rodriguez, A.A., Bowen, J.D. *et al.* (2004) Social support among veterans with multiple sclerosis, *Rehabil Psychol* 49: 106–113.
- Young, C.R., Weiss, E.L., Bowers Jr, M.B. and Mazure, C.M. (1997) The differential diagnosis of multiple sclerosis and bipolar disorder, *J Clin Psychiatry* 58: 123.
- Zéphir, H., de Seze, J., Dujardin, K., Dubois, G., Cabaret, M., Bouillaguet, S. *et al.* (2005) One-year cyclophosphamide treatment combined with methylprednisolone improves cognitive dysfunction in progressive forms of multiple sclerosis, *Mult Scler* 11: 360–363.
- Zhu, J., Wei, X., Feng, X., Song, J., Hu, Y. and Xu, J. (2008) Repeated administration of mirtazapine inhibits development of hyperalgesia/allodynia and activation of NF-kappaB in a rat model of neuropathic pain, *Neurosci Lett* 433: 33–37.
- Zorzon, M., deMasi, R., Nasuelli, D., Ukmar, M., Mucelli, R.P., Cazzato, G. *et al.* (2001) Depression and anxiety in multiple sclerosis. A clinical and MRI study in 95 subjects, *J Neurol* 248: 416–421.

Visit SAGE journals online
<http://tan.sagepub.com>

SAGE JOURNALS
 Online