

The Goldman Consensus statement on depression in multiple sclerosis

Goldman Consensus Group*
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Background. In January 2002 the New York City Chapter of the National Multiple Sclerosis Society convened a panel of experts to review the issue of depressive affective disorders associated with multiple sclerosis (MS). This Consensus Conference was supported by a grant from the Goldman family of New York City. **Results.** The panel reviewed summaries of current epidemiologic, neurobiologic, and therapeutic studies having to do with depressive disorders among MS patient populations. Depressive disorders occur at high rates among patients with MS, and there is reason to believe that the immunopathology of the disease is involved in the clinical expression of affective disorders. The depressive syndromes of MS have a major, negative impact on quality of life for MS sufferers, but are treatable. At the present time, most MS patients with depression do not receive adequate recognition and treatment. **Conclusions.** The Goldman Consensus Conference Study Group provides recommendations for improved screening, diagnosis, and clinical management for depressive affective disorders among patients suffering from MS. Multiple Sclerosis (2005) 11, 328–337

Key words: affective disorders; cognition; depression; multiple sclerosis; neuropsychiatry

The Lillian Goldman Consensus Conference on the Identification and Treatment of Mood Disorders in Multiple Sclerosis (MS) was convened in New York City on 17 and 18 January 2002, under the administrative leadership of the New York City Chapter of the National Multiple Sclerosis Society. The scientific participants are listed as an appendix to this document. Background presentations were given concerning our current state of knowledge about the affective disorders associated with MS. Depressive spectrum mood disorders were selected as the focus of the conference. There is reason to believe that these mood disorders occur at high rates among persons with MS, and that they are eminently treatable. The consensus statement which follows provides a summary of current knowledge about these disorders, as well as recommendations from the conference for alterations in clinical practice.

This document has been reviewed and approved by the Medical Advisory Board of the National Multiple Sclerosis Society, and by the Medical Advisory Board of the New York City Chapter of the National Multiple Sclerosis Society.

Lillian Goldman Consensus Conference on the Identification and Treatment of Depressive Mood Disorders in Multiple Sclerosis, 17–18 January 2002, New York City.

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Epidemiology of depressive disorders associated with MS

The major disease burdens for the 21st century are likely to be different from those which received the greater share of medical resources during the previous one hundred years. The neuropsychiatric disorders, especially depression, already dominate the lists of leading causes of disability worldwide.¹ The depressive spectrum disorders which occur in conjunction with various neuromedical disorders such as MS present special challenges for recognition and successful treatment.² These disorders include the affective disorders which are classified in the Diagnostic and Statistical Manual of the American Psychiatric Association, fourth edition,³ as Major Depressive Disorder (MDD), Dysthymia, and others which fall short of criteria for MDD or Dysthymia yet still cause pain and suffering.

Reported measures of lifetime risk for depressive spectrum disorders are quite high in persons diagnosed with MS.⁴ Point prevalence rates for major depressive syndromes in MS clinic populations are in the range of 14%, but may be even higher in community samples.⁵ Lifetime risk for MDD in the MS population may be as high as 50%, while risk for all depressive disorders is even higher.^{6–9} These rates of major depressive disorders are significantly elevated when compared with rates of depression reported in the general US population.¹⁰ Almost all comparison studies have reported higher rates of depression among MS patient cohorts than among those with other chronic illnesses, including other neurologic disorders.^{11,12} We conclude from these reports that clinicians who care for patients with MS should expect to encounter depressive affective disorders at rates higher than those in most other chronic medical disorders.

Clinical course and natural history of depression in MS

The depressive syndromes associated with MS occur with significant frequency across the natural history of the neurological disease, including in patients with very mild forms of MS.^{13,14} The presence of depressive symptomatology does not correlate well with the severity of neurologic disability as measured by such instruments as the Kurtzke scales, the most commonly used, standardized measures of neurologic impairment in MS.¹⁵ There is reason to believe that these depressive disorders do not remit spontaneously at high rates, but may even worsen over time if not treated.¹⁶

Neuromedical treatments for MS

The present neuromedical treatments for MS emphasize agents that are immunologically active, including corticosteroids, beta interferons, glatiramer acetate, and immunosuppressants. Corticosteroids and some interferons are suspected to affect mood, at least in some individuals.

Corticosteroids, which are often used in high doses to treat MS exacerbations, are associated with a variety of neuropsychiatric side effects. Typically, their short-term use produces increased energy, decreased sleep, and variable euphoria.¹⁷ Depressive symptoms may also occur, however, following initial administration, with long-term use, or with discontinuation of steroid dosing.¹⁸

