

Review

Psychological aspects of multiple sclerosis

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Abstract

A significant incidence and prevalence of psychological disorders in multiple sclerosis (MS) has been reported. Their underlying mechanisms and the extent to which they are reactive to psychosocial factors or symptoms of the pathological process itself, remain unclear. Depression is the predominant psychological disturbance with lifetime prevalence around 50% and annual prevalence of 20%. Depression is commoner during relapses, may exacerbate fatigue and cognitive dysfunction and no firm evidence exists of its induction by interferon; instead, treating depression improves adherence to disease-modifying drugs. Anxiety is also frequent, occurs in newly diagnosed patients, and its co-morbidity with depression has been suggested to increase the rate of suicidal ideation. The relationship between stress and MS is an attractive issue because some studies pointed to an association between stressful life-events and MS onset/relapses; however, the evidence supporting this hypothesis is not conclusive so far. Other psychiatric illnesses, as bipolar affective disorder, pathological laughing and crying or psychosis occur less frequently in MS. Therapeutic strategies include psychotherapy, cognitive behavioural therapy, strengthen of coping, and specific medications. The “art” of the MS team in providing the best individualized care is emphasized, aiming to reduce the burden of the disease and improve the patients’ quality of life.

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1. Introduction

A significant incidence and prevalence of psychological and psychiatric symptoms in patients with multiple sclerosis (MS), compared to individuals with similar degrees of disability, has been reported in the literature [1–5]. Anyway, it is worth of note that this group of symptoms has already been amazingly reported by Charcot in his first descriptions of the disease, a long time ago [6–8]. Actually, experienced health teams working in MS Clinics are very much aware that the complete management of these patients includes a supportive understanding of the psychological idiosyncrasy of every single patient in order to disclose and treat any possible psychological or psychiatric impairment as early as possible.

The occurrence of psychological changes may even be noticed before diagnosis, when the patients experience the unexpected first neurological symptoms and feel vulnerable, and then after receiving the diagnosis, as reported in retrospective studies where MS patients were interviewed about this issue [9,10]. In both situations the patients reported a world of conflicting emotional reactions as shock, anxiety, fear, sadness, sorrow, anger, uncertainty, shame, loss of identity, abandonment or confidence, which may play a role in the future development of psychological impairment [9]. One important result of these studies was the feeling of relief that some patients expressed when they finally knew the diagnosis [9,10], and in this setting could somehow experience positive reactions to manage MS, such as acceptance, reappraisal, seeking help and hope [9,10].

As a whole, the psychological symptoms may be ascribed to the many facets related with this chronic, progressive and unpredictable neurological disease which typically begins in young adulthood. MS affects many spheres of functioning, reduces physical functions, leads to disability, and is likely to provoke disruptions in education, employment, sexual and family functioning, friendships and daily living activities [11]. As the disease develops and disability increases, it can have a substantial impact on the individual's sense of self, which implies that patients have constantly to re-define their own self-image to overcome the limitations imposed by MS [12]; disease progression may also lead to perceived lack of social support, isolation and social withdrawal, which further contributes to the “profound impact of MS on the patients' social roles and their relatives' well-being” observed by Hakim et al. [13]. Moreover, feelings of uncertainty about daily health and loss of self-esteem, due, for instance, to the possibility of an upcoming new relapse in relapsing-remitting forms (RRMS) or to disagreeable side effects from medications, greatly disturb the quality of life [11,14,15]. Still, MS relapses disrupt the *status quo* for patients and families, eliciting emotional feelings that may be even more disturbing when medicated patients with disease-modifying drugs were somehow not expecting new relapses [16]. As well, the presence of demyelinating lesions in critical, still poorly defined, brain regions, might, at least hypothetically, explain the occurrence of some psychological symptoms, as has been

elsewhere reported for depression [17]. However, as relevant as these investigations can be, the underlying physiopathological mechanisms of the psychological disorders in MS are not fully understood and warrant further studies.

2. Depression

Depression is by far the most common psychological disturbance in MS, though other mood disorders can occur. Several studies have reported high rates of depressive symptoms in MS patients compared to controls with other chronic neurological conditions, with an overall lifetime frequency of major depression reaching 50% [18–21] and an annual prevalence around 20% [22]. It has been pointed out that these numbers may be rather oversized due to sampling selection, in as much as most prevalence studies considered mainly patients attending MS Clinics than those coping well in the community [17]. To clarify this issue, Patten et al. [22] conducted a study based on a population survey and reached similar values for the prevalence of major depression in MS. Even so, depression in people with MS is often not detected and not treated [17,21]. In a recent review of depression in MS, Siegert and Abernethy [17] raised many important points to the full exploration of this condition which are worth to analyse.

