LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their thrice-weekly rounds, Dr. Stern and other members of the Psychiatric Consultation Service discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Neuropsychiatric Manifestations of Multiple Sclerosis

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Have you ever wondered how often multiple sclerosis (MS) is complicated by neuropsychiatric symptoms such as depression, mania, or cognitive impairment? Do you wonder how to evaluate MS patients for these neuropsychiatric sequelae and how best to manage them? If so, the following case vignette and discussion should serve to highlight these and other issues relevant to the care of patients with MS.

Case Vignette

Mr. A, a 41-year-old man with long-standing MS and depression, was involuntarily admitted to an inpatient psychiatric unit after expressing thoughts of suicide to family members following a romantic breakup. Preceding this admission, he experienced 1 month of mixed manic and depressive symptoms, including irritability with marked mood swings, rapid speech, distractibility, decreased sleep, and impulsive spending (up to $10,000 per month). In addition, cognitive decline (with prominent impairment in his short-term memory) led family members to wonder if he could continue to live independently.

Mr. A was diagnosed with relapsing-remitting MS at age 18 years after the onset of optic neuritis; subsequently, his illness followed a progressive course with spastic diplegia and gait disturbance, which required use of a cane. He was treated with interferon-β1a for maintenance therapy and pulse corticosteroids as needed for acute MS symptoms. He had been living alone in an apartment, spending his days gambling and "trying to pick up women." He had refused multiple attempts by health care providers and family members to arrange home support services, including visiting nurses, physical therapy, occupational therapy, meal delivery, and ride assistance.

Following civil commitment to the psychiatric unit, he was treated with a combination of lithium carbonate and olanzapine for his mania with psychotic features. His mood symptoms improved, although he remained mildly irritable and disinhibited when interacting with staff—his "baseline personality" according to family. He also continued to demonstrate cognitive deficits with poor spontaneous recall of words, impaired attention and concentration and concrete thinking, and evidence of frontal network dysfunction with impairment on the Luria and Go/No-Go test of response inhibition.[1] Luria's fist-edge-palm test, in which a patient is asked to mimic a series of hand movements, is a useful bedside examination for detecting frontal lobe damage and has been associated with perseveration and impaired constructional ability. The Go/No-Go task requires the patient to perform a simple motor response (e.g., raising his or her hand) in response to 1 cue (e.g., 2 taps on the table) while inhibiting the response in the presence of another cue (e.g., 1 tap on the table); patients with impaired impulse control have a difficult time

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Table 1. McDonald Diagnostic Criteria for Multiple Sclerosis With 2005 Revisions[a]

Clinical Presentation	Supportive Data Needed for Diagnosis
≥ 2 neurologic attacks ≥ 24 hr each Objective clinical evidence of ≥ 2 lesions	None
≥ 2 neurologic attacks ≥ 24 hr each Objective clinical evidence of 1 lesion	Dissemination in space by 1 of the following: MRI[b] criteria met ≥ 2 MRI lesions *and* CSF oligoclonal bands or raised IgG index Future clinical attack at different site
1 neurologic attack ≥ 24 hr Objective clinical evidence of ≥ 2 lesions	Dissemination in time by 1 of the following: MRI[c] criteria met Second clinical attack
1 neurologic attack ≥ 24 hr Objective evidence of 1 lesion	Dissemination in space by 1 of following: MRI[b] criteria met ≥ 2 MRI lesions *and* CSF oligoclonal bands or raised IgG index *and* Dissemination in time by 1 of the following: MRI[c] criteria met Second clinical attack
Insidious neurologic progression suggestive of multiple sclerosis	Continued progression of symptoms for 1 year *and* 2 of the following present: ≥ 9 T2 brain lesions or ≥ 4 T2 brain lesions + positive VEP[d] 2 focal T2 spinal cord lesions CSF oligoclonal bands or raised IgG index