Initial studies of interferon-beta 1b, an immunomodulatory cytokine used to reduce MS disease activity over prolonged periods, found increases in depression following initiation of treatment,¹⁹ and increased risk of suicide attempts.²⁰ A more recent report indicates that increases in depressive symptoms associated with interferon-beta-1b are more related to pretreatment levels of depressive symptomatology than to the administration of the interferon itself.²¹ A prospective study of patients assigned to interferon-beta 1b treatment has reported that the crude rate of major depression among patients receiving the interferon fell during a one year follow-up period, from about 21% to about 6% after initiation of antidepressant pharmacotherapy.²² The majority of subjects with major depression in this study had a history of psychiatric illness prior to treatment with interferon-1b. The 1a interferons also have FDA labeling precautions for depression and suicide, although in the SPECTRIMS trial of Rebif in secondary progressive MS depression ratings were followed prospectively in treatment and placebo groups and no differences were found.²³ Zephir and colleagues evaluated a cohort of MS patients before and twelve months after initiation of treatment with interferon-beta 1a and found no change on the Beck Depression Inventory.²⁴ Glatiramer acetate does not seem to be associated with depressive side effects. Corroborating reports from the internal medicine literature concerning a relationship between affective disorders and the interferons have appeared, reporting rates of new onset

major depression in association with the use of interferon-alpha to treat infectious and malignant syndromes approaching 50%.²⁵ These conflicting data, along with the methodologic flaws in many of the studies, forbid a determination yet that the administration of interferons to patients with MS definitely increases risk for depressive disorders.²⁶

Clinical impact of depression in MS patients

There is evidence that the comorbidity of depression and MS adversely impacts functional status in several neuropsychiatric domains. Depressed MS patients perform more poorly than non-depressed MS controls on tests of cognitive function.^{27,28} Standardized measures of quality of life are lower in depressed MS patients than in non-depressed MS controls.^{29–31} Intercurrent depression in MS populations is associated with increased time lost from work.³² Depressed MS patients experience disruption of their social support and family systems, beyond what can be attributed to neurologic disease factors alone.^{33,34} There is also evidence that comorbidity of depression and MS may adversely affect long-term health outcomes by decreasing adherence to neuromedical treatment regimens for MS.³⁵

It is not known whether emotional states, including depression, can actually affect the neurobiologic course of MS. Emotionally stressful experiences are commonly reported prior to clinical exacerbations in MS.³⁶ A series of prospective studies has reported a relationship between stressful life events and increased exacerbation rates in MS populations.^{37–39} A carefully designed prospective study which assessed rates of appearance of new gadolinium enhancing lesions found a correlation between measures of conflict and of disruption of routine, and the appearance of enhancing brain lesions.⁴⁰ One prospective study has reported a contradictory finding, however, of reduced exacerbation rates in people with MS under threat of military attack.⁴¹ In the animal model most often associated with MS, experimental allergic encephalomyelitis, there are conflicting reports of the effects of various stress models on disease severity and course.⁴² Stress is a different behavioral construct from depression, however, and none of these studies bears directly upon a potential relationship between depression and disease activity in MS. At this time, we know very little about the latter question.

The Consensus Group concludes that the depressive mood disorders which occur commonly in MS are functionally impairing, even though we do not yet understand the connections between these behavioral disorders and the underlying neurobiology of the disease.

Risk for suicide

Reported rates of completed suicide in MS populations are high.^{43,44} Death-certificate based reviews indicate that

suicide may be the cause of death for MS clinic attenders in as many as 15% of all cases.⁴⁵ The most important risk factor for suicide to emerge from retrospective analyses of completed suicides in MS populations is depression.⁴⁶ The presence of clinical depression is the most powerful determinant of suicidal intent in living MS patients, although social isolation is a co-determinant.⁴⁷ There is often a previous history of suicide attempts in completed suicides, and the suicide often follows a recent functional deterioration in the MS course.⁴⁸ Level of neurological disability, per se, is not known to be an important risk factor for suicide. Most completed suicides in MS patients are among persons with a moderate level of disability, perhaps because severely disabled persons do not have the means.

These data concerning frequency and risk factors for suicide in MS patients add an additional dimension of clinical concern to the problem of depression in this population. The single most useful step we can take with regard to primary prevention of suicide in MS is the better identification and treatment of the depressive disorders.

Neurobiological factors

Several lines of evidence suggest that neurobiological risk factors specifically associated with MS contribute to the increased risk of depressive disorders among these patients.

Hypothalamic feedback regulation is abnormal in many MS patients, with or without depressive symptoms. The dexamethasone suppression test measures the inhibitory feedback sensitivity of the hypothalamic pituitary axis to an exogenous dose of the glucocorticoid, dexamethasone. In a normal axis a small dose of dexamethasone, 1.5 or 2.0 mg in the evening, suppresses glucocorticoid secretion for twenty four hours. Fifty percent of MS patients demonstrate 'escape,' or failure of suppression. This abnormality on the dexamethasone suppression test in nondepressed MS patients is similar to the pattern of abnormalities seen in many patients with major depressive episodes.⁴⁹ Failure to respond to dexamethasone challenge has also been associated with the presence of gadolinium enhancing lesions on magnetic resonance imaging in MS patients, suggesting that disease activity could be related to some of the depressive symptomatology in MS.^{50,51}

Some of the many in vitro immune system parameters that are altered in MS patients may, directly or indirectly, act in concert with measures of depression. For example, Mohr and colleagues have reported that stimulated interferon gamma production by lymphocytes decreases in depressed MS patients as the depression improves.⁵² Foley and colleagues have reported that depressed and anxious MS patients demonstrate a relative depletion of peripheral CD8 positive lymphocytes compared with MS patients with no affective or anxiety disorder.⁵³

