Depression in multiple sclerosis: a review

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Several studies have reported high rates of depression in multiple sclerosis (MS) with a lifetime prevalence of ~50% and an annual prevalence of 20% not uncommon. Concern about the potential of new drug treatments to exacerbate or precipitate depression in MS has led to increased interest in the relation between MS and depression. This review on MS and depression identifies the following key issues: How common is depression in people with MS? Is depression in MS associated with lesions in specific regions of the central nervous system? Is there an increased risk of suicide in MS? Is there a higher than expected incidence of anxiety disorders in MS? Are fatigue and depressed mood related in MS? Is there a relation between depression and cognitive impairment in MS? Which psychosocial variables affect the development of depression in MS? Does treatment with interferon increase the risk of depression? How effective are treatments for MS patients with depression? Each of these issues is briefly reviewed with critical commentary, and some priorities for future research are suggested.

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The presence of psychiatric symptoms in multiple sclerosis (MS) has been known since Charcot gave the first detailed clinico-pathological description of ''disseminated sclerosis'' in his lectures at the Salpêtrière hospital in the nineteenth century.[1] Among the psychiatric symptoms noted by Charcot were pathological laughing and weeping, euphoria, mania, hallu-cinations, and depression. Indeed, Charcot's patient Mademoiselle V was described as experiencing a fit of *lypemania* (or severe depression), along with hallucinations and paranoia.[2] However, it was not until the 1950s that empirical research on the frequency of depression among people with MS really began.[3] In addition to the neurological symptoms that characterise MS, major depression is common, with estimates of lifetime prevalence of major depression in MS as high as 50%.[4] Whereas historically it has been difficult to disentangle the direct effects of the disorder upon mood from the non-specific effects of chronic illness, a recent study suggests that the annual prevalence of major depression in MS is elevated compared with that in both healthy people and other chronic conditions.[5] In that study, Patten *et al* reported a 12 month prevalence rate of 25.7% for major depression in people with MS in the 18–45 years age range. Of further concern is the finding that suicidal ideation is relatively common

among people with MS, and that depression in people with MS is often not detected and treated.[4 6] Moreover, depression is an important determinant of quality of life (QoL) in MS and may well be the most important determining factor.[7–9] Recently considerable interest has been generated about the possible role of interferon beta in precipitating depression in MS, and although these concerns may not be warranted, the issue of major depression in MS remains a significant issue notwithstanding.[10 11] The aims of the present review are to:

- provide a brief overview of research on depression in multiple sclerosis
- highlight some of the issues emerging from this research
- suggest priorities for future research on this topic.

PREVALENCE OF DEPRESSION IN MS

Unipolar or major depression is a mental disorder characterised by the presence of five of the following symptoms for at least two weeks:

- a sad mood for most of the day/most days
- a loss of pleasure or interest in one's usual activities
- sleeping problems
- fatigue
- psychomotor retardation or agitation
- reduced appetite with weight loss (or the converse)
- a negative self-image
- feelings of guilt and self-blame
- reduced concentration and suicidal thinking.

The five symptoms must include sad, depressed mood and/or loss of interest and pleasure in usual activities.[12] A recent Australian study reported a 12 month prevalence rate for major depression in the community of 6.3%.[13] In a 1990 review[3] of affective disturbances in MS, Schiffer noted that most studies had reported a higher incidence and prevalence for depressive symptoms in MS compared with controls with a different neurological illness. However, he also commented that all these studies had design weaknesses of varying degrees. In particular, Schiffer noted that in most of these studies the clinicians diagnosing depression were not blind to the patient's condition or to the hypotheses at issue. He also noted problems relating to

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Abbreviations: BDI, Beck Depression Inventory; CBT, cognitive behavioural therapy; CES-D, Centre for Epidemiological Studies' Depression Scale; MS, multiple sclerosis; SSRI, selective serotonin reuptake inhibitor

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selection, diagnostic criteria and the vexed issue of the most appropriate control group to compare MS patients with. Notwithstanding these methodological issues, the finding of a high rate of depression in MS seemed quite consistent.