[a]Adapted with permission from Polman et al.[11]
[b]At least 3 of 4 criteria met: (1) 1 gadolinium-enhancing brain or spinal cord lesion or 9 total T2-hyperintense lesions, (2) ≥ 1 infratentorial or spinal cord lesion, (3) ≥ 1 juxtacortical lesion, and (4) ≥ 3 periventricular lesions.
[c]Either (1) presence of a gadolinium-enhancing lesion ≥ 3 months after the onset of a clinical event, if not at site implicated in the original event, *or* (2) new gadolinium-enhancing lesion on second scan compared with a reference scan performed ≥ 30 days after onset of a clinical event.
[d]Delayed VEP with well-preserved wave form.
Abbreviations: CSF = cerebrospinal fluid, MRI = magnetic resonance imaging, VEP = visual-evoked potential.

performing this task accurately. Mr. A's frustration tolerance was low, and he resisted attempts at assistance with activities of daily living. An expanded 100-point mental status examination indicated global dysfunction predictive of impaired ability to live independently, and an occupational therapy evaluation revealed deficits in planning and executing basic home care functions such as meal preparation. A brain magnetic resonance image (MRI) with gadolinium revealed findings typical of advanced MS, including numerous T2 white matter hyperintensities and diffuse cortical atrophy.

What Is Multiple Sclerosis?

Multiple sclerosis is the most common chronic neurologic condition affecting young adults in the United States with a prevalence of approximately 1 in 1000.[2] Multiple sclerosis affects twice as many women as men, and the prevalence climbs as geographical distance from the equator increases.[3] Previously thought of as an inflammatory, demyelinating disease primarily affecting central nervous system (CNS) white matter, more recent imaging studies have shown that significant damage to cortical gray matter also occurs.[4–6] Common clinical features include visual disturbances (diplopia, blurred vision), weakness, gait disturbance, vertigo, fatigue, urinary retention and incontinence, and speech and swallowing difficulties.[3] Neuropsychiatric symptoms are also commonplace and are occasionally the first presentation of MS.[7,8] As many of the characteristic signs and symptoms are nonspecific and pseudoneurologic in nature, patients are often suspected of suffering from a primarily psychiatric condition,[9] and diagnosis may be delayed.

Multiple sclerosis is a clinical diagnosis based on the presence of neurologic symptoms disseminated in space and time (Table 1).[10,11] Supporting laboratory data include the presence of oligoclonal IgG bands on cerebrospinal fluid analysis, abnormalities of visual-evoked potentials, and characteristic MRI lesions corresponding to "plaques" of demyelination.[3] Four MS subtypes corresponding to the course of illness have been described: relapsing-remitting (66%), secondary-progressive (16%), primary-progressive (15%), and benign MS.[8] In relapsing-remitting MS, patients recover fully between exacerbations, whereas in the primary-progressive subtype, patients experience accumulating symptoms and disability from disease onset without remission. In the secondary-progressive subtype, from which Mr. A suffers, patients experience exacerbations and apparent recovery early in the disease course, although eventually symptoms are progressive and re-

mission is no longer obtained. A small minority of patients with benign MS experience only a single MS episode with no further exacerbations.[8]

Acute MS exacerbations are typically treated with pulse intravenous (IV) corticosteroids (methylprednisolone 1g IV daily × 3–5 days).[3] In relapsing-remitting MS, chronic treatment with disease-modifying agents can reduce the frequency of exacerbations as well as slow down the accumulation of physical disability.[3,8] These agents include interferon-β1a and interferon-β1b, which act by suppressing the autoimmune response resulting in damage to the myelin sheath. Another treatment, glatiramer acetate, is composed of amino acids believed to mimic myelin basic protein, diverting reactive lymphocytes in circulation before they cross the blood-brain barrier. Supportive treatment strategies target the specific physical and cognitive symptoms of MS and aim to maximize function, including physical therapy, occupational therapy, and environmental modifications.[3]

What Psychiatric Symptoms Are Associated With Multiple Sclerosis?