Imaging studies of brain lesion distribution and metabolism have contributed some suggestion that depressed

MS patients may differ from non-depressed MS patients, but there is no clear consensus about what these differences may be. When depressed and non-depressed MS populations are compared after controlling for Kurtzke ratings, one study indicated that the depressed patients demonstrated a more pronounced pattern of superior frontal and superior parietal hypointense lesions on T1 sequences.⁵⁴ Pujol and colleagues performed an MRI imaging protocol on a cohort of MS patients who were sorted across a spectrum of depression severity according to scores on the Beck Depression Inventory, and found a pattern of left hemisphere supra-sylvian lesions in the more depressed subjects.⁵⁵ Berg and colleagues found more right hemisphere temporal lobe lesions in depressed MS patients.⁵⁶ Some MRI-based comparative studies have found no differences between depressed and non-depressed MS groups with regard to lesion distribution.^{57,58}

It is difficult to draw any definite conclusions from these studies about the role of neurobiologic processes in MS as risk factors or generators of depression. We are left with the suggestion that a variety of interactions exist between the neuroimmunology of MS and the depressive disorders, but relatively little is presently known about the specific nature of these interactions.

Cognitive interactions of affective disorders

Cognitive impairments also occur commonly among patients suffering from MS.⁵⁹ The pattern of these cognitive impairments tends to be more circumscribed and less obvious to observers than the cognitive loss syndromes associated with the major dementing illnesses, such as Alzheimer's disease. The cognitive functions most often affected in MS are recent memory, both visual and verbal, various dimensions of information processing, executive functions, and visual-spatial processing.⁶⁰ A recent consensus conference has recommended a specific, ninety minute neuropsychologic battery to be used in the assessment of MS patients, called the Minimal Assessment of Cognitive Function in MS (MACFIMS).⁶¹

Some of the vulnerability to affective disorders in MS patients may be conferred by these alterations in cognition, which also occur. There are reports that MS-associated mood disorders occur more commonly in MS patients with cognitive impairments, than in those who are cognitively intact.⁶² Depressed MS patients also perform more poorly than matched, non-depressed MS patients on cognitive measures which involve attention and concentration functions.⁶³ Less sophisticated coping strategies may amplify the severity of mood disorders.⁶⁴ Not all studies, however, have found a relationship between affective disorders and cognitive dysfunction in MS patients.^{65,66} We are left with the conclusion that the cognitive loss syndromes of MS occur with and without coexisting depression.

Psychosocial factors in depression associated with MS

Coping strategies are psychological defense mechanisms that assist in adaptation to a variety of stressful life problems, including chronic disease. A large number of coping strategies exist, including such mechanisms as escape-avoidance, planful problem solving, seeking social support, positive reappraisal, and others.⁶⁷

Mohr and his group assessed a cohort of MS patients and found lower levels of depression to be associated with active problem solving strategies, and cognitive reframing.⁶⁸ This group found strategies such as escape-avoidance, and emotional avoidance to be associated with higher levels of depression. The latter two coping strategies are similar in that they entail avoidance of the source of stress, either by attempting to escape stressful situations or attempts to disengage emotionally from stressful emotions by fantasy. Similar results, favoring self-actuating coping strategies, have been reported by other investigators.^{69,70} Interestingly, duration of illness seems inversely correlated with level of adjustment in this, and other, studies of coping in MS.⁷¹

The results described in these studies provide strategic direction for clinicians who advise, or counsel MS patients with depression. Depression is more than a failure of coping with psychosocial challenges, but often the psychotherapeutic treatment of depression involves a review of coping strategies.

Measurement issues in depression associated with MS

The current gold standard for diagnosis of depressive spectrum disorders is the Diagnostic and Statistical Manual, edition IV, from the American Psychiatric Association.^{72,73} In the real world of clinical practice, however, depression exists on a spectrum of severity, and need not meet full DSM-IV criteria to be of clinical significance.⁷⁴ The Goldman Group expressed general agreement that some sort of scale-based assessment of depression in MS populations would be helpful in screening for these depressive disorders.

Mohr and his colleagues have reviewed the problem for any screening instrument that there is considerable overlap between symptoms and signs of depression, and some symptoms and signs of MS.⁷⁵ Four of the nine core symptoms of depression in the Diagnostic and Statistical Manual IV (DSM-IV) of the American Psychiatric Association also occur in MS; fatigue, psychomotor retardation, decreased concentration, and sleep disturbance.⁷⁶ Experienced clinicians agree that the depression associated neuropsychiatric symptoms can be distinguished from MS associated symptoms during the clinical interview. But commonly used rating scales for depression often confound these symptoms. The most commonly used depression scale in MS associated depression has been the Beck Depression Inventory, a self-report scale with 21 items.⁷⁷ A cut-off score of 13 on the Beck seems to screen for about 70% of MS patients with significant depression

in ambulatory settings, while still missing about 30% of such patients.^{78,79} An abbreviated version of the Beck Depression Inventory, the Beck Depression Inventory-Fast Screen, has been developed to select out items most sensitive to the more neurologic symptoms in MS.⁸⁰

Other screening instruments that have been proposed for use in case finding for significant depression in MS populations include the Center for Epidemiologic Studies – Depression Scale (CES-D), which has gained visibility in several large World Health Organization epidemiologic studies,⁸¹ and the Chicago Multi-Scale Depression Inventory.⁸² The latter has subscales which help to separate depressive symptomatology that is vegetative/physical from that which is affective and cognitive. The Inventory of Depressive Symptomatology (IDS) has been used in several recent, large scale studies of depression in psychiatric populations, and has the advantage of having both clinician-rated and self-report versions.⁸³

The Consensus Group felt that the best approach to screening for depression in general MS populations at the present time was to use the Beck Inventory, with a cutoff score of 13.