As regards the mechanisms of depression in MS, the consensual view favors a multifactorial origin, including genetic, immunological and psychosocial factors. Actually, a genetic predisposition has been suggested [23] but seems uncertain up to now, and a correlation was found between depression and brain inflammatory markers, evidenced by the presence of gadolinium-enhanced lesions in brain magnetic resonance imaging (MRI) and of pleocytosis in the cerebrospinal fluid [24]; in addition, the role played by perceived psychosocial stressors has been reported, too [25]. On the other hand, depression may be not only a consequence of MS but also be a direct symptom of the disease itself, bearing in mind the descriptions of an association between depression and the occurrence of lesions in specific brain regions. Regarding this subject, a right/left asymmetry was found with predominance of the lesions in left [26–28] than in the right [29] hemisphere. In the left side, depressive symptoms were associated with lesions in the arcuate fasciculus [27], in the medial orbito-frontal regions (together with atrophy of the ipsilateral anterior temporal regions) [28] and with perfusion asymmetry in the limbic system with higher cerebral flow on the left than on the right hemisphere [26]. In the right hemisphere, depressive symptoms were correlated with frontal lesion load and with temporal brain volume [29]. In spite of these findings, the identification of specific brain locations to underpin depression in MS is so far an unsolved question, instead complex interactions between brain pathology and environmental factors may determine psychological and psychiatric symptoms in MS [30]. Moreover, as Thomas et al. [11] consider, the relationship between depression/mood disorders and MS

is complex, and the extent to which they might be consequences of the pathological process itself or psychological reactions to it remains unclear.

Clinically, depressive symptoms of anxiety, irritability, anger and somatic disturbances are more frequently reported than apathy and withdrawal [30]. In a longitudinal study comparing the variation of different depression symptomatic clusters in MS patients during 3 years, Arnett and Randolph [31] verified that mood symptoms were significantly more variable over time than neurovegetative or negative evaluative symptoms. Additionally, this study suggested a close correspondence between decreased use of active coping strategies over time and increased mood disturbances [31]. Depression is usually more common during relapses than in remission phases in RRMS [14,32] and when the neurological disability is progressive [30], but has also been detected in 54% patients with benign MS [33]. On the contrary, no close relationship was observed between depressive symptoms and disease duration or degree of physical impairment in RRMS [30,32].

The frequency of depression in MS addresses the risk of suicide and suicidal attempts. In this way, a few studies conducted in northern countries reported higher rates of suicide in MS patients [19,34,35], reaching values 7.5 times greater than in normal age-matched populations [19]. The higher risk was found in younger, male patients, within the first 5 years of diagnosis [34]. In another study, focused in suicidal ideation and attempt in MS patients attending a MS Clinic, Feinstein [35] found a lifetime prevalence for suicidal intent of 28.6% and that 6.4% patients had already attempted suicide; moreover, living alone, severe depression and alcoholism were factors that presented altogether a 85% predictive accuracy for suicidal intent. However, taken these results together, it remains unclear whether all suicides are related to depression in MS patients. Further studies enrolling large number of patients assisted in different health units, and not only in MS Clinics, are necessary to better clarify this topic, although this may signify an arduous task considering the multiplicity of suicide causes.

With respect to the association between interferon beta and depression in MS, it is commonly thought that this treatment induces or aggravates prior depressive symptoms. This belief resulted from some isolated case reports of suicide or attempts of suicide in treated patients [36,37] and then after the study “Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study” (CHAMPS), where a higher rate of depression (20%) was found in the treated patients than in the placebo arm (13%) [38]. Moreover, in the abovementioned longitudinal study of depression in MS, Arnett and Randolph [31] found that patients with worsening depressive symptoms were significantly more likely to have been taking interferon beta than those with unchanged mood functions; however, these results must be cautiously figured out given the previously alluded “close correspondence between decreased use of active coping strategies over time and increased mood disturbances” [31]. On the contrary, other studies did not show any correlation between interferon

beta treatment and depression in MS [39–43]. Namely, in the study “Prevention of Relapses and Disability by Interferon beta 1-a Subcutaneously in Multiple Sclerosis” (PRISMS) no differences in the levels of depression among groups of patients and placebo arm were observed [40]. More recently, Porcel et al. [43] analysed the emotional state of MS patients treated with interferon beta during 4 years and their data support the absence of emotional worsening with this long-term therapy. Therefore, there is no firm evidence that interferon treatment may induce depression in MS patients. Instead, the presence of baseline depressive symptoms was observed to predict the presence of depression at follow-up [39–41,43].

