Objective: To report the occurrence, type, causes, and management of psychiatric manifestations in multiple sclerosis (MS).

Method: Review of recent, relevant literature.

Results: Psychiatric illness, especially depression, occurs much more frequently than expected in patients with MS, is frequently unrecognized or ignored, and is treatable using standard methods, although patients with MS may be unusually sensitive to side effects of tricyclic antidepressants.

Conclusions: Research is needed to better define the causes of psychiatric syndromes in patients with MS. Those treating MS should increase their awareness of and sensitivity to the likelihood of psychiatric disorder in these patients.

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Key Words: psychiatric disorders, multiple sclerosis, review

Multiple sclerosis is most commonly thought of as a physically disabling, often progressive disease. Visual loss, weakness, spasticity, bladder dysfunction, sexual dysfunction, and fatigue are among the primary symptoms considered in the management of this illness (1). There is, however, an increasing awareness of the role that psychiatric symptoms play in the disease course.

Proceedings from the 1992 International Conference on Multiple Sclerosis reported a consensus that patients with MS have an increased vulnerability to psychiatric illness. Further, cross-sectional studies revealed that nearly two-thirds of patients have detectable psychopathological conditions, although not all require or receive psychiatric treatment (2).

When you add that information to the numbers of individuals diagnosed with MS in Canada, the need for psychiatrists and other mental health workers to be involved with this population is clear. A report on the prevalence rates of MS in Alberta by the Provincial Medical Consultant’s Office in 1993, using census records rather than MS clinic statistics, indicated an overall crude prevalence rate of 216.7 per 100 000 population (3). The Multiple Sclerosis Society of Canada reports an overall prevalence rate of 200 per 100 000 population (personal communication).

Changes in mood, personality, and cognitive functioning are among the most disabling and distressing symptoms for individuals diagnosed with MS, yet patients and their families receive little understanding or help with these problems (4). When behavioural changes are addressed, the changes are described simply as emotional reaction to the life situation or poor adjustment to chronic illness (5). Recent research, however, indicates that there are additional risk factors to explain the high incidence of psychiatric conditions and psychological problems. These include side effects of steroid use for management of exacerbations of symptoms and increasing evidence of an organic explanation involving lesions in specific areas of the brain (6).

Attention has recently been given to dementia and the mood disorders associated with MS that can be produced by demyelination within various brain regions. When classifying the major causes of dementia according to the most significant neuropathology, MS is considered to be subcortical. MS is characterized by patchy, multifocal demyelination, but involvement appears to be concentrated in the frontal lobes (7). This region is significantly involved in cognitive, characterological, and affective functioning. Compromise to this
area yields symptoms of dementia, personality alterations, and psychosis.

While there is obviously a reactive component causing psychiatric symptoms in MS patients, the use of technologies such as magnetic resonance imaging (MRI) will help delineate neuroanatomic links between psychopathology and central nervous system (CNS) changes due to disease. MRI is highly sensitive in detecting abnormalities in the CNS. The periventricular region is the most common site for abnormalities in patients with MS (8); however, lesions are more frequently located in the temporal lobes when MS occurs with a psychiatric disorder. The temporal lobes may contain tracts important in regulation of affect, especially depression (9).

This paper is a review of recent literature that addresses the relationship between psychopathology and MS.

Affective Disorders

It is common for MS patients to describe transient mood changes, irritability, and anxiety. Two-thirds of individuals with MS experience some of these symptoms in the course of a year. For a third of those individuals, the symptoms will be severe enough to merit the diagnosis of a major depressive disorder (10). These behaviours are difficult for patients and family members to understand, but often they are not addressed by neurologists.

Affective disorders in MS are described in the literature primarily as depression, bipolar affective disorder, late-stage euphoria, and pathologic crying and laughing (11). In general, they are more common during exacerbations and in patients with a chronic progressive course. Affective symptoms do not appear to be closely related to degree of physical disability. As in earlier studies, Arias Bal and associates (12) found little association between the presence of psychopathology (depression, emotional lability, and anxiety) and clinical characteristics of the disease such as level of disability.