Treatment efficacy in depression associated with MS

The Goldman Consensus Group reported that individuals with MS and depression-spectrum illness generally respond well both to medical and psychotherapeutic treatments for depression. The consensus judgment of these clinicians is that integrated medical and psychotherapeutic approaches are the best. Those controlled observations which are available mostly corroborate this clinical judgment.⁸⁴ There is additional evidence from general psychiatry that a combination of cognitive-behavioral psychotherapy and antidepressant medication is more effective than either alone in the treatment of chronic depressive disorders.⁸⁵

Despite the favorable impression with regard to treatment response of the affective disorders in MS populations, these disorders are not recognized by treating clinicians, and do not routinely receive treatment.⁸⁶ Suicide prevention is partly separable from the treatment of depression, but also begins with clinical recognition of suicidal ideation and depression. The interactions between the clinician and the MS patient that result in this failure to recognize depressive syndromes are not fully understood, but probably include resistance to disclosure on the part of the patient, as well as failure to actively screen and diagnose on the part of the clinician. The current realities of medical economics in private practice settings are presently perceived as constraining appropriate attention to psychosocial issues in patient care.

With regard to the psychotherapies, most clinical reports have described results from group, or from cognitive-behavioral techniques.

Mixed psychotherapies using a group format, and a cognitive-behavioral orientation for the interventions have been shown to reduce depression severity in treated MS groups compared with wait-listed controls.⁸⁷ Indivi-

dual psychotherapy using a cognitive-behavioral approach and a six-session format has been shown to lower self-report measures of depression compared with 'usual' neuromedical treatment.⁸⁸ There is also a report that a 25-week course of insight-oriented group therapy lowered depressive symptoms on the Minnesota Multiphasic Personality Inventory.⁸⁹

There is one controlled study of desipramine versus placebo in a cohort of MS patients with major depressive disorder, showing significant improvement in depression in the pharmacologically treated group over a six-week period.⁹⁰ There is an open trial report of the efficacy of the serotonin reuptake inhibitor, sertraline, in 11 depressed MS patients.⁹¹ All 11 patients were able to tolerate a dose of 100 mg per day, and all but one improved with regard to depressive features over a three-month period.

A recent comparative outcome trial randomly assigned 63 patients with comorbid diagnoses of MS and major depressive episode to one of three 16-week treatments; an individual cognitive behavioral psychotherapy focused on teaching coping skills, a supportive-expressive group psychotherapy focused on facilitating expression of emotions and provision of social support, or sertraline with a modal dose of 150 mg per day.⁹² The cognitive behavioral psychotherapy and sertraline were equivalent in efficacy, and both were superior to the supportive-expressive group psychotherapy. This study also provided evidence of in vitro alteration of interferon-gamma production by T lymphocytes during the course of the treatment, suggesting a way in which the treatment of depression could theoretically affect the neurobiology of the disease.

The treatment of depression is a complex matter, which has to be individualized for each person. Still, the Consensus Group felt that some integrated approach involving psychotherapy and medication was the gold standard to be used, at least for the more severe depressions.

Summary and recommendations

The summary conclusions from this conference were that persons with MS are at increased risk for depressive spectrum disorders, which are a cause of significant suffering and disability. The etiology of depressive spectrum disorders in MS is not completely understood, but is thought to be multifactorial, with psychological, social and neurobiological factors all playing a role – and potentially immunologic and genetic factors as well. The natural history of depressive spectrum disorders in the MS population is not definitely known. However, the administration of various psychotherapeutic and psychopharmacologic treatments is generally accepted as effective for these depressive syndromes in MS patients. Despite the availability of such effective therapies to treat these disorders, our present care delivery systems in the US fail to identify over half of patients with these depressive disorders. When depressed MS individuals are identified, many are not properly treated. There was a strong consensus among conference participants that resources

should be directed toward improving the application of currently available knowledge regarding the identification and treatment of depressive spectrum disorders (broadly defined) in MS. In addition, it would be desirable to have a better understanding of the pathophysiology of depression in MS, and better information concerning efficient approaches to treatment.