Minden and colleagues examined 50 patients with MS selected quasi-randomly from a patient register using a structured psychiatric interview and standardised rating scales for depression.[14] They reported that 54% of their sample met the research diagnostic criteria (RDC) for major depression at least once since their diagnosis whereas only 14% had met these criteria prior to it. Joffe et al assessed 100 consecutive patients attending an MS clinic in Canada using the RDC for major depression and reported a lifetime prevalence of 42%.[15] This figure did not include a proportion of their sample that met the criteria for bipolar affective disorder. In a study of 221 consecutive patients attending an MS clinic in Vancouver, Sadovnick et al reported a lifetime prevalence of 50% using a structured psychiatric interview.[16] They noted that this figure was considerably higher than the rates of depression typically reported for samples with chronic illness. Chwastiak et al undertook a mail survey of 1374 members of the Multiple Sclerosis Association in King County, WA with 739 responses (a 54% response rate).[17] They found that 42% of that sample had ''clinically significant depressive symptoms'' according to the Centre for Epidemiological Studies' Depression Scale (CES-D) and 29% scored in the moderate or severe range.

In a recent study, Patten et al used data from the Canadian Community Health Survey (CCHS) to provide a population based perspective on major depression and MS.[5] The point here is that previous studies mostly relied upon patients attending MS clinics, or on current health centre registers, and consequently could have overestimated the prevalence of depression. Patten and colleagues examined a sample of 115 071 participants, aged 18 or older, from the CCHS and found 322 with MS. The 12 month prevalence of depression was 25.7% compared with 8.9% for people without MS.

In summary, studies have repeatedly reported that the prevalence of depression in MS is high even when compared with other groups with a chronic illness. For example, lifetime prevalence rates of 40–50% and 12 month prevalence rates around 20% have been typically reported for samples taken from patients attending MS clinics. However, a number of methodological issues suggest caution in interpreting these figures. Most of the prevalence studies have taken samples from patients attending an MS clinic, and those patients coping well in the community might be underrepresented. Another issue concerns the wide variety of measures used to diagnose and quantify the severity of depression. There seems little or no consensus among researchers as to the clinical ''gold standard'' for diagnosing depression in patients with MS. Added to this is the risk with MS that the somatic symptoms, such as fatigue, may lead to inflated estimates of depression. This is perhaps most likely when behavioural rating scales that were designed for use in a general psychiatric setting are relied upon. Consequently, it might be prudent to use those screening measures validated in populations of patients with chronic illness.[18–20] It also behoves us to remember that many of the issues involved in screening for depression among patients with MS, such as missing the diagnosis or failing to treat the depression, are also important issues in primary health care and not unique to the neuropsychiatry of MS.[21]

LOCATION OF BRAIN LESIONS

The question as to whether or not depression in MS is associated with lesions in specific areas of the central nervous system has generated considerable interest recently. This question has particular relevance for understanding and treating depression in patients with MS. It may also be important for developing a clearer understanding of the complex relation that exists between biological and psychosocial factors in the genesis of depression.[22] In one of the earlier studies of this nature Rabins et al examined the computed tomography (CT) scans of 37 patients who were part of a larger sample of 102 patients with MS in whom psychiatric symptoms were studied longitudinally.[23] They observed that MS patients with brain lesions were more depressed than those patients with lesions only in the spinal cord and also that depression was positively correlated with the extent of neurological impairment. However, the 37 patients whose scans were compared, were those for whom a CT scan had already been completed prior to the study or where one was requested during the study as part of their ongoing medical care. Hence they may not be fully representative of the larger group of 102 patients in that study or of patients with MS in general.

