Chapter 2
Depression and Multiple Sclerosis: Clinical Aspects, Epidemiology, and Management

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Abstract Multiple sclerosis (MS) is associated with a broad array of neuropsychiatric problems of which depression is the commonest. Defining depression can present a potential problem because certain symptoms that underpin the diagnosis of depression may also be caused by multiple sclerosis. Certain self-report scales that take this symptom overlap into account have been validated for MS patients (Beck Fast Screen for Medical Patients and the Hospital Anxiety and Depression Scale). MS-related major depression has a lifetime prevalence of 25–50 %, well above the rate in the general population. Depression is linked to a poor quality of life, potentially greater cognitive impairment, an increase in suicidal ideation, and less compliance with disease-modifying drugs. Notwithstanding the high prevalence of depression in MS and its multiple adverse effects on the MS population, there are only two randomized trials of antidepressant medication (paroxetine and desipramine). Results are modest and side effects can be troubling. Treatment of choice is therefore cognitive behavioral therapy. Mindfulness-based therapy and exercise may also offer benefits to the depressed MS patient.

Keywords Depression • Anxiety • Beck Fast Screen for Medical Patients • Hospital anxiety and depression scale • Epidemiology • Suicide • Quality of life • Cognition • Antidepressant drug • Behavioral cognitive therapy • Mindfulness-based therapy • Exercise

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Introduction

Multiple sclerosis is associated with a broad array of neuropsychiatric problems of which depression is the commonest. This chapter will describe the clinical features and epidemiology of depression before concluding with a section devoted to treatment. In a disease without cure, symptom management takes on an even greater weight, and this is particularly true for depression for as the chapter will make clear, the effects of low mood can be pervasive and severely debilitating.

Clinical Aspects

Depression is a broad term encompassing, on the one hand, the symptom of sadness and, on the other, the full syndrome diagnosis of major depression. The latter has been defined by the American Psychiatric Association as a collection of nine signs and symptoms of which five or more have to be present for at least a 2-week period in order to achieve the diagnosis. The symptoms include depressed mood for most of the day, a loss of interest or pleasure in activities that were formerly enjoyable, changes in appetite linked to weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or inappropriate and excessive guilt, a reduction in concentration, and recurring thoughts of death. For clinicians working with MS patients, this definition can present a potential problem because certain of the symptoms that underpin the diagnosis of depression may also be caused by multiple sclerosis itself. Here, the most frequent overlapping symptoms are those of fatigue, reduced concentration, and difficulties with sleep.

Researchers have attempted to address this symptom overlap in a number of ways. Psychometric, self-report scales have been developed specifically for use in medically unwell patients with the aim of removing the somatic confounders. The best examples of these are the Beck Fast Screen for Medical Patients (BFS) [1] and the Hospital Anxiety and Depression Scale (HADS) [2]. Both of these self-report measures have been validated for use in patients with multiple sclerosis [3, 4]. The advantage of the HADS is that the scale contains an index for anxiety too. Both measures are easy and quick to complete and can be introduced into routine clinical practice without difficulty. They have also been translated into different languages. In addition to these two indices, Mohr and colleagues [5] recommend the two-question approach, i.e., asking patients about pervasively low mood and the inability to enjoy activities, as before. An even briefer approach is the Yale Single Question screen for depression [6]. The brevity of such an approach is attractive, but the sensitivity is understandably on the lower side. A recent critical review from the American Academy of Neurology (AAN) endorses the Beck Depression Inventory (Revised Edition) and the two-question approach mentioned above [7]. Clinicians therefore have considerable choice in selecting a measure, but in doing so should remember that only two scales, namely, the BFS and HADS, have been specifically validated for use in an MS population.

Anxiety

As occurs in the general population, depression in MS patients is often associated with anxiety. The [8, 9] clinical importance of this kind of morbidity should not be overlooked because MS patients who have both anxiety and depression are more likely to have increased thoughts of self-harm, greater somatic complaints, and more extensive social dysfunction than MS patients with depression or anxiety alone [10, 11]. Anxiety as a symptom occurs more frequently than depression as a symptom [10, 12], and rates of generalized anxiety, panic disorder, obsessive-compulsive disorder, and social phobia are all increased significantly in MS patients relative to the general population [13].