Psychiatric symptoms in MS are highly prevalent and frequently overlooked in clinical settings.[12–14] In 1 study of relapsing-remitting patients with MS in remission, 95% reported significant psychiatric symptoms, most frequently dysphoria (79%), agitation (40%), anxiety (40%), and irritability (35%).[15]

Major depressive disorder (MDD) is particularly common, with a lifetime prevalence rate of approximately 50%,[12–14,16] as compared to a rate of 10% to 15% in the general population. Rates of suicide are also significantly higher in those with MS, and in 1 study, depression superceded physical disability and cognitive function as a significant determinant of quality of life.[13] Several factors related to MS symptomatology, disease course, and treatment may contribute to the exceedingly high rates of depression and its complications seen in patients with MS. For example, MS and depression share several neurovegetative symptoms (including fatigue, poor concentration, and disturbances of sleep and appetite), which can complicate the diagnosis of depression in this population.[13] However, studies generally support the strikingly high prevalence of depression in MS patients, finding high rates of MS-associated depressive disorders even when somatic complaints are not included in the diagnostic criteria.[17]

The burden of accepting a lifelong, progressive, and incurable illness likely plays a role in the development of depression as well. Shorter duration of illness (< 1 year) has been associated with depression, perhaps reflecting the difficulty of adjusting to a new diagnosis of this chronic, unpredictable illness[12,18]; this finding highlights the need for frequent screening for depression in newly diagnosed MS patients. Consistent with this observation, the patient presented in the case vignette, Mr. A, experienced his first episode of MDD shortly after his initial diagnosis of MS at age 18 years, culminating in an unsuccessful suicide attempt. Data on the relationship between physical disability and depression are mixed,[12,16,18] although depressed patients with MS may experience the impact of their disability as greater than nondepressed patients.[12,18] Furthermore, physical disability in MS often leads to social isolation, loss of independence, and loss of recreational activities, factors that may contribute to the development of depression.[19] Mr. A was facing a decline in his ability to function without assistance at home, yet he fiercely defended his independence, often making statements of how hospital and home care made him "more depressed." Other psychological characteristics predictive of depression in people with MS include feelings of uncertainty about the future, hopelessness, and emotion-centered coping (as opposed to active, problem-centered coping strategies).[16]

Finally, effects of treatment for MS, particularly interferon, may occasionally cause or exacerbate depressive symptoms. While studies have not demonstrated a well-defined relationship between treatment with interferon and depression, such studies are plagued by methodological flaws, and results are conflicting.[8,20] Glatiramer acetate has generally not been associated with deterioration in mood.[20]

The aforementioned characteristics of illness (neurovegetative symptoms, physical disability, and progressive course) are not unique to MS, yet for unclear reasons, MDD remains more common in MS than other chronic neurologic conditions that affect the CNS.[12,17] Major depressive disorder in MS patients has been associated with characteristic CNS changes, including cortical atrophy and lesions in specific regions of the frontal lobes, which may account for some of this observed difference.[19] Major depressive disorder in patients with MS, therefore, is unlikely to represent a simple reaction to the physical disability, uncertainty, and decreased independence that the illness entails, but given its prevalence, may be considered a symptom of the illness itself and reflective of CNS cortical damage.

Bipolar disorder is also twice as common in MS patients as in the general population[13,21] and often presents later in the course of MS, as in the case of Mr. A, who presented with his first episode of mania at age 41 years. While treatment with high doses of corticosteroids may precipitate mania, the increased prevalence of bipolar disorder does not appear related to this treatment alone.[14] Though rare, there have been case reports of patients diagnosed with MS only after presenting with acute, late-onset mania in the absence of neurologic signs.[8] Mr. A's late onset of manic symptoms would be highly atypical

for primary bipolar disorder and suggests that MS lesions in critical brain regions may be a substantial contributing factor to his presentation.[21] For example, lesions along the orbitofrontal prefrontal cortex circuit lead to impulsivity, mood lability, and personality changes, symptoms frequently seen in acute mania.[8] On the other hand, a history of manic or hypomanic symptoms in Mr. A may have been long overlooked given the complexity of his neurologic and cognitive presentation, leading to a delay in diagnosis of bipolar disorder.