Honer et al used magnetic resonance imaging (MRI) to compare eight MS patients with psychiatric disorders with eight matched control MS patients and concluded that these disorders were associated with temporal lobe lesions.[24] However, this rather small sample comprised a mixed group of psychiatric diagnoses and it is not clear how specific that conclusion might be with regard to depression. A study by Ron and Logsdail compared rate of psychiatric morbidity in a sample of 116 MS patients with a control group with physical disabilities.[25] They reported a significantly higher frequency of psychiatric 'caseness' in the MS group. The focus of this study was not on depression per se but rather on psychiatric illness in general. However, the authors did note that flattened affect (and also delusions and thought disorder) was associated with greater pathology in the temporal-parietal region. Pujol et al examined 45 consecutive out-patients at an MS clinic in Barcelona and looked for a relation between scores on the Beck Depression Inventory (BDI) and lesion location and volume.[26] Although no relation was found between total lesion volume and depression, they did find that BDI scores were significantly associated with lesions in the arcuate fasciculus of the left hemisphere. This relation accounted for 17% of the total variance in BDI scores. However, it should be noted that only seven of the patients had scores in the moderate to severe range according to the BDI (that is, >17). Thus it is uncertain quite what the implications of their results might be for patients with MS diagnosed as having major depression.

Zorzon and colleagues reported an MRI study of 95 consecutive patients with definite MS at a clinic in Trieste.[27] They used the Hamilton Rating Scales for Depression and Anxiety and a psychiatric interview by a clinician who was blind to the hypotheses. Of their 95 patients 18 (19%) met the criteria for major depression. The regional brain volumes and lesion loads of the depressed and non-depressed patients were compared. The authors reported that severity of depression and a diagnosis of major depression were correlated with right frontal lesion load and with right temporal brain volume. They also noted that severity of depressive symptoms correlated significantly with total temporal volume as well as right hemisphere volume. However, although statistically significant, these correlations were all modest and in the range 0.20–0.30.

The most recent imaging study of MS and depression, and arguably the strongest in methodological terms, was reported by Feinstein and colleagues, who used brain MRI to compare 21 MS patients with major depression with 19 carefully matched non-depressed MS patients.[28] A feature of this study was that the depressed patients all met the DSM-IV criteria for major depression as assessed by a structured psychiatric interview. In addition, the authors screened over a thousand

consecutive patients at an MS clinic according to rigorous exclusion criteria. For example, any patient with a premorbid history of psychiatric disorder, including depression, was excluded. The major finding from this study was that the depressed MS patients had ''more hyperintense lesions in the left inferior medial frontal regions and greater atrophy of left anterior temporal regions''.[28] Together, these two brain regions accounted for ~42% of the variance in a logistic regression model for predicting depression.

In summary, imaging studies to date vary widely in both their design and rigour and there are few if any unequivocal conclusions that can be made. However, on balance the evidence seems to favour an association between depression in MS with greater neuropathology in the left anterior temporal/parietal regions. There is a need for further research on this question. Perhaps what is most lacking thus far is any clear theoretical model of the neuropathology of depression and how precisely this relates to MS. Given recent advances in our understanding of the neuropathology, neuropsychology and neuroimaging of depression, this may soon occur.[29–31]

SUICIDE AND MS

The high prevalence rates for depression in MS raise the question as to whether or not patients with MS might then be at elevated risk of suicide. Sadovnick and colleagues analysed the causes of death in a large sample of patients at two Canadian MS clinics, one in Ontario and one in British Columbia.[32] The combined sample from both clinics comprised ~3126 patients and a total of 145 deaths occurred in the time period 1972–88. The cause of death was able to be clearly established from records for 119 patients of whom 56 died as a direct result of complications of MS. Out of the remaining 63 patients whose deaths were not as a result of MS complications, 18 (28.6%) died by suicide. A further two patients whose deaths came under the category of ''miscellaneous causes'' were suspected suicides. The authors concluded that the proportion of suicides as a cause of death was 7.5 times that for the age-matched general population. The authors noted that earlier studies had not reported such high rates of suicide in MS samples. In addition, one might expect higher rates of distress in a sample of clinic attendees.