Depression

Although depression is a common and expected reaction to a progressive disease that may lead to disability, it is the hallmark of psychiatric presentations in patients with MS. A lifetime prevalence for the diagnosis of depression in this population ranges from 40% to 50% (11), and risk for suicide is particularly elevated for young men within the first 5 years after diagnosis (13).

Results of a metaanalysis of 5 studies (14) supported the hypothesis that MS patient groups have higher rates of depression than comparison groups, even when comparison groups are comprised of other patients with chronic illnesses.

In an earlier review article, Minden and Shiffer (11) reported that patients with MS have more depressive disturbances than do the general population, patients with various medical illness, and patients with non-CNS disabling disorders such as spinal cord injury or amyotrophic lateral sclerosis (ALS). MS patients with primarily cerebral disease appear to have higher rates of depression than do patients with primarily spinal cord disease.

Bipolar Disorder

There have been a number of studies concerning the coexistence of mania and MS. Schiffer and Wineman (15) reported on 10 patients who had both MS and bipolar affective disorder. This number was almost twice the number expected based on epidemiologic data. Joffe and colleagues (16) reported that 13% of 100 patients with MS also had bipolar disorder, a rate that is 13 times higher than what would be expected.

Hutchinson, Stack, and Buckley (17) reported on 7 patients who presented with symptoms of a bipolar affective disorder prior to the onset of MS symptoms. They posed 2 possibilities, although not mutually exclusive, mechanisms to explain this. Bipolar affective disorder may be an initial symptom of MS, preceding other neurological symptoms. Alternatively, there may be a shared genetic predisposition to bipolar affective disorder and MS.

While manic episodes in MS may be precipitated by steroid therapy (18), there is increasing evidence that affective disturbance may be due to organic changes in the brain. Dupont and colleagues used MRI to detect subcortical abnormalities in 19 patients with bipolar disorder (19). Although not a study of individuals with both MS and bipolar disorder, this and other laboratory studies may reveal the possibility of a shared anatomical site of the demyelinating process.

Euphoria and Pathologic Weeping and Laughing

Both euphoria and pathologic weeping or laughing in MS patients have been reported in numerous publications. Once considered psychiatric manifestations of the disease, these symptoms are now suggested to be neurologically based conditions.

Euphoria, a persistent cheerfulness and optimism about the future despite awareness of disability, is thought to be the result of structural brain damage, showing as enlarged ventricles on computed tomography scan. It has been described in connection with a progressive disease course and advanced dementia (20). Recent investigations suggest it occurs in a much smaller percentage of patients than was originally thought (21).

The lack of emotional control manifested as pathologic laughing and weeping may be triggered with little provocation. This behaviour involves the display of emotion without subjective content. Although early studies of MS patients reported prevalence rates of pathologic laughing and weeping as high as 95%, more recent studies indicate prevalence rates of 7% to 10% (11). Though the neuroanatomical basis of pathologic laughing and weeping is not fully understood,
studies of stroke patients demonstrating this behaviour implicate pontine brain stem lesions or lesions connecting the middle right cerebral hemisphere with the pons (22).

Characterological Changes

There is a high risk of characterological or personality changes when lesions are present in the frontal lobes. Characterological functions involve a variety of responses related to behavioural traits or functioning. For example, patients may become more impulsive and less inhibited in their social interactions. The resulting problems are particularly problematic for family members living with the “changed” individual.

Based on evidence that the lesions characteristic of MS may isolate prefrontal cortex from other regions of the brain, Grigsby and others (23) hypothesized that deficits in behavioural regulation, typical of frontal lobe dysfunction, are a significant factor in behavioural disturbances among persons with MS. Since these patients are unable to regulate their actions independently, they often require increased help from families and professional caregivers.