Epidemiology

It is estimated that major depression has a lifetime prevalence of 25–50 % [8, 9, 14–16]. These figures generally come from tertiary referral clinics and as such the data may be slightly skewed. That said, community-based data support the elevated prevalence. In a study of 115,071 adult Canadians, the 12-month prevalence of depression in MS subjects was elevated relative both to healthy individuals and those with long-term medical difficulties. The highest rate of depression was found in individuals aged 18–45 years where the 1-year prevalence rate for depression approached 25 % [9]. Additional evidence supporting the frequency of MS-related depression comes from administrative data bases which have the advantage of robust sample sizes [17–19]. Here, the frequency of depression is comparable to that reported in the community and tertiary clinics reported above. It is also important to note that data do not support an increase prevalence of depression prior to the onset of multiple sclerosis [20]. This observation is important for it points to a closer link between neuropathological changes and/or psychosocial factors and a disturbance in mood.

Disease Duration, Disability, and Depression

There is no clear association between the presence of depression and disease-related variables. The relationship with physical disability is equivocal [21, 22]. The same situation pertains to disease duration [8]. The reasons for these mixed findings could be due to the diversity of the disease itself. For example, patients with the same disease duration may have a markedly differently relapse rate or disease course. Moreover, the degree of physical disability may be determined by a combination of cerebral and spinal involvement, each having a potentially different effect on mood. Therefore, the important determinant for mood may be less closely related to the

Expanded Disability Status Scale (EDSS) than how the individual adjusts to adversity and the adaptive strategies he or she uses.

The Clinical Significance of Depression

Depression is linked to a poor quality of life, greater cognitive impairment, an increase in suicidal ideation, and less compliance with disease-modifying drugs (DMDs). Each of these will be discussed in turn.

Quality of Life Depression in MS is associated with decreased quality of life whatever the neurological or functional impairments associated with MS [23]. Carta et al. [24] revealed that patients with MS and a co-morbid lifetime diagnosis of a mood disorder had significantly lower scores on the SF-12 (a measure of quality of life) than MS patients with no history of mood disturbance. Significantly, MS patients with a past history of depression, whatever their mood status at the time of that evaluation, endorsed significantly lower MSQOL-54 scores relating to energy, mental health, cognitive function, general quality of life, and sexual function [25].

Depression and Cognition Approximately 40–70 % of MS patients will have cognitive dysfunction depending on the disease type. Evidence now suggests that clinically significant depression may lead to a further deterioration in a patient's cognitive abilities. Works from Arnett and colleagues have shown that depression can impair working memory, in particular the executive component of this [26–28]. These findings raise the intriguing possibility that successfully treating depression could, in theory, lead to a concomitant improvement in an MS patient's cognitive ability. To date, no specific study has explored this possibility.

Adherence to Disease-Modifying Drugs (DMDs) A number of studies have connected depression with poor compliance with respect to DMDs [29–31]. Bruce et al. [29] showed that MS patients with a current mood or anxiety disorder are almost five times less likely than MS patients with no psychiatric diagnosis to adhere to disease-modifying therapy. Significantly, treating depressed MS patients for at least 6 months with antidepressant medication has been associated with better compliance with DMDs.

Suicidal Risks One in three MS patients will entertain thoughts of suicide [32]. The predictors here are the presence of a major depression, the severity of the depression, social isolation, and concomitant alcohol abuse [33]. Suicidal intent is also a risk factor for a suicide attempt. Epidemiological data from Scandinavia reveal that MS patients are twice as likely to commit suicide as individuals in the general population [34–36]. The figure from British Columbia in Canada is significantly higher than this with a 7.5 increase documented [37]. The data also suggest that males within the first 5 years of diagnosis may be at a particularly high risk for suicide [36, 38].