A Danish study employed the Danish Multiple Sclerosis Registry and the Danish National Register of Cause of Death to examine the prevalence of suicide among people with MS.[33] The authors were able to examine data covering ~5525 cases for whom the onset of MS occurred between 1953 and1985. They reported a total of 53 suicides over this period and noted that the expected number of suicides in a group of this size (adjusting for age and so forth) would be 28. They noted that the risk was highest among the younger, male patients. In a recent study, Feinstein examined a sample of 140 consecutive patients attending an MS clinic in Canada using standardised measures to detect suicidal ideation and intent.[6] He reported a lifetime prevalence for suicidal intent of 28.6% (40 participants) and nine (6.4%) had actually attempted suicide. Feinstein examined those variables that predicted suicidal intent using logistic regression and found that living alone, severe depression and alcohol problems together accounted for ''an 85% predictive accuracy for suicidal intent''. Of particular concern in that study were that two thirds of those patients with ''current major depression'' were not receiving antidepressants and a third of suicidal patients had not received any psychological assistance.

ANXIETY AND DEPRESSION IN MS

The high rate of comorbidity among anxiety and mood disorders might suggest that anxiety disorders will also be common in people with MS. Whereas the existing literature tends to support this notion the amount of rigorous epidemiological evidence seems limited compared with that for depression. For example, in a recent review of research on the assessment of emotional problems in people with MS, only five of the 15 cited studies had included a standardised measure of anxiety.[34] However, those studies that have specifically assessed anxiety have typically reported quite high rates. For example, Smith and Young assessed the prevalence of both anxiety and depression in a sample of 88 consecutive patients attending an MS clinic, using the BDI and the Hospital Anxiety and Depression Scale (HADS).[35] They reported that 34% scored as ''cases'' for anxiety on the HADS with 22 patients (25%) needing treatment for it. In a study where the focus was on the neural correlates of depression and anxiety in MS, Zorzon et al assessed ''95 consecutive unselected patients with clinically definite MS'' in Trieste.[27] They reported a median anxiety score on the HADS of 18 (the usual cut-off for highly probable cases is 10/11). Janssens and colleagues surveyed 101 newly diagnosed patients and their partners and found high rates of anxiety in both the patients (34%) and their partners (40%).[8]

Thus several recent studies have reported high levels of anxiety in people with MS. However, these studies have all employed samples taken from patients attending clinics who might well have higher levels of symptoms than a community based sample of people with MS. Moreover, even among the patients attending clinics there is no detailed information regarding the specific subtypes of anxiety disorder present.

FATIGUE AND DEPRESSION IN MS

One puzzling aspect of MS for clinicians and researchers alike is the nature of the relation between depression and fatigue in MS. Fatigue is a common symptom in both depression and MS. Mohr et al note that ''A relationship between fatigue and depression has long been suspected in MS'', but ''While depression and fatigue are often assumed to be related in MS, why or how this relationship might exist has remained generally unarticulated''.[36] They also note two studies in which medication that has been effective for fatigue in MS has not shown any concomitant impact upon depression. It appears that earlier studies examining fatigue and depression in MS actually found little evidence for a close link between the two. For example, Krupp et al compared 32 consecutive patients attending an MS clinic in New York with healthy controls matched by age and sex.[37] Although 47% of the MS patients had scores suggesting clinical depression on the CES-D, they found no significant correlation with fatigue as measured by a visual analogue scale. Nor was fatigue correlated with neurological disability as measured by the Expanded Disability Status Scale (EDSS). However, fatigue was a common and distressing symptom among the MS group and the authors' conclusion emphasised the importance of viewing fatigue as a discrete symptom of MS that is not accounted for by depression. A subsequent study by this group also reported no correlation between depression and fatigue in patients with either MS or systemic lupus erythematosus.[38] Similarly, a study in the Netherlands by Vercoulen et al observed that fatigue was a common and troubling symptom in patients with MS but found no correlation with depression (BDI) or disability (EDSS).[39] In contrast with these earlier studies more recent research has tended to report a relationship between depression and fatigue.