Specific recommendations from the Goldman Consensus Conference of 2002 include the following:

- 1) Clinical groups which routinely care for MS patients should institute regular screening measures for the identification of depression, such as the Beck Depression Inventory, using a threshold of 13 for positive screens.
- 2) Patients who meet screening thresholds for depression, or who endorse any positive responses to suicide inquiries, should be actively assessed for severity and quality of depression, and considered for follow-on treatment recommendations.
- 3) Treatment plans for depression among MS patients should be individualized, using psychotherapeutic, psychopharmacologic, or integrated approaches, depending upon individual circumstances, and preferences. Available evidence suggests that pharmacotherapy and certain psychotherapies are equally effective for depressive disorders in MS populations, yet the Consensus Group strongly recommends that these treatment modalities be combined in an integrated biopsychosocial treatment plan whenever possible. Treatment plans should be followed through to eradication of depressive symptomatology.
- 4) Greater standardization of the therapeutic approach to depression in MS should be sought, through the development and testing of an algorithm which is uniquely crafted to this clinical domain.
- 5) Continuing clinical research should be encouraged into the neurobiologic and psychologic bases of depressive disorders in MS patients, and into therapeutic responses to currently available and newly developing treatment modalities.

References

- 1 World Health Report. *Mental Health, New Understanding, New Hope*, Chapter 2. Geneva: World Health Organization, 2001: 20–45.
- 2 Schiffer RB, Rao SM, Fogel BS. *Neuropsychiatry*, 2nd edition. Baltimore: Lippincott Williams and Wilkins, 2003.
- 3 Andreasen NC, Schmidt CW, Barlow DH, Schuckit MA, Campbell M, Shaffer D. *American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*. Washington, DC: American Psychiatric Association, 2000.
- 4 Minden SL, Schiffer RB. Affective disorders in multiple sclerosis: Review and recommendations for clinical research. *Archives of Neurology* 1990; **47**: 98–104.
- 5 Chwastiak L, Ehde DM, Gibbons LE, Sullivan M, Bowen JD, Kraft GH. Depressive symptoms and severity of illness in multiple sclerosis: epidemiologic study of a large community sample. *Am J Psychiatry* 2002; **159**: 1862–68.