The association between depression and fatigue is other relevant point. In fact, whenever depression is evaluated in MS patients, fatigue is usually assessed at the same time, not only because these are both common symptoms in MS, but also because it is tempting to ascribe the presence of depression to fatigue and *vice-versa*. Fatigue is a persistent somatic symptom reported by almost 75% MS patients [44] using different expressions, as, for instance, overwhelming sense of tiredness not explained by exertion, lack of energy or feeling of exhaustion, that usually increases during the day. With a multidimensional nature [45,46], fatigue is the single symptom that patients identify as interfering most with daily activities [47], may occur in any stage of MS [48], even in benign cases [33], and seems to be independent from disability or mobility [46,48,49]. Although some studies point to positive correlations between fatigue and mood levels [45,49], particularly as concerns depression and mental fatigue [45], the relationship between depression and fatigue in MS is not entirely clarified [50].

The relation between depression and cognition in MS is another important issue, in as much as depression may worsen cognitive functioning and cognitive dysfunction may induce depression. Indeed, cognitive impairment in MS is often a hidden condition, which brings great difficulties for the patient in terms of daily performance, which in turn contributes even more to depression, anxiety, distress and fatigue. Yet, in the vicious circle between cognitive and psychological impairment, the role played by each type of symptoms remains unsettled. Given that, when MS patients are evaluated for cognitive tasks, it is a common practice to assess other symptoms as depression, anxiety and fatigue along with neuropsychological tests. The high frequency of cognitive changes in MS is well recognized, affecting 40–60% of patients [51], and can have a significant impact on social and occupational functioning. Cognitive impairment can be an early feature of demyelinating process [52–54], may be detected in patients with clinical isolated syndromes [55] and in benign MS [33], but is more frequent and more severe in patients with progressive forms of MS than in RRMS [56] and correlates with the rate of physical disability [57]. Therefore, the possibility of aggravation of cognitive dysfunction by a frequent symptom as depression may represent a substantial problem in MS patients with a negative impact in the daily quality of life. Recent studies found out that depression may

actually exacerbate cognitive dysfunction [58] and decrease the accuracy of patient reported cognitive impairment [59], giving consistency to the correlation between depression and worsening cognitive impairment. Moreover, some studies demonstrated that the adverse effect of depression in cognition is mainly noticed on particular aspects of the cognitive capacity, namely the executive functions of working memory [60–62].

Finally, the risk of relapse induced by depression is an interesting topic that has been addressed in several studies, the results of which are conflicting. Whereas some studies reported a positive association between depression and the occurrence of MS relapses [32,63,64], with depression scores higher in patients with relapse than in those in remitting stages [65], other studies lacked to find any relationship [66]. Recently, in a 2-year prospective study designed to determine relapse predictors in 101 RRMS patients, the relapses were not predicted either by depression or by anxiety [67]. Therefore the impact of depression in the occurrence of relapses is a doubtful issue.

3. Anxiety

Anxiety has been less investigated than depression in MS, although it is a cause of disability in these patients, too. In the literature the prevalence of anxiety in MS widely varies from 19% up to 90% [1,32,68–71], which means that some studies found out that anxiety is even more frequent than depression and mood changes in MS [32,70]. As well, higher rates of anxiety in MS patients than in controls were found in newly diagnosed patients (34%) and in their partners (40%) [72]. Moreover, in a longitudinal 2-year study conducted in 101 recently diagnosed patients, the same group observed that MS patients and their partners continued to have high levels of anxiety and distress in the first years after diagnosis, and found that baseline screening for anxiety at diagnosis can be used to predict the levels of anxiety and distress in that period of follow-up [73]. In another study carried out in 140 consecutive MS patients the lifetime prevalence of any anxiety disorder was 35.7%, with panic disorder (10%), obsessive compulsive disorder (8.6%), and generalized anxiety disorder (18.6%), the most common diagnoses obtained [71]. These authors identified as risk factors, female gender, a co-morbid diagnosis of depression, and restricted social support, and further verified that the diagnosis of anxiety disorders had been overlooked in most subjects, so they had not received any treatment [71]. The co-morbidity of anxiety with depression in MS patients had already been addressed before and was found to be associated with increased rates of suicidal ideation as compared with patients with little or no anxiety [70]. Depression and anxiety were also found to be associated with disease activity, but not with disease duration or severity [32]. Still, as already mentioned, some studies reported that anxiety was one of the emotional feelings that some patients reported even before they knew the diagnosis of MS [9,10].