One of the first studies to report a statistically significant correlation between depression and fatigue in people with MS was an investigation of psychosocial correlates of fatigue in 139 American patients with MS. However, the correlations were low, with fatigue severity and depression correlating at only 0.17.[40] A stronger association was noted by Ford et al

who examined fatigue and depression in 78 consecutive patients attending an MS clinic and claimed to be the "first reported study to … demonstrate a significant correlation between fatigue and mood level".[41] Although that claim might be debatable in the light of the aforementioned study, a notable feature of Ford's study was that it conceptualised fatigue as multidimensional with separate scores for *mental*, *physical*, and *total* fatigue. Depression was more strongly related to mental fatigue ($r = 0.54$, p<0.0001) than physical ($r = 0.31$, p<0.01). Subsequent research has mostly tended to confirm the relation between fatigue and depression but has also highlighted its complexity—emphasising the multidimensional nature of fatigue and the influence of moderating variables such as helplessness and recreational activity.[42–45] One longitudinal study found that the relation was dynamic as "relationships of fatigue with physical and mental health change during the course of a year".[42] Another found that depression and fatigue were independent predictors of QoL in MS.[7]

Although fatigue is well recognised as a somatic symptom accompanying depression and anxiety, prolonged fatigue is also common in community based studies of psychological morbidity.[46] Moreover it appears that some people who appear to have no other explanation experience fatigue as the main feature of a psychological illness.[13 46] For this reason some psychiatrists interested in the epidemiology and classification of psychological illness have recommended the recognition of neurasthenia to account for this group of patients and to analyse the value of treatments.[47] Whether or not fatigue results directly from brain lesions in MS or as a psychological reaction to the illness in a predisposed person remains uncertain. However, there is increasing acknowledgement that fatigue in MS is multidimensional and that both mental and physical fatigue need to be assessed.[41 42 48]

Treating depression in MS patients does seem to produce improvements in self-reports of fatigue. However, the evidence to date is based upon one uncontrolled study of patients who received either cognitive behaviour therapy (CBT) or supportive group therapy or sertraline.[36] This approach would not be expected to be as effective in those patients without any symptoms of depression. The serotonin selective reuptake inhibitors (SSRIs) have been shown not to be useful in the treatment of chronic fatigue syndrome, reversible inhibitors of monoamine oxidase inhibitor-A (RIMAs) are helpful in treating some aspects of fatigue syndromes, and CBT is beneficial.[39 49–51] Whether a CBT approach is also as useful in MS is unknown at present.

COGNITIVE IMPAIRMENT AND DEPRESSION IN MS

There is a substantial body of evidence that impaired cognitive functioning is common in MS with prevalence rates in community samples typically around 40% or higher.[52–54] For example, a British study of 200 people selected quasi-randomly from an MS register, reported cognitive impairment in 46% with memory problems in 34% and executive problems in 33%.[54] In contrast with the confusing picture about depression and lesion location noted above Rao has observed that "The degree and pattern of cognitive dysfunction is highly correlated with the amount and location of white-matter disease within the cerebral hemispheres".[55] Cognitive impairment is also now well documented in depression, although this may only be the case for depression in older and middle aged patients with a history of severe depression.[56] Consequently, it is important to understand the nature of the relation, if any, between cognitive impairment and depression in MS.

As with fatigue, most of the earlier studies reported no clear relation between cognitive dysfunction and depression in MS whereas more recent research has tended to report a positive correlation. For example, in his 1986 review of the neuropsychology of MS, Rao noted that: "Euphoria, apathy, lack of interest, and irritability are frequently noted to occur in patients with widespread cerebral involvement, while depression, postulated to be of a reactive type, is more commonly seen in patients without cognitive dysfunction or with only mild involvement".[57] Similarly, in 1995 he observed that "Recent studies have suggested that measures of cognitive dysfunction and depression are not correlated suggesting that depression is not a causative factor in the development of cognitive dysfunction".[55] The same conclusion was reached by Brassington and Marsh in a more recent review of the neuropsychology of MS.[58] In that paper they summarised 10 studies that addressed this issue and concluded thus: "Numerous studies have reported no association between cognitive impairment and depression in patients with MS".