- 6 Joffe RT, Lippert GP, Gray TA, Sawa G, Horyath Z. Mood disorder and Multiple Sclerosis. *Archives of Neurology* 1987; **44**: 376–78.
- 7 Patten SB and Metz LM. Depression in Multiple Sclerosis. *Psychotherapy and Psychosomatics* 1997; **66**: 286–92.
- 8 Sadovnick AD, Eisen K, Ebers GC, Paty DW. Cause of death in patients attending multiple sclerosis clinics. *Neurology* 1991; **41**: 1193–96.
- 9 Feinstein A, Feinstein K. Depression associated with multiple sclerosis. Looking beyond diagnosis to symptom expression. *Journal of Affective Disorders* 2001; **66**: 193–98.
- 10 Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *J Am Med Assoc* 2003; **289**: 3095–105.
- 11 Minden SL, Orav J, Reich P. Depression in Multiple Sclerosis. *General Hospital Psychiatry* 1987; **9**: 426–34.
- 12 Schiffer R, Babigian HM. Behavioral disorders in multiple sclerosis, temporal lobe epilepsy, and amyotrophic lateral sclerosis: An epidemiologic study. *Archives of Neurology* 1984; **41**: 1067–69.
- 13 Sullivan MJL, Weinshenker B, Mikail S, Bishop SR. Screening for major depression in the early stages of multiple sclerosis. *Canadian Journal of Neurological Sciences* 1995; **22**: 228–31a.
- 14 Sullivan MJL, Weinshenker B, Mikail S, Edgley K. Depression before and after diagnosis of multiple sclerosis. *Multiple Sclerosis* 1995; **1**: 104–108b.
- 15 Moller A, Wiedemann G, Rohde U, Backmund H, Sonntag A. Correlates of Cognitive Impairment and Depressive Mood Disorder in Multiple Sclerosis. *Acta Psychiatrica Scandinavica* 1994; **89**: 117–21.
- 16 Mohr DC, Goodkin DE. Treatment of depression in multiple sclerosis: Review and meta-analysis. *Clinical Psychology: Science and Practice* 1999; **6**: 1–9.
- 17 Kershner P, Wang-Cheng R. Psychiatric Side Effects of Steroid Therapy. *Psychosomatics* 1989; **30**: 135–39.
- 18 Patten SB, Williams JV, Love EJ. Self-reported Depressive Symptoms following treatment with Corticosteroids and Sedative-hypnotics. *International Journal of Psychiatry in Medicine* 1996; **26**: 15–24.
- 19 Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA. Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Archives of Neurology* 1997; **54**: 531–33.
- 20 Lublin FD, Whitaker JN, Eidelman BH, Miller AE, Arnason BGW, Burks JS. Management of Patients Receiving Interferon beta-1b for Multiple Sclerosis: Report of a Consensus Conference. *Neurology* 1996; **46**: 12–18.
- 21 Mohr DC, Goodkin DE. Treatment of depression in multiple sclerosis: Review and meta-analysis. *Clinical Psychology: Science and Practice* 1999; **6**: 1–9.
- 22 Feinstein A, O'Connor P, Feinstein K. Multiple Sclerosis, Interferon Beta 1b and Depression. *J Neurol* 2002; **24**: 815–20.
- 23 Patten SB, Metz LM. Interferon Beta 1a and depression in secondary progressive MS: data from the SPECTRIMS trial. *Neurology* 2002; **59**: 744–46.
- 24 Zéphir H, De Seze J, Stojkovic T, Delisse B, Ferriby D, Cabaret M. Multiple sclerosis and depression: influence of interferon Beta therapy. *Multiple Sclerosis* 2003; **9**: 284–88.
- 25 Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS. Paroxetine for the Prevention of Depression Induced by High-Dose Interferon Alpha. *New Engl J Med* 2001; **344**: 961–66.
- 26 Feinstein A. Multiple sclerosis, disease modifying treatments and depression: a critical methodological review. *Multiple Sclerosis* 2000; **6**: 343–48.
- 27 Gilchrist AC and Creed FH. Depression, Cognitive Impairment and Social Stress in Multiple Sclerosis. *J Psychosomatic Research* 1994; **38**: 193–201.
- 28 Arnett PA, Higginson CI, Voss WD, Wright B, Bender WI, Wurst JM. Depressed mood in multiple sclerosis: Relationship to capacity-demanding memory and attentional functioning. *Neuropsychology* 1999; **13**: 434–46.
- 29 Wang JL, Reimer MA, Metz LM, Patten SB. Major depression and quality of life in individuals with multiple sclerosis. *International Journal of Psychiatry in Medicine* 2000; **30**: 309–17.
- 30 Gulick EE. Correlates of quality of life among persons with multiple sclerosis. *Nursing Research* 1997; **46**: 305–11.
- 31 Jonsson A, Ravnborg MH, Dock J. Quality of life as a measure of rehabilitation outcome in patients with multiple sclerosis. *Acta Neurologica Scandinavica* 1996; **93**: 229–35.
- 32 Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A Health-Related Quality of Life Measure for Multiple Sclerosis. *Quality of Life Research* 1995; **4**: 187–206.
- 33 McIvor GP, Riklan M, Reznikoff M. Depression in Multiple Sclerosis as a Function of Length and Severity of Illness, Age, Remissions, and Perceived Social Support. *J Clin Psychology* 1984; **40**: 1028–33.
- 34 O'Brien MT. Multiple Sclerosis: The Relationship Among Self-Esteem, Social Support, and Coping Behavior. *Applied Nursing Research* 1993; **6**: 54–63.
- 35 Mohr DC, Goodkin DE, Likosky W, Gatto N, Baumann KA, Rudick RA. Treatment of depression improves adherence to interferon beta-1b therapy for multiple sclerosis. *Archives of Neurology* 1997; **54**: 531–33.
- 36 Grant I, Brown GW, Harris T, McDonald WI, Patterson T, Trimble MR. Severely Threatening Events and Marked Life Difficulties Preceding Onset or Exacerbation of Multiple Sclerosis. *J Neurol Neurosurg Psychiatry* 1989; **52**: 8–13.
- 37 Franklin GM, Nelson LM, Heaton RK, Burks JS, Thompson DS. Stress and its Relationship to Acute Exacerbations in Multiple Sclerosis. *J Neurologic Rehab* 1988; **2**: 7–11.
- 38 Sibley WA. Risk factors in multiple sclerosis. In Raine CS, McFarland HF, Tourtellotte W eds. *Multiple sclerosis: clinical and pathogenetic basis*. London: Chapman and Hall, 1997: 141–48.
- 39 Ackerman KD, Rabin B, Heyman R, Anderson BP, Houch PR, Frank E. Stressful Life Events Precede Multiple Sclerosis Disease Exacerbations. *Psychosomatic Medicine* 2000; **62**: 147.
- 40 Mohr DC, Goodkin DE, Bacchetti P, Boudewyn AC, Huang L, Marrietta P. Psychological stress and the subsequent appearance of new brain MRI lesions in MS. *Neurology* 2000; **55**: 55–61.
- 41 Nispeanu P, Korczyn AD. Psychological Stress as Risk Factor for Exacerbations in Multiple Sclerosis. *Neurology* 1993; **43**: 1311–12.
- 42 Levine S and Saltzman A. Nonspecific stress prevents relapses of experimental allergic encephalomyelitis in rats. *Brain Behavior Immunity* 1987; **1**: 336–41.
- 43 Stenager EN, Stenager E, Koch-Henriksen N, Bronnum-Hansen H, Hyllested K, Jensen K. Suicide and Multiple Sclerosis: an epidemiological investigation. *J Neurology Neurosurgery and Psychiatry* 1992; **55**: 542–45.
- 44 Stenager EN, Koch-Henriksen N, Stenager E. Risk factors for suicide in multiple sclerosis. *Psychotherapy and Psychosomatics* 1996; **65**: 86–90.