Pseudobulbar affect is a syndrome observed in up to 10% of people with MS; it is characterized by a disconnection between mood and affect, leading to "laughter without mirth" and "tears without sadness."[13,22] Pseudobulbar affect is common in other neurologic disorders and may be caused by disruption of neuronal connections arising from the brainstem and cerebellum that are involved in regulation of emotional expression.[22] Inappropriate episodes of crying and laughing are often embarrassing to patients and may severely limit social interactions.

Like bipolar disorder, psychosis is 2 to 3 times as common in people with MS as it is in the general population, although there has been limited study of this topic.[23] Various MRI studies have demonstrated a high lesion load in the medial temporal regions of the cortex among MS patients with psychosis, again suggestive of a role for demyelinating lesions in critical brain regions in the development of neuropsychiatric symptoms.[13]

What Cognitive Symptoms Are Associated With Multiple Sclerosis?

Cognitive deficits are common in patients with MS, with 40% to 65% demonstrating some degree of cognitive dysfunction on neuropsychological testing.[13] Cognition is often affected early in the course of illness, occasionally prior to the onset of physical disability.[5] However, functional MRI studies indicate that the brain may adapt to compensate for these deficits, reflected by altered connectivity between different brain regions to limit expression of pathology, a concept known as "functional reorganization."[24] Functional reorganization, specifically bihemispheric recruitment, in response to cognitive tasks mirrors findings from studies of motor deficits in MS patients. This effect may in part explain why observed lesions in MS do not necessarily correlate with observed deficits and why patients can recover function despite accumulating lesions.[24,25]

The most commonly affected cognitive domains include speed of information processing, memory (particularly working memory), and attention.[6,26,27] Depression can also lead to impairments in attention, concentration, and memory, potentially compounding deficits in cognition. In keeping with these observations, Mr. A exhibited difficulty with short-term recall of 3 words and tasks of attention and concentration (e.g., performing serial 7s and spelling "WORLD" backward). He also demonstrated motor perseveration on the Go/No-Go motor task, indicating difficulty in changing behavior in response to environmental cues, a common problem in MS. In contrast, general intelligence and language skills are typically preserved in MS.[27]

Neuroimaging studies indicate that cognitive dysfunction is associated more strongly with the degree of gray and white matter atrophy rather than with MS lesion load.[4,25] In particular, white matter volume loss is related to impairment of information processing speed and working memory, likely reflecting the fact that temporarily holding and manipulating information (as in working memory) requires rapid neural communication between different brain regions via white matter tracts.[4] Gray matter volume loss, in contrast, is predictive of deficits in verbal memory.[4] It is important to remember that cognitive changes may be prominent even in the absence of active or visible MS lesions,[28] and these impairments can lead to occupational difficulties and to problems in everyday function. Patients may benefit from environmental modifications (such as schedules and reminder systems) to lessen the impact of cognitive deficits.

How Can Neuropsychiatric Symptoms in Multiple Sclerosis Be Assessed and Treated?

Given the high rates of mood disorders, psychosis, and cognitive impairments associated with MS, clinicians should routinely screen all MS patients for neuropsychiatric symptoms. If detected, prompt intervention affords the opportunity to greatly enhance quality of life for these patients.

In screening for depression, simply asking patients about depressed mood ("Are you depressed?") and anhedonia ("Do you still find pleasure in things you used to enjoy?") can quickly identify patients who may require a more thorough evaluation. Asking patients about hope for the future and their capacity to experience pleasure can be particularly helpful in the detection of true depression in MS patients with prominent somatic complaints. Furthermore, gauging a patient's sense of hope for the future is not only a useful tool in screening for depression, but as in other depressed patients, is also important in assessing risk for suicide. Alternatively, a brief self-report survey for depression such as the 9-item Patient Health Questionnaire-9[29] can be completed in the waiting room for review during the appointment. Upon detecting depressive symptoms, physicians should then attempt to identify any contributing factors (e.g., stress of diagnosis, disability, treatment with steroids or interferon) to tailor the approach to treatment.