This lack of any association between depression and cognitive impairment in MS seems rather surprising given the mounting evidence for the neuropsychological deficits that can accompany depression.[30 56 59] If physically healthy people with depression are prone to cognitive dysfunction it seems paradoxical that this is not the case for people with MS who are depressed. However, a recent programme of research by Peter Arnett and colleagues may shed some light on this seeming paradox.[60–62] Arnett has suggested that it is *effortful* rather than *automatic* information processing that is most likely to be 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 speeded tests of information processing, working memory and complex tests of executive functioning.[60–63] Additional support for a link comes from the work of Demaree and DeLuca.[64–66] These authors have criticised some of the earlier studies for relying upon correlation analyses and using neuropsychological measures that are not sensitive to the cognitive effects of depression. They note that the relation between depression and cognitive impairment is best established for severe depression and primarily in relation to information processing speed and working memory. Arnett and colleagues have also reported that cognitive impairments in patients with MS seem to be closely correlated with mood and negative self-evaluations but less so with the vegetative symptoms of depression.[62]

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 information processing speed, working memory and executive functioning may indeed be affected in cases where the depression is in the moderate to severe range. Whether or not these impairments are reversible upon treating the depression remains unknown.

PSYCHOSOCIAL FACTORS

A growing body of research attests to the importance of psychosocial factors in determining whether or not a person with MS develops depression.[67–69] The variables that have attracted the most attention are coping style and social support. The research findings on coping with MS closely resemble those in the broader literature 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.[70] However, it is our impression that some methodological and theoretical advances in research on coping have yet to be fully used in the research on coping in MS. For example, Folkman has suggested that narrative research methods can supplement standardised checklists to determine ways of coping that are not tapped by such measures.[70] This might be

important when considering coping in people dealing with one specific illness such as MS.

Social support is also associated with better adjustment although the relation is clearly not a simple linear one. For example, Pakenham examined the stress and coping model of illness in people with MS and found that social support had a beneficial effect on adjustment but only under circumstances of high perceived threat.[69] Uccelli and colleagues found that participating in a peer support group for MS patients had little consistent positive effect upon mood and may have actually been a negative influence on those participants who were coping well at the outset of the study.[71] A recent study by Mohr and colleagues has suggested that treating depression actually results in improvements on a number of aspects of social support. Such findings are not as perplexing as might first seem and there is evidence that depression may actually cause reduced social support.[72] Once again, we suspect that clarification of the complex relation between depression and social support in people with MS, will be achieved by closer integration with the broader literature on stress, coping, and social support. Other psychosocial variables that might affect mood in MS include illness intrusiveness, uncertainty, hope, and spirituality.[73–76]

INTERFERON AND DEPRESSION IN MS
With the advent of interferon beta as a treatment for relapsing remitting MS in the early 1990s concern arose regarding the potential for this drug to cause or exacerbate depression.[10] The initial concern apparently sprang from reports of a suicide and four attempted suicides that occurred among the treated group in the first clinical trial.[77] A more recent case report may have added to this concern with the authors claiming that the case ''suggests a causal link between interferon beta-1a treatment of MS and major depressive disorder''.[78] 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. As this issue was comprehensively reviewed by Feinstein in 2000, we will limit our discussion to studies published since that review. In that review Feinstein concluded that ''Given the many methodological pitfalls inherent in all studies to date, it is premature to conclude that disease modifying drugs are associated with depression''.[10] However, data from the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) study was published soon after, in which a significantly higher rate of depression (20%) was reported among the 193 patients treated with interferon than among the 190 controls who received only a placebo (13%).[79]