- 45 Sadovnick AD, Eisen K, Ebers GC, Paty DW. Cause of Death in Patients Attending Multiple Sclerosis Clinics. *Neurology* 1991; **41**: 1193–96.
- 46 Feinstein A. Multiple sclerosis, depression, and suicide. *British Medical Journal* 1997; **315**: 691–92.
- 47 Feinstein A. An examination of Suicidal Intent in patients with multiple sclerosis. *Neurology* 2002; **59**: 674–78.
- 48 Stenager EN, Koch-Henriksen N, Stenager E. Risk factors for suicide in multiple sclerosis. *Psychotherapy and Psychosomatics* 1996; **65**: 86–90.
- 49 Reder AT, Makowicz RL, Lowy MT. Adrenal size is increased in multiple sclerosis. *Archives of Neurology* 1994; **51**: 151–54.
- 50 Fassbender K, Schmidt R, Mossner R, Kischka U, Kuhlen J, Schwartz A. Mood Disorders and Dysfunction of the Hypothalamic–pituitary–adrenal Axis in Multiple Sclerosis. *Archives of Neurology* 1998; **55**: 66–72.
- 51 Dalos NP, Rabins PV, Brooks BR, O'Donnell P. Disease Activity and Emotional State in Multiple Sclerosis. *Annals of Neurology* 1983; **13**: 573–83.
- 52 Mohr DC, Goodkin DE, Islar J, Hauser SL, Genain CP. Treatment of depression is associated with suppression of nonspecific and antigen-specific TH1 responses in multiple sclerosis. *Archives of Neurology* 2001; **58**: 1081–86.
- 53 Foley FW, Miller AH, Traugott U, LaRocca NG, Scheinberg LC, Bedell JR. Psychoimmunological Dysregulation in Multiple Sclerosis. *Psychosomatics* 1988; **29**: 398–403.
- 54 Bakshi R, Czarnecki D, Shaikh ZA, Priore RL, Janardhan V, Kaliszky Z. Brain MRI lesions and atrophy are related to depression in multiple sclerosis. *Neuroreport: For Rapid Communication of Neuroscience Research* 2000; **11**: 1153–58.
- 55 Pujol J, Bello J, Deus J, Marti-Vilalta JL, Capdeila A. Lesions in the left arcuate fasciculus region and depressive symptoms in multiple sclerosis. *Neurology* 1997; **49**: 1105–10.
- 56 Berg D, Supprian T, Thomas J, Warmuth-Metz M, Horowski A, Zeiler B. Lesion pattern in patients with multiple sclerosis and depression. *Multiple Sclerosis* 2000; **6**: 156–62.
- 57 Sabatini U, Pozzilli C, Pantano P, Koudriavtseva T, Padovani A, Millefiorini E. Involvement of the limbic system in multiple sclerosis patients with depressive disorders. *Biological Psychiatry* 1996; **39**: 970–75.
- 58 Moller A, Wiedemann G, Rohde U. Correlates of Cognitive Impairment and Depressive Mood Disorder in Multiple Sclerosis. *Acta Psychiatrica Scandinavica* 1994; **89**: 117–21.
- 59 Fischer JS, Foley FW, Aikens JE, Ericson GD, Roa SM, Shindell S. What do we really know about cognitive dysfunction, affective disorders, and stress in Multiple Sclerosis? *J Neuro Rehab* 1994; **8**: 151–64.
- 60 Demaree H, DeLuca J, Guadino EA, Diamond BJ. Speed of Information Processing as a key Deficit in Multiple Sclerosis: Implications for Rehabilitation. *J Neurology Neurosurgery and Psychiatry* 1999; **67**: 661–63.
- 61 Benedict RHB, Fischer JS, Archibald CJ, Arnett PA, Beatty WW, Bobholz J. Minimal neuropsychological assessment of MS patients: a consensus approach. *Clinical Neuropsychologist* 2002; **16**: 381–97.
- 62 Gilchrist AC, Creed FH. Depression, Cognitive Impairment and Social Stress in Multiple Sclerosis. *J Psychosomatic Research* 1994; **38**: 193–201.
- 63 Arnett PA, Higginson CI, Voss WD, Wright B, Bender WI, Wurst JM. Depressed mood in multiple sclerosis: Relationship to capacity-demanding memory and attentional functioning. *Neuropsychology* 1999; **13**: 434–46.
- 64 Arnett PA, Higginson CI, Voss WD, Randolph JJ, Grandey AA. Relationship between coping, depression, and cognitive dysfunction in multiple sclerosis. *Clinical Neuropsychologist* 2002; **16**: 341–55.
- 65 Millefiorini E, Padovani A, Pozzilli C, Loredio C, Bastianello S, Buttinelli C. Depression in the early phase of MS: Influence of Functional Disability, Cognitive Impairment, and Brain Abnormalities. *Acta Neurologica Scandinavica* 1992; **86**: 354–58.
- 66 Rao SM, Leo GJ, Bernardin L, Unyerzagt F. Cognitive Dysfunction in Multiple Sclerosis. I. Frequency, Patterns, and Prediction. *Neurology* 1991; **41**: 685–91.
- 67 Folkman S, Lazarus R. *Manual for the Ways of Coping Questionnaire*. Palo Alto, California: Consulting Psychologists Press, 1988.
- 68 Mohr DC, Goodkin DE, Gatto N, Van Der Wende J. Depression, coping, and level of neurological impairment in multiple sclerosis. *Multiple Sclerosis* 1997; **3**: 254–58.
- 69 Shnek ZM, Foley FW, LaRocca NG, Smith CR, Halper J. Psychological predictors of depression in multiple sclerosis. *Journal of Neurologic Rehabilitation* 1995; **9**: 15–23.
- 70 Aikens JE, Fischer JS, Namey M, Rudick RA. A replicated prospective investigation of life stress, coping, and depressive symptoms in multiple sclerosis. *Journal of Behavioral Medicine* 1997; **20**: 433–45.
- 71 Pakenham KI. Adjustment to multiple sclerosis: application of a stress and coping model. *Health Psychology* 1999; **18**: 383–92.
- 72 Andreasen NC, Schmidt CW, Barlow DH, Schuckit MA, Campbell M, Shaffer D. *American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*. Washington, DC: American Psychiatric Association, 2000.
- 73 First MB, Spitzer RL, Gibbon M. *Structured Clinical Interview for Axis I DSM-IV Disorders – Patient Edition (SCID-I/P, Version 2.0)*. New York: Biometric Research Department, New York State Psychiatric Institute, 1994.
- 74 Rapaport MH, Judd LJ, Schettler PJ, Yonders KA, Thase ME, Jupfer DJ. A Descriptive Analysis of Minor Depression. *Am J Psychiatry* 2002; **159**: 637–43.
- 75 Mohr DC, Goodkin DE, Likosky W, Beutler L, Gatto N, Langan MK. Identification of Beck Depression Inventory items related to multiple sclerosis. *Journal of Behavioral Medicine* 1997; **20**: 407–14.
- 76 Andresen NC, Schmidt CW, Barlow DH, Schuckit MA, Campbell M, Shaffer D. *American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)*. Washington, DC: American Psychiatric Association, 2000.
- 77 Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An Inventory for Measuring Depression. *Arch Gen Psych* 1961; **4**: 561–71.
- 78 Sullivan MJL, Weinshenker B, Mikail S, Bishop SR. Screening for major depression in the early stages of multiple sclerosis. *Canadian Journal of Neurological Sciences* 1995; **22**: 228–31a.
- 79 Sullivan MJL, Weinshenker B, Mikail S, Edgley K. Depression before and after diagnosis of multiple sclerosis. *Multiple Sclerosis* 1995; **1**: 104–108b.
- 80 Benedict RHB, Fischer JS, Archibald CJ. Minimal neuropsychological assessment of MS patients: a consensus approach. *Clinical Neuropsychologist* 2002; **16**: 381–97.
- 81 Verdier-Taillefer MH, Gourlet V, Fuhrer R, Alperovitch A. Psychometric Properties of the Center for Epidemiologic Studies – Depression Scale in Multiple Sclerosis. *Neuroepidemiology* 2001; **20**: 262–67.
- 82 Nyenhuis DL, Rao SM, Zajacka JM, Luchetta T, Bernardin L, Garron DC. Mood disturbance versus other symptoms of

