Chapter 4
Anxiety and Multiple Sclerosis

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Abstract Normal worry and fear are largely adaptive, pervading anxiety is considered maladaptive and, in its various forms, it can characterize clinical disorders. Anxiety levels and anxiety disorders are more frequent in MS patients than in general population; nevertheless, they are overlooked and undertreated. The increase of anxiety in MS patients, more frequent in women than in men, seems related mainly to the diagnostic work-up period and prognostic uncertainties; the groundless fear of becoming rapidly wheelchair dependent plays some role. Exacerbations are also related to anxiety increase, while anxiety decreases as time elapses after the diagnosis and in the remitting phase. Anxiety levels have been studied in relationship with many other variables of interest in MS patients. The outcome of anxiety, the role of coping strategies, and other aspects are of support to the reactive nature of pathological anxiety. Few studies have investigated possible organic contributors, mainly with negative results. Several studies show how high levels of anxiety are associated with low health-related quality of life and decreased performance of some cognitive functions. Unfortunately, some of the available studies have important limitations (e.g., small samples, retrospective collection of data, exclusion of some subjects). In the matter of treatment, randomized controlled trials assessing pharmacologic and non-pharmacologic therapies for anxiety in MS showed inconsistent results. An important effort in covering the existing gaps, particularly about assessment and treatment of anxiety in MS patients, seems timely and relevant.

Keywords Anxiety • Anxiety disorders • Multiple sclerosis • Assessment • Clinical features • Treatment • Diagnosis • Pharmacologic therapy • Psychotherapy

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Definition of Anxiety

According to the definition given by the American Psychological Association, anxiety is "an emotion characterized by feelings of tension, worried thoughts, and physical changes like increased blood pressure" which emerges from an expectation of future threat or a motivational conflict [1]. It is an emotional state defined by aversive cognitive (thoughts of apprehensive expectations), physiological (hyperarousal and somatic activation), and behavioral (i.e., avoidance, paralysis) components [2]. Anxiety can be partially distinguished from fear, as the latter is the emotional response to immediate threat, although fear and anxiety are strictly related [3]. Moreover, fear and anxiety can be distinguished on the basis of duration, temporal focus, threat specificity, and motivated direction: while fear is immediate, focused on the present, and targeted to a specific threat in order to avoid it, anxiety has a longer duration without a specific threat. Following danger, fear and anxiety activate a sequence of adaptive behaviors aiming to reduce the unpleasant physiological response and to escape the environmental threat or resolve the underlying motivational conflict.

As the Roman philosopher Lucius Annaeus Seneca once wrote, "There is nothing so wretched or foolish as to anticipate misfortunes. What madness it is in your expecting evil before it arrives!" [4]. Normal anxiety and fear are largely adaptive, as they mobilize one's resources in order to cope with an environmental challenge. Nevertheless, pervading anxiety is considered maladaptive, and in its various forms it can characterize clinical disorders, in so far as it compromises the normal functioning and quality of life of the individual. Moreover, abnormal anxiety also occurs as a symptom in other psychiatric disorders, such as clinical depression.

Anxiety disorders appear to have a number of biological and environmental contributing factors [3]. For example, dysfunctional anxiety can be "learned" from the social environment (i.e., the family) in the presence of a biological predisposition [3], or it can be the result of negative life events such as accumulated trauma [5].

Anxiety Disorders According to the Diagnostic and Statistical Manual of Mental Disorders *Fifth Edition*

According to the *Diagnostic and Statistical Manual of Mental Disorders* fifth edition [6], anxiety disorders differ from normal fear or anxiety in as much as they are persistent (generally lasting 6 months or more) and characterized by overestimation of the danger represented by the situation that is feared or avoided.

Anxiety disorders can be distinguished on the basis of the underlying cognitive ideation and the eliciting contexts that induce anxious and fearful behaviors. The various forms of phobias and anxiety disorders in the DSM-V include separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder/panic attack, agoraphobia, generalized anxiety disorder (GAD), substance-/

medication-induced anxiety disorder, anxiety disorder due to another medical condition, and other specified anxiety disorders and unspecified anxiety disorders. Selective mutism (code 312.23) and separation anxiety (309.21) are typically considered developmental disorders and have been recently reclassified and moved into the broader category of the anxiety disorders.