Notwithstanding that finding most recent studies have found little in the way of firm evidence that interferon treatment is likely to result in depression among people with MS.[80–82] For example, the Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) clinical trial included ~560 participants with relapsing remitting MS from 22 centres across nine countries randomly allocated to two treatment arms or a placebo control group and used three standardised measures of depressive symptoms. The authors concluded that pre-treatment depressed mood was the best predictor of subsequent depressive symptoms but found no differences in reported levels of depression across the three groups.[80] Moreover, the finding that the best predictor of depression in MS patients treated with interferon is a previous history of depressed mood has been consistently reported elsewhere.[83 84]

A subsequent study by this group also concluded that ''depression is not a side effect of interferon B1a'' when used to treat patients with secondary progressive MS.[81] Patten and colleagues have also reported that rates of depression are the same for patients treated with interferon as for patients treated with glatiramer acetate in clinical settings.[11] Evidence is also accumulating from other research groups that the concerns about interferon treatment and depression may have been undue.[82] Perhaps the important message here for clinicians is that screening for depression and monitoring of mood should be a feature of the medical management of *all* patients with MS—regardless of whether or not they are receiving interferon.

TREATMENT OF DEPRESSION IN MS
There is a small but growing literature on the treatment of depression in patients with MS. Schiffer and colleagues reported the first and only double blind, controlled trial of antidepressants in the treatment of depression in people with MS.[85] In that study they found that tricyclics (desipramine) were more effective than a placebo while noting that some patients had problems with anticholinergic side effects which limited their dosage. Interestingly, significant improvements were observed according to clinical judgement and the Hamilton Rating Scale for Depression but not on the BDI. There is also some evidence from open label trials that SSRIs and the monoamine oxidase inhibitor moclobemide can be effective treatments. Feinstein cautions that SSRIs may have impaired sexual functioning as a side effect and this is a particular concern given that it is also a common symptom of MS.[4]

Mohr and Goodkin found five studies that they considered rigorous enough for inclusion in a meta-analysis.[86] They concluded that depressed MS patients responded well to treatment with either psychotherapy or antidepressants (desipramine) but noted that psychotherapy with an emphasis on coping skills was more likely to be effective than insight oriented therapy. The results of their meta-analysis also suggested that if left untreated depression in people with MS was likely to worsen. Interestingly, these authors also speculate 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. The same laboratory has since reported that both CBT and sertraline (an SSRI) were effective in the treatment of depression in MS patients compared to supportive-expressive group therapy.[87]

In summary, there is a small body of controlled studies indicating that depression in people with MS responds well to two treatments—psychotherapy that emphasises the development of active coping skills (such as CBT) and antidepressant medication. In cases where a patient with MS fails to respond to SSRIs, Feinstein advises clinicians to consult the general psychiatric literature.[4]

CONCLUSIONS
Depression is common in MS with annual prevalence rates as high as 20% reported and lifetime prevalence rates of 50% not uncommon. There is some evidence that depression in MS is associated with greater neuropathology in the left anterior temporal/parietal region although the evidence for a close association between depression and lesion locality is not strong. There is some evidence that MS patients may have an increased risk of suicide and this is probably most true for younger male patients and those patients who are socially isolated, severely depressed and have alcohol problems. Anxiety disorders also seem more prevalent in MS although the research here is both less extensive and less rigorous than for depression and it is largely reliant upon data from samples attending MS clinics. Earlier research on fatigue and depression in MS consistently found no obvious relation although recent studies have tended to report a correlation. At the same time, these recent studies have also suggested

that the relation is a complex, dynamic one and that fatigue is best conceptualised as multidimensional. Early studies also found little evidence for a relation between depression and cognitive impairment. However, recent studies suggest that cognitive impairment is likely to be exacerbated when depression is in the moderate to severe range. The initial concern about interferon treatment causing depression in patients with MS seems unwarranted in the light of several recent studies addressing this issue. While all of these issues merit further research the outstanding question continues to be why depression among people with MS is not routinely screened. Moreover, given the evidence for its responsiveness to treatment why is it that depression in people with MS is so infrequently treated?

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