When considering treatment for depression, assessing patients for current or past manic symptoms is also critical,

as antidepressants may precipitate manic, hypomanic, or rapid cycling of mood episodes in patients with underlying bipolar disorder. As with depression, a few simple screening questions ("Have you ever felt so good or so 'hyper' that people thought you were not your normal self, or were so 'hyper' that you got into trouble?"; "Have you had a period of time in which you got much less sleep that usual and found you didn't really miss it?") can identify patients needing more in-depth inquiry of manic symptoms.

Cognitive impairment may manifest as noticeable difficulties at work or even in tasks of daily living, and patients should be asked frequently about any perceived difficulties with memory or concentration. The Folstein Mini-Mental State Examination[30] is a useful tool to monitor gross cognitive performance over time. If cognitive abilities are impaired to the degree that daily activities have become difficult, referral to an occupational therapist for functional assessment may be helpful in determining appropriate community supports and interventions.

When assessing for psychiatric syndromes, it is tremendously useful to speak to family members, treatment providers, and others who know the patient well to discuss their observations of the patient's mood, behavior, and thought process. Such information can be critical in making a diagnosis and determining severity of symptoms; this is especially true regarding manic symptoms and cognitive impairment, as patients themselves often have limited insight into these conditions.

With respect to treatment of MS-associated psychiatric syndromes, randomized controlled trials addressing psychopharmacologic and psychological treatments for depression in MS are lacking. Therefore, treatment is guided by data from general psychiatric populations and by careful consideration of the individual's unique constellation of symptoms.[14] Desipramine, a tricyclic antidepressant (TCA), has demonstrated benefit in the treatment of depressed MS patients,[14] although anticholinergic side effects of TCAs are frequently limiting and may be particularly bothersome in patients already troubled by fatigue, urinary retention, gait instability, and other such physical symptoms. Selective serotonin reuptake inhibitors (SSRIs) are generally considered the treatment of choice for depression in MS given their proven efficacy in patients with primary depressive disorders and their relatively favorable side effect and safety profiles. Citalopram, escitalopram, and sertraline have fewer associated drug-drug interactions than other SSRIs, which make them ideal first-choice antidepressants for patients taking multiple medications. Patients with prominent somatic symptoms or neuropathic pain might gain additional benefit from treatment with venlafaxine or duloxetine, the serotonin-norepinephrine reuptake inhibitors (SNRIs).

Clinicians should be mindful of the common side effect of erectile dysfunction with SSRIs and SNRIs, as erectile dysfunction is also a common symptom among male patients with MS. Phosphodiesterase inhibitors, such as sildenafil, can be helpful in treating erectile dysfunction associated with SSRIs, and bupropion may be used to enhance libido in patients not deemed at risk for seizures. Also, if fatigue persists despite optimal treatment of depression, a trial of a stimulant medication (e.g., modafinil) along with regular physical activity can be helpful.

Among the various psychological interventions for the treatment of depression in MS, cognitive-behavioral therapy is the only modality that shows modest benefit.[31] Cognitive-behavioral therapy may be particularly helpful in improving functional outcome by coaching the patient to actively re-engage in daily activities despite fatigue, low energy, and lack of motivation. Optimal treatment requires careful consideration of the factors contributing to depression in any individual patient. For example, a patient with the onset of depression shortly after a new diagnosis of MS may benefit from a peer support group or individual psychotherapy, whereas antidepressant medication may be most helpful for a patient who develops depression shortly after beginning interferon therapy. In many patients, the cause of depression will be multifactorial, requiring an individualized and flexible approach to treatment.

As with depression, treatment of manic episodes in MS patients is based on data from general psychiatric populations, and mood stabilizers (such as lithium and valproic acid) remain the treatments of choice. Clinicians should keep in mind that both lithium and valproic acid are associated with cognitive side effects, which may exacerbate preexisting cognitive impairments. Mr. A was first treated with lithium for his mixed-manic and depressive state, although he remained acutely agitated and at times aggressive toward staff, prompting the addition of an atypical antipsychotic, olanzapine, for further stabilization. Atypical antipsychotics (including olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone) may be used as monotherapy or as adjunctive medications for acute mania, although several carry significant risk of weight gain and metabolic derangements, of particular concern in sedentary patients with fatigue and physical disability. Nutrition and exercise regimens can be helpful in controlling weight gain associated with mood stabilizers and antipsychotics, with the additional benefit of improving overall mood. Olanzapine is particularly effective in managing acute agitation associated with mania, yet carries the highest potential for weight gain with long-term use. Aripiprazole, on the other hand, has not been associated with significant weight gain and may be a preferable choice for overweight patients with less severe agitation and sleep disturbance.