The high rates of anxiety described in MS are somewhat expected, bearing in mind the chronic and unpredictable course of the disease implying continuous adjustments of the patient's sense of self. These adjustments are crucial to accept the progressive limitations imposed by MS, to perceive and adapt to the resulting family and social demands, to deal with unpleasant self-injectable medications and to handle with the generalized pressure of frequent reports about new potentially more effective medications. Indeed, the assumption that anxiety emerges as a reactive phenomenon to a variety of situations is strengthened by the lack of association between anxiety and MRI abnormalities [29]. This aforementioned study, aimed to investigate the relationship between the involvement of specific brain areas and the occurrence of depression and anxiety in MS patients, did not evidenced any significant correlation as concerns anxiety, thus putting apart the hypothesis of specific brain locations for this condition [29].

Anxiety may also be disclosed by acute relapses in RRMS, which are experienced by the patients as unexpected disrupting events in daily life and a remembrance that they do have MS, as pointed out by Kalb [16]. This aspect has been addressed in the controlled study of McCabe [14], designed to determine the impact of relapses in the mood and self-esteem of 243 MS patients during 18 months, who concluded that the relapse group of patients showed the highest levels of anxiety as compared with the remission group or the general population. On the contrary, there are studies addressing the possibility that anxiety may induce the occurrence of relapses, the results of which are conflicting. Whereas Noy et al. [32] described an association between anxiety and disease activity, expressed by the number of disease relapses per year, in the alluded to above prospective study about relapse predictors, Brown et al. [67] observed that the relapses were not predicted by anxiety. So, the understanding of the relationship between anxiety and relapses is still limited.

In addition, a specific condition leading to anxiety in MS has emerged after the introduction of self-injectable immunomodulatory drugs designed “self-injection anxiety”, which may affect 50% of MS patients [74]. This situation is well-known in daily practice of MS Clinics and requires specialized approaches.

4. Stress

Stress is a widespread symptom that has been much studied in MS as a potential enhancing factor either to the onset of the disease or to the occurrence of subsequent relapses in RRMS. There are various definitions and classifications of stress. Currently, stress is considered some kind of change in an individual's life, the “stressor”, which requires readjustments that surpass the ability of coping, and leads to psychological or biological harm. Thus, as referred by Mohr [75], it is necessary to analyse the environmental stressor, the psychosocial response, and their consequences. Stress may

be classified according to duration (acute or chronic stressors), frequency, severity and type of impact in the individual (negative or positive). Besides, it is well-known that the same events may be more stressful to one individual than to another [76].

As regards MS onset, there is a classical and old supposition that stressful events may be precipitating factors in that process. This hypothesis came to light after Charcot studies which suggested that grief or anger might have a role in the occurrence of some neurological diseases including MS [6]. Thereafter, some case reports and controlled studies were published about this matter showing divergent results. Yet, two controlled studies with larger number of patients gave some reliable evidence that MS patients reported to have been significantly more exposed than control subjects to unusual stress in the 2 years (most evident in the 6 months) prior to disease onset and further described a greater number of stressful life situations, or single events, than the controls [77,78]. However, the role played by stressful events in MS onset awaits further clarification.