Results of an investigation by Arnett and others (24) suggest a relationship between frontal lobe white matter lesions in MS patients and impaired conceptual reasoning skill as measured by the Wisconsin Card Sorting Test. Anecdotal information suggested that these deficits were accompanied by a deterioration in personal insight, judgement, and affective regulation, which created significant management problems for the families of these patients.

Other Psychiatric Conditions

Psychotic illness in patients with MS is rare. Feinstein and colleagues (25) reported a study of 10 patients with MS and psychosis. The presentation, course, and symptoms were analyzed, and correlations of size and location of brain lesions were compared with a matched group of nonpsychotic MS patients. Results pointed to pathological changes in temporal periventricular areas. The most common psychotic symptoms noted in these patients were persecutory delusions, and all patients demonstrated a lack of insight.

The incidence of schizophrenia in MS is no greater than in the general population, but short-lived psychoses indistinguishable from schizophrenia have been reported and are probably associated with temporal lobe disease. Fontaine and colleagues (26) presented a case study of a patient with visual hallucinations with religious and mystical themes. This young woman’s MRI showed large plaques in the white matter of left frontal and left temporal lobes.

The association between MS and panic attacks has been reported in the form of case studies (27,28), but more information is needed before the co-occurrence of the 2 can be considered anything more than idiosyncratic.

Cognitive Impairment

With the increased interest in cognitive–behavioural changes in MS patients, accurate prevalence rates of cognitive impairment and clear descriptions of the psychiatric and/or behavioural changes that result from cognitive changes are needed. Neuropsychological testing may be used to assess cognitive impairment and has been found to yield more accurate estimates of cognitive impairment than the standard clinical neurological examination (29). More research is needed, however, to find sensitive and reliable tests to measure the kinds of behavioural problems MS patients experience and the neurological links that help explain the changes.

Using MRI, Moller and fellow researchers (30) found that atrophy of the corpus callosum correlated with the severity of overall cognitive impairment. Euphoria was related to enlarged ventricles, and patients with chronic progressive course were more impaired in their neuropsychological test performance.

Increasing numbers of MS cases for which the major problems described are of a cognitive and/or psychiatric nature are being reported. Mendez and Frey (31) described 2 cases in which individuals who suffered from subcortical dementia associated with MS showed symptoms of slowed information processing, poor memory retrieval, mood disturbances, and disturbed executive functions. They suggested that the neuropsychological deficits of MS may be associated primarily with demyelination of white matter pathways emanating from the prefrontal cortex.

Similarly, Fontaine and colleagues (26) described the cases of 2 women affected by MS who presented with dementia. They explained the behavioural changes of the first patient as being related to the disconnection of the frontal lobes from other parts of the cerebral hemispheres. MRI indicated large plaques in the white matter of left frontal and left temporal lobes of the second patient.

Presentation of MS as a Pure Psychiatric Disorder

The question has been asked whether MS ever presents as a pure psychiatric disorder (32). Since cerebral involvement occurs almost universally in MS patients, it would not be surprising if occasionally the first detectable clinical features of MS were psychological rather than neurological symptoms. Felgenhauer (33) reported on 19 patients suffering from the encephalitic form of MS who presented with psychiatric symptoms; neurological signs were either absent or overlooked.

Hotopf and colleagues (34) reported on 2 men with progressive dementia in the absence of any substantial neurological symptoms. The cognitive changes in these patients were attributed to psychiatric illness. Later, a diagnosis of MS was
made based on MRI, cerebrospinal fluid, and electrophysiological findings.

## Treatment of Psychopathology

With regard to pharmacological interventions for MS-related depression, tricyclic antidepressant medications have been shown to be effective in neurologic disorders, but few studies have been done specifically with MS patients. Schiffer and Wineman (35) performed a double-blind trial of desipramine in patients with MS and major depressive disorder. Results indicated that a significantly greater proportion of treated patients had improved depressive symptoms compared with untreated controls and that this effect was unrelated to disability status. Side effects were experienced in approximately 50% of the treated patients. The authors concluded that desipramine is beneficial for MS patients experiencing serious depression, but the side effects from this medication may be more common in this population than in other patient groups.