- depression in multiple sclerosis. *Journal of the International Neuropsychological Society* 1995; **1**: 291–96.
- 83 Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The Inventory of Depressive Symptomatology (IDS): Psychometric Properties. *Psychological Medicine* 1996; **26**: 477–86.
- 84 Mohr DC, Goodkin DE. Treatment of depression in multiple sclerosis: Review and meta-analysis. *Clinical Psychology: Science and Practice* 1999; **6**: 1–9.
- 85 Keller MB, McCullough JP, Klein DN, Arnow B, Kunner DL, Gelenberg AJ. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *New Engl J Med* 2000; **342**: 1462–70.
- 86 Feinstein A. An examination of Suicidal Intent in patients with multiple sclerosis. *Neurology* 2002; **59**: 674–78.
- 87 Larcombe NA, Wilson PH. An Evaluation of Cognitive-Behavior Therapy for Depression in Patients with Multiple Sclerosis. *Br J Psychiatry* 1984; **145**: 366–71.
- 88 Foley FW, Bedell JR, LaRocca NG, Scheinbert LC, Reznikoff M. Efficacy of Stress-Inoculation Training in Coping with Multiple Sclerosis. *J Consulting and Clinical Psychology* 1987; **55**: 919–22.
- 89 Crawford JD, McIvor GP. Group Psychotherapy: Benefits in Multiple Sclerosis. *Arch Phys Med Rehab* 1985; **66**: 810–13.
- 90 Schiffer RB and Wineman NM. Antidepressant Pharmacotherapy of Depression Associated with Multiple Sclerosis. *Am J Psychiatry* 1990; **147**: 1493–97.
- 91 Scott TF, Nussbaum P, McConnell H, Brill P. Measurement of Treatment Response to Sertraline in Depressed Multiple Sclerosis Patients Using the Carroll Scale. *Neural Research* 1995; **17**: 421–22.
- 92 Mohr DC, Goodkin DE, Islar J, Hauser SL, Genain CP. Treatment of depression is associated with suppression of nonspecific and antigen-specific TH1 responses in multiple sclerosis. *Archives of Neurology* 2001; **58**: 1081–86.

Appendix I

Lillian Goldman Consensus Conference on the Identification and Treatment of Affective Disorders in MS

17–18 JANUARY 2002

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