With respect to stress and MS relapses (for review see Mohr [75]), there is a growing body of evidence regarding the association between stress and relapses [75,79]. However, this association seems theoretically unexpected on physiological grounds, since stress stimulates the hypothalamic-pituitary-adrenal axis (HPA) leading, as a result, to increased levels of circulating endogenous cortisol. In its turn, cortisol is a biological way of controlling inflammation, so the implicit abortion of eventual relapses should be a logical consequence. Actually, this mechanism could explain the results of a study conducted during the Gulf war in MS patients exposed to acute stress consequent to daily missile attacks, which showed a reduced risk of relapse [80]. Nevertheless, as shown in a meta-analysis review about the association between stressful life-events and relapses, all but the latter study [80] suggested that stress was associated with increased risk of relapse [79]. As recently highlighted by Mohr [75], all studies he analysed in the meta-analysis [79] showing an increased risk of relapse associated with stress, were performed in stable western countries where stress is “generally more chronic (lasting at least weeks or months) related to family, work or financial tensions”. For instance, in a longitudinal 2-year prospective study in RRMS, Franklin et al. [81] found that patients who reported significant negative stressful life-events were 3.7-times more likely to have a relapse than the unexposed patients; Sibley [82] also found a significant association between conjugal or job stress and MS relapses. These results were further corroborated by the finding of a significant increase in the risk of new gadolinium-enhanced MRI brain lesions after exposure to moderate (family and work stress), but not to major, stressful life-events [83]. Hence, it could be hypothesized that acute stress induces higher levels of endogenous cortisol than chronic stress, therefore having a major impact in reducing the risk of MS relapses, which fits the assumption of Martinelli [84] that “stress may have either an immune-

suppressive or an immune-increasing effect depending on its intensity and duration”. The physiopathology of the relation between chronic stress and relapse may be explained by the hypothesis of glucocorticoid resistance, in which there is a down-regulation of glucocorticoid receptors on the immune cells secondary to chronic stress, thus decreasing the capacity of the HPA to control inflammation [85]. In line with the fact that acute and chronic stressful life-events have different degrees of impact in the risk of relapses in RRMS, the results of a 2-year prospective study conducted in 101 MS patients to explore some stress-related parameters, including stress duration, are interesting [86]. Actually, in this recent study, Brown et al. [86] verified that chronic stressors related with life-events did not predict later relapses in contrast with acute stressors, further showing that the number rather than severity of acute stressors was most important to the relapse risk. These results are opposite to the abovementioned studies [80–82]. Moreover, the risk of relapse was higher in male patients and in patients in early phases of disease with low disability scores (EDSS) and, most important, a bi-directional stress-illness hypothesis was confirmed, that is, stressors predicted relapse, and relapse separately predicted stressors [86]. This study led the authors to advice that “MS patients should be encouraged to reduce acute stressors during times of high stress, and feel reassured that disease related chronic stressors do not increase their relapse risk” [86]. The importance of stress regulation in MS led an international panel of researchers to establish consensus statements that were recently published [87], hereby summarized: (1) so far, the evidence supporting the hypothesis of an association between stressful life-events and MS relapses is not conclusive and does not allow the establishment of firm causal relationships; (2) human experimental data suggest the existence of a weakened cytokine response to psychological and physical stressors; (3) HPA reactivity may vary by disease subgroup and stage: hyporeactive HPA axis may contribute to overshooting inflammation in early MS; with disease progression, the HPA axis hyperactivity may be linked to the neurodegenerative component of the disease; (4) Dysfunction of the autonomous nervous system might correlate with inflammatory activity and MS progression, given the evidence for a dampened response of the sympathetic system to inflammation and for a correlation between parasympathetic dysregulation and disease progression.

5. Other psychiatric disorders

Besides the previously described psychological conditions, various psychiatric illnesses can complicate the evolution of MS in many patients, contributing to morbidity and to enlarge the burden of the disease to both patients and relatives. As the spectrum of psychiatric illnesses is large, four groups will be focused: mood and affect disturbances, psychosis, hysteria and behavioural changes. Conversely, these situations may be iatrogenic in some patients as a

consequence of treatment with corticosteroids, which may induce anxiety, acute confusional states, depression, mania and psychosis [88].

5.1. *Mood and affect disorders*

The leading group of psychiatric abnormalities embodies the mood and affect disorders, whose symptoms in MS patients are alike those ones observed in the general population suffering from these disturbances [58,89]. Feinstein [58] divides the mood and affect disorders in four broad categories which include major depression (presented above in a specific heading), bipolar affective disorder, euphoria, and pseudo bulbar affect [90], which will be summarized hereby.