It is important to note, when treating MS patients, that many of the heterocyclics produce sedation and may lead to symptoms that mimic those of MS such as fatigue, muscle weakness, and dizziness. It may be challenging to sort out which symptoms are caused by medication and dosage and which are actually physical symptoms of MS (36).

Furthermore, the use of tricyclic antidepressants should be avoided when patients are taking corticosteroids, since they may exacerbate psychotic symptoms in this combination (37). Systematic studies of the use of newer antidepressants (the selective serotonin reuptake inhibitors [SSRIs]) have not been reported. Anecdotal reports and clinical experience, however, suggest a good response to SSRIs with fewer side effects than with tricyclic antidepressants.

While treatment of depression in patients with neurologic disease has received little systematic study, preliminary evidence indicates that patients respond to conventional pharmacotherapy and to electroconvulsive therapy (38).

Well-designed drug studies of patients with MS and bipolar disorder are not available. In Minden and Schiffer’s early review (11), lithium carbonate was as effective in controlling mania in patients with MS as it was in those without MS.

Pathologic laughing and weeping may respond dramatically to low-dose amitriptyline, 25 to 75 mg per day. Levodopa has also been found to be useful (11). Tricyclic antidepressants and SSRIs have shown some efficacy in the treatment of poststroke pathologic weeping (39). There is no known treatment for euphoria.

Individual psychotherapy, group psychotherapy, and couple and family therapy have all been cited as beneficial for the management of psychopathology in MS patients (36). Cognitive–behavioural approaches have proven to be effective in the management of emotional disturbance (40,41).

## Conclusion

There is evidence that psychiatric disorders, especially major depression, occur at a rate higher than expected in patients with MS. The etiology of psychopathology appears to be multifactorial. Possible causes include response to chronic illness, brain lesions, and corticosteroid treatment.

Research is needed in order to delineate the most effective management of psychiatric disorders in MS patients. Problems of side effects and medication sensitivity need to be addressed. Psychotherapeutic management, in conjunction with pharmacological treatment, also needs to be more fully explored.

Although psychiatric manifestations are relatively common among patients with MS, these symptoms are often ignored or down-played by professionals, thus impeding the adjustment process and creating more stress for patients and their families. By listening more closely to their concerns, we stand to learn a great deal about the debilitating consequences of psychiatric disturbances in this population.

### Clinical Implications

- MS patients are vulnerable to psychiatric disorders of either organic or functional origin.
- MS treatment may induce psychiatric disorders and complicate treatment.
- Exercise caution with medication dosage because of patient sensitivity.
- Individual, group, and cognitive behavioural therapies are useful.

### Limitations

- This is a review.
- There are few systematic studies of treatment of psychiatric disorders in MS patients.

### References


Résumé

Objectif : Présenter la manifestation, le type, la cause et la traitements des aspects psychiatriques de la sclérose en plaques (SP).

Méthode : Dépouillement de la documentation récente pertinente.

Résultats : Les problèmes psychiatriques, en particulier la dépression, surviennent beaucoup plus fréquemment qu’ils le pensent chez les personnes atteintes de SP. Néanmoins, ils passent souvent inaperçus ou les ignorent, même si on peut les soigner par des méthodes bien établies, quels que soient les personnes atteintes de SP peuvent montrer une sensibilité inhabituelle aux effets secondaires des antidépresseurs tricycliques.

Conclusion : Il faudrait entreprendre des recherches pour mieux cerner les causes des syndromes psychiatriques des personnes souffrant de SP. Les médecins soignant ces malades devraient être plus conscients des risques de troubles psychiatriques chez leurs patients et être plus ouverts à une telle situation.