Specific phobias (300.29) affect individuals who fear and avoid particular things or situations in a way clearly exaggerated in respect to the real risk posed by the situation, and the emotional reaction arises immediately and lastingly in response to the feared situation (i.e., animals, injections, a specific place, etc.). Social anxiety (300.23) is diagnosed when there is a persistent fear of being awkward, humiliated, or rejected. These cognitive ideations force individuals suffering from social anxiety to avoid social situations.

Panic disorder (300.01) is characterized by frequent panic attacks, which are abrupt episodes of intense fear and apprehension of variable duration (from minutes to hours) that can be expected or unexpected. Since individuals suffering from this disorder constantly fear panic attacks, they often change their habits in a dysfunctional way in order to avoid their insurgence.

Agoraphobia (300.22) is the fear of being in open spaces or uncontrollable social situations such as public transportations, malls, or crowds. Fear of these situations is accompanied and elicited by the cognitive ideation of being unable to escape or get help once the anxiety symptomatology has arisen.

Individuals suffering from generalized anxiety disorder (300.02) are excessively and chronically anxious about many things and situations (i.e., health, money, and family). The persistence of generalized anxiety results in anguish and several functional impairments due to the physical symptoms experienced by the individual, such as restlessness, irritability, lack of concentration, and muscle tension.

In the substance-/medication-induced anxiety disorder, the prominent anxiety symptoms are due to the effects of a psychoactive substance, while anxiety disorder due to another medical condition (293.84) is clinically significant anxiety that can be attributed to the secondary effects of the different medical condition.

Anxiety Disorders in Multiple Sclerosis

Although anxiety disorders are often diagnosed in patients with MS, they are often overlooked and have been investigated less deeply than other neuropsychiatric disorders, such as depression [7]. Nevertheless, the prevalence of anxiety disorders in MS is significantly higher if compared to the general population [7]. According to Korostil and Feinstein [7], lifetime rates of anxiety in MS are higher than in other chronic medical illnesses such as diabetes [8], chronic obstructive airway disease [9], and rheumatoid arthritis [10]. Nevertheless, these disorders are underdiagnosed and undertreated [7]. Therefore, a deeper understanding of anxiety disorders in this pathology is necessary.

Epidemiology

Although many studies assessed anxiety in MS, much of the literature on the subject is affected by several limitations, such as the absence of clinical interviews, which are necessary in order to formulate a clinical diagnosis. Indeed, although informative, the majority of the studies regarding emotional disturbances in MS uniquely relied on self-report instruments (such as the Hospital Anxiety and Depression Scale [HADS]) for the assessment of clinically significant anxiety (see Table 4.1), with few exceptions. One study conducted in Italy [11] recorded the presence of anxiety disorders in 36 % of a sample of 50 outpatients with definite MS using the Structured Clinical Interview for DSM-IV disorders (SCID-IV). Moreover, MS patients were more likely to meet diagnostic criteria for obsessive-compulsive disorder, a result replicated by another study conducted on Iranian patients with MS [12]. A large Canadian study conducted on 140 participants with a definite MS diagnosis using both the SCID-IV and the HADS reported a lifetime prevalence of anxiety disorders of 35.7 % [7]. In particular, the authors reported a lifetime prevalence of 7.8 % for social phobia, 8.6 % for obsessive-compulsive disorder, 10 % for panic disorder, 10.8 % for specific phobias, and 18.6 % for GAD. In this study, risk factors for developing an anxiety disorder included being female, comorbid depression, and lack of social support. The authors also reported that anxiety disorders were largely underdiagnosed in their sample, thus preventing the possibility of a necessary targeted treatment. Differences in the occurrence of specific anxiety disorders in MS patients between the study by Korostil and Feinstein and the other two studies could be attributed to the difference in sample size and sample selection. In another study conducted in Mexico on 37 consecutive MS patients and 37 healthy controls using the SCID-IV and the Hamilton Anxiety Rating Scale (HARS), 21.6 % of the people with MS had clinically relevant anxiety [13]. Notably, a Dutch study showed that 8 months after the diagnosis of MS