5.1.1. *Bipolar affective disorder*

Likewise major depression, bipolar affective disorder seems to be more prevalent in MS than in the general population, either in retrospective [18,91] or prospective studies [92]. Joffe et al. [18] evaluated 100 consecutive patients attending a MS Clinic and verified that 13% fulfilled criteria for manic-depressive illness and Schiffer et al. found increased rates of bipolar disorder with a lifetime risk twice that of the general population [91]. More recently, Edwards and Constantinescu [92] studied a cohort of 658 consecutive outpatients attending a MS Clinic and found significantly increased rates of bipolar disorder compared to the general population. On the other hand, there are studies suggesting that MS is more often diagnosed in patients with mania attending psychiatric hospitals than it could be suspected [93]. However, the literature about bipolar disorder in patients with MS is scarce and the relationship between both conditions seems complex.

5.1.2. *Euphoria*

Conversely to bipolar disorder euphoria is uncommon in MS, but is more frequent in severely disabled patients, where a median prevalence of 25% has been described [94], and is closely associated with cognitive impairment and with the presence of extensive brain lesions [95].

5.1.3. *Pathological laughing and crying*

Pathological laughing and crying, also named pseudo bulbar affect, is defined as sudden and involuntary episodes of laughing or crying, or both, without associated subjective feelings of depression or euphoria. This disorder has been reported in 10% of MS patients, mainly in those with severe disability, cognitive impairment and longer disease duration, is unrelated with MS relapses [96] and seems to be associated with dysfunction of the prefrontal cortex [97].

5.2. *Psychosis*

Psychosis is unusual in MS patients and may be related with a predominance of lesions in the temporal lobes

[30,58,98]. Brief episodes of psychosis similar to schizophrenia may occur as manifestation of MS [99], sometimes as the onset relapse followed by remission [100]. In a clinical and MRI study, Feinstein et al. [98] found that psychotic symptoms were usually transient, developed later than MS onset and appeared in later ages in MS patients than in non-MS individuals; moreover, psychotic patients usually presented larger lesions around the temporal horn of the lateral ventricles than non-psychotic MS patients.

5.3. *Hysteria*

Hysterical pictures have been observed in some MS patients, too. These symptoms are classically associated with the search of secondary gain consequent to some need and may be a major handicap in patients with minimal physical disability [101,102]. This is illustrated in the report of Caplan and Nadelson [102] of two definite MS patients who were incapacitated due to nonorganic symptoms.

5.4. *Behavioural disorders*

In the literature there are isolated case reports of behavioural changes associated to MS, usually in patients with extensive brain lesions, as confabulation, paranoid ideas, belligerence, pathological increased libido, Kluwer-Bucy syndrome, alcohol and substance abuse [101], that require specialized psychiatric management.

6. *Treatment*

The treatment of psychological disorders in MS, as a whole, must rely upon an organized and focused MS team that must be able to provide an integrated approach to each single patient. The communication of diagnosis, education about MS taking into account each particular patient and its family, capacity of listening, open discussion of medications, expectations, prognosis, re-assurance and explanation how the local MS team is organized are of utmost importance and correspond to the very first step in the medical management of MS. These tasks should be shared by all members of the MS team and not only left to neurologists or specialized psychologists. Patients must understand that the commitment with the care team is expected to be long lasting, so, the most open these relationships are the best for everybody.

Therapeutic strategies include psychotherapy, cognitive behavioural therapy, strengthen of coping, and drugs to overcome depression, anxiety, stress and fatigue. This means that the treatment of psychological changes of MS integrates the symptomatic therapy and comprises pharmacologic and non-pharmacologic techniques. At this point it is important to stress that MS patients must be confident that these disabling psychological disorders all are treatable conditions which is quite an important message of hope. In addition, physicians should be aware that treatment must be individualized and

should be able to manage different groups of drugs and deal with their side effects, which sometimes may worsen other sufficient disabling symptoms on its own.

The symptomatic therapy of MS is well described in the literature, for instance in the study of the *Multiple Sclerosis Therapy Consensus Group of the German Multiple Sclerosis Society* [103] and in the reviews of Kesselring and Beer [47], Ameis and Feinstein [104] and Thomas et al. [11].