The syndrome of pseudobulbar affect is typically treated with a combination of dextromethorphan and quinidine to improve affective lability, leading to self-reported improvement in quality of life and relationships.[22] Dextromethorphan is thought to suppress glutamatergic (excitatory) activity in the corticobulbar circuits involved with emotional regulation, whereas quinidine inhibits breakdown of dextromethorphan by the cytochrome P450 2D6 enzyme, allowing dextromethorphan to cross the blood-brain barrier.[22] Low-dose amitriptyline and SSRIs have also been used to treat this syndrome with some success.[13]

With respect to treatment of cognitive deficits in MS, definitive therapeutic options are also lacking. Disease-modifying agents (e.g., interferon) may also limit progression of cognitive decline, although little supportive data exist.[13] It has been hypothesized that demyelination and axonal degeneration in periventricular cortical pathways that utilize acetylcholine as a neurotransmitter may disrupt cortical pathways and lead to cognitive changes in MS.[32] Acetylcholinesterase inhibitors, particularly donepezil, have been associated with marginal benefit in verbal learning and memory in patients with MS.[32] Environmental interventions (written schedules, reminder systems) can be particularly helpful to minimize functional impairment from cognitive deficits.

Widely used treatments for the management of neurologic symptoms of MS can have an impact on a patient's mood and behavior, and these effects should be anticipated. Clinicians who treat acute MS exacerbations with corticosteroids must remain especially vigilant for neuropsychiatric sequelae, including depression, mania, and psychosis. Although any patient may experience these side effects, family history is important to identify patients at elevated risk for these complications, as adverse reactions may reflect a genetic predisposition. As with mania due to bipolar disorder, lithium is often effective for the treatment of steroid-induced mania.[13] Available data generally do not support an association between treatment with interferon and the onset of depression, although idiosyncratic reactions are possible.[8,20] As with corticosteroid treatment, premorbid depression and family history of mood disorders may predispose a patient to development of depression with interferon treatments. For patients with a known history of major depressive episodes, clinicians should consider initiation of treatment with an SSRI prior to beginning interferon. Core MS treatments may also decrease psychiatric symptoms, and health care providers should also consider that delay of physical disability with interferon treatment may improve self-esteem and contribute to independence, thereby reducing risk for depression.

Conclusions

Multiple sclerosis is a CNS disorder with protean manifestations. Neuropsychiatric changes, both affective and cognitive, are common in MS and are often considered core symptoms of this prevalent neurologic disorder. These symptoms may be equally or more important than physical disability in the prediction of quality of life. Therefore, appropriate screening and thoughtful management of neuropsychiatric sequelae by care providers is critical for the optimal care of patients with MS.