Management of Depression

It comes as a surprise to find that notwithstanding the high prevalence of depression in MS and the multiple adverse effects of depression on the MS population, there are only two controlled treatment studies of an antidepressant medication that are considered methodically robust by the Cochrane review committee [39]. The first of these studies involves the old tricycle drug desipramine which was found to be partly effectively in treating depression. However, treatment was linked to troubling anticholinergic side effects for patients, such as dry mouth, sedation, and constipation among others, thereby, in some cases, limiting the attainment of a therapeutic dose [40]. While not mentioned in the report, one of the disadvantages of a drug like desipramine is that it is potentially fatal in overdose. This point is important given the frequency with which MS patients think of suicide and the high completed suicide rate of this population. This concern does not pertain to the second drug that is mentioned in the Cochrane review, namely, paroxetine, a selective serotonin reuptake inhibitor (SSRI) [41]. Paroxetine, like desipramine, was found to be modestly effective in helping mood, but the drug is also with side effects, most notably sexual dysfunction. This has introduced challenges with treatment compliance. Should sexual side effects lead to treatment discontinuation, clinicians may wish to consider two other antidepressant medications, namely, bupropion and mirtazapine, both of which spare sexual function. Neither have, however, been assessed in an MS-related RCT. Here it is germane to note that the recent AAN critical review article concluded that there are no sufficient data at present to endorse the use of antidepressant medication for MS-related depression [7]. While once cannot refute the AAN's rigorous review process in arriving at this conclusion, it is important for clinicians not to lose sight to the fact that antidepressant medication can bring about some symptom relief. Should there be no recourse to psychotherapies, and this is a reality faced by many practitioners in a smaller health care setting, rather than admit to therapeutic defeat, a trial of an SSRI is warranted. Here, the old neuropsychiatric dictum of start low and go slow with dosing applies. Drug management is presented in more detail in Chap. 8.

More promising data have been reported with certain psychotherapies. Cognitive behavioral therapy (CBT) has emerged as a treatment of choice for MS-related depression [42–44] and is endorsed by both the Cochrane review committee [45] and the AAN [7]. Moreover, CBT may be effectively given over the telephone to MS patients [46], an important observation given that mobility issues can make it difficult for some patients to attend clinic. CBT of course does not come with the troubling side effects of sexual dysfunction, dry mouth, and weight gain that can bedevil the use of an SSRI, but in many centers CBT might not be available. A recommendation from the Goldman consensus panel [47] was that in a situation such as this, a neurologist should treat the depressed MS patient with medication. No specific drug was endorsed.

Other treatments reportedly effective in helping MS-related depression are mindfulness-based therapy [48, 49] and exercise [50]. In relation to the latter, a

number of studies have been undertaken with exercise as a secondary outcome variable. The definitive study is therefore awaited, but preliminary evidence suggests that exercise may not only elevate depressed mood; it may also lead to improvement in certain cognitive difficulties as well [51]. Finally, an intriguing observation has recently emerged with respect to stress management therapy (SMT). A randomized controlled treatment study over 24 weeks revealed that SMT was effective in reducing cumulative new T2 and contrast-enhancing lesion burdens relative to MS patients who had not received the therapy [52]. Unfortunately, these improvements in brain MRI metrics were not accompanied by benefits with respect to the patients' mood, this point underscoring the complex relationship between brain MRI changes and depression.

Finally, any treatment recommendation would be incomplete without brief mention of electroconvulsive therapy, reserved for severe depression often medication refractory or associated with intense suicidal intent where time is of the essence in providing symptom relief. The treatment is generally well tolerated in MS patients although the literature here is small [53].

Conclusion

There is inconvertible evidence linking clinically significant depression in people with MS to a multiplicity of negative effects with respect to activities of daily living. It is therefore imperative that clinicians from many disciplines who treat MS patients not miss the diagnosis. This point is further underlined by studies that demonstrate the effectiveness of treatments for depression in this population. Not only will successful treatment reduce the morbidity associated with MS; it holds out the promise of also lessening suicide-related mortality.

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