The treatment of depression and mood changes in general is based on various psychological interventions (psychotherapy and cognitive behavioural techniques) and antidepressants [11,17,103–107]. In the Cochrane review about psychological interventions for MS, Thomas et al. [11] verified that psychotherapy may be of help in depression and that a sound evidence exists for cognitive behavioural approaches to be beneficial in the treatment of depression and in helping patient to adjust and cope with having MS; however, these results must be cautiously interpreted, since the authors emphasize that no definite conclusions can be made from this review. Antidepressant drugs include selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine or sertraline, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors, reversible inhibitors of monoamine oxidase type A, serotonin-norepinephrine reuptake inhibitors and others, but the most used belong to the first two groups [103–107]. As elsewhere reported [108], drug selection must be individualized, due to some side effects of the SSRIs (sexual dysfunction) and of the TCAs (confusion). Mirtazapine may be helpful in patients that already have sexual dysfunction because it does not interfere with sexual function, since it selectively targets the 5-HT₁ receptors; however it may cause weight gain and sedation [104]. Furthermore, in the study of the *Goldman Consensus Group*, cognitive behavioural therapy and antidepressants were found, on the grounds of empirical data, to be equally effective for MS depressed patients, and the use of combined modalities adapted to each individual case and to the peculiarities of the disease was recommended [108]. In summary, the existence of many therapeutic choices to manage depression in MS patients must be emphasized and special attention must be paid to its early diagnosis, so that appropriate treatment may be offered. Above and beyond improving the quality of life, patients are more prone to adhere to long-term self-injectable immunomodulatory drugs. Indeed, as regards interferon beta, depression is recognizably a relevant cause of poor adherence [109,110].

Anxiety and stress in MS patients are usually treated with psychotherapy, cognitive behavioural therapy and anxiolytic drugs, that is, with the same techniques used in the general population.

For self-injection anxiety, successful specific forms of cognitive behavioural therapy have been described, aiming to promote the patient self-efficacy and confidence to develop manual skills to inject medications [74,111].

Finally, the treatment of major neuropsychiatric disorders in MS patients must be established according to the guidelines

of psychiatric practice [104]. Thus, bipolar affective disorders in MS are usually treated with lithium or anticonvulsants [104,112], psychoses are treated with typical and atypical antipsychotics and pathological laughing and crying may be controlled with TCAs, SSRIs and dopaminergic agents [104].

7. Conclusion

Psychological and psychiatric disorders, especially depression, have a remarkable frequency in MS. However, their relationship with MS is complex and the extent to which they might be reactive to countless psychosocial factors, or symptoms resultant of the pathological process itself, remains unclear. In general, these disorders contribute to aggravate physical symptoms like fatigue, lead to disability, suffering and significant disruption of family, work, and social life, which represents a huge increase in the overall burden of the disease. This implies that health professionals must be aware that early diagnosis of this co-morbidity is essential to provide treatment as soon as possible and thus improve the patients' quality of life. In this sense, screening of depression and mood changes at baseline, and thereafter, should be considered an important issue in the medical management of all MS patients, bearing in mind that baseline anxiety, distress and depressive symptoms predict the presence of these disturbances at follow-up. On the other hand, the co-morbidity of anxiety with depression in MS patients appears to be associated with increased rates of suicidal ideation. Still, one has to be familiar with the "self-injection anxiety", a new form of anxiety that emerged in MS after the introduction of disease-modifying drugs. Clinically, depression and anxiety seem to be associated with disease activity but not with duration or severity; in its turn, depression may worsen already impaired cognitive capacity, mainly the executive functions of working memory. Regarding the hypothesis of an association between depression or anxiety with relapses, and between stressful life-events and either MS onset or acute relapses, the evidence is not conclusive so far and does not allow the establishment of firm causal relationships. Patients should be informed about these aspects, although the avoidance of situations generating distress and other emotional reactions should be recommended as a public health measure applied to anyone else. Besides, it is necessary to be aware and reassure patients that psychological and psychiatric disorders are treatable conditions, and that no definite evidence exists supporting the association between interferon beta and depression. Instead, the control of these symptoms seems to improve the adherence to long-term disease-modifying drugs. The management of these diseases in MS patients is based on standard psychiatric treatment guidelines used in any other individuals and its ultimate objective is to strengthen the patient's coping strategies. The most severe but less common psychiatric illnesses, like bipolar affective disorder, psychoses or behavioural changes, require the prompt intervention of a psychiatrist. Finally, the "art" of the MS

team to provide the best care to each single patient must be strongly emphasized.

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