REFERENCES

1. Caplan JP, Cassem NH, Murray GB, et al. Delirium. In: Stern TA, Rosenbaum JF, Fava M, et al, eds. Massachusetts General Hospital Comprehensive Clinical Psychiatry. Philadelphia, Pa: Mosby/Elsevier; 2008:217–229
2. Rubin E, Farber JL, eds. Pathology. 3rd ed. Philadelphia Pa: Lippincott-Raven; 1999:1496–1498
3. Calabresi PA. Diagnosis and management of multiple sclerosis. Am Fam Physician 2004;70:1935–1944
4. Sanfilipo MP, Benedict RHB, Weinstock-Guttman B, et al. Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. Neurology 2006;66:685–692
5. Rovaris M, Giancarlo C, Massimo F. MRI markers of destructive pathology in multiple sclerosis-related cognitive dysfunction. J Neurol Sci 2006;245:111–116
6. Portaccio E, Amato MP, Bartolozzi ML, et al. Neocortical volume decrease in relapsing-remitting multiple sclerosis with mild cognitive impairment. J Neurol Sci 2006;245:195–199
7. Hurley RA, Taber KH, Zang J, et al. Neuropsychiatric presentation of multiple sclerosis. J Neuropsychiatry Clin Neurosci 1999;11:5–7
8. Asghar-Ali AA, Taber KH, Hurley RA, et al. Pure neuropsychiatric presentation of multiple sclerosis. Am J Psychiatry 2004;161:226–231
9. Brosseau KM, Arciniegas DB, Carmosino MJ, et al. The differential diagnosis of Axis I psychopathology presenting to a university-based multiple sclerosis clinic. Mult Scler 2007;13:749–753
10. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Ann Neurol 2001 Jul;50(1): 121–127
11. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." Ann Neurol 2005; 58:840–846
12. McGuigan C, Hutchinson M. Unrecognised symptoms of depression in a community-based population with multiple sclerosis. J Neurol 2006; 253:219–223
13. Ghaffar O, Feinstein A. The neuropsychiatry of multiple sclerosis: a review of recent developments. Curr Opin Psychiatry 2007;20:278–285
14. Feinstein A. Neuropsychiatric syndromes associated with multiple sclerosis. J Neurol 2007 May;254 (suppl 2):II73–II76
15. Diaz-Olavarrieta C, Cummings JL, Velazquez J, et al. Neuropsychiatric manifestations of multiple sclerosis. J Neuropsychiatry Clin Neurosci 1999;11:51–57
16. Lynch SG, Kroencke DC, Denney DR. The relationship between disability and depression in multiple sclerosis: the role of uncertainty, coping, and hope. Mult Scler 2001;7:411–416
17. Patten SB, Beck CA, Williams JVA, et al. Major depression in multiple sclerosis: a population-based perspective. Neurology 2003;61: 1524–1527
18. Chwastiak L, Ehde DM, Gibbons LE, et al. Depressive symptoms and severity of illness in multiple sclerosis: epidemiologic study of a large community sample. Am J Psychiatry 2002;159:1862–1868
19. Feinstein A, Roy P, Lobaugh N, et al. Structural brain abnormalities in multiple sclerosis patients with major depression. Neurology 2004;62: 586–590
20. Feinstein A. Multiple sclerosis, disease modifying treatments and depression: a critical methodological review. Mult Scler 2000;6:343–348
21. Krishnan KR. Psychiatric and medical comorbidities of bipolar disorder. Psychosom Med 2005;67:1–8
22. Panitch HS, Thisted RA, Smith RA, et al. Randomized, controlled trial of dextromethorphan/quinidine for the pseudobulbar affect in multiple

sclerosis. Ann Neurol 2006;59:780–787
23. Patten SB, Svenson LW, Metz LM. Psychotic disorders in MS: population-based evidence of an association. Neurology 2005;65: 1123–1125
24. Cader S, Cifelli A, Abu-Omar Y, et al. Reduced brain functional reserve and altered functional connectivity in patients with multiple sclerosis. Brain 2006;129:527–537
25. Rovaris M, Giancarlo C, Massimo F. MRI markers of destructive pathology in multiple sclerosis-related cognitive dysfunction. J Neurol Sci 2006;245:111–116
26. Calabrese P. Neuropsychology of multiple sclerosis—an overview. J Neurol 2006 Feb;253(suppl 1):I10–I15
27. Nocenti U, Pasqualetti P, Bonavita S, et al. Cognitive dysfunction in patients with relapsing-remitting multiple sclerosis. Mult Scler 2006;12:77–87
28. Pantano P, Mainero C, Caramia F. Functional brain reorganization in multiple sclerosis: evidence from fMRI studies. J Neuroimaging 2006; 16:104–114
29. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606–613
30. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State:" a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189–198
31. Thomas PW, Thomas S, Hillier C. Psychological interventions for multiple sclerosis. Cochrane Database Syst Rev 2006 Jan;(1):CD004431
32. Christodoulou C, Melville P, Scherl WF, et al. Effects of donepezil on memory and cognition in multiple sclerosis. J Neurol Sci 2006;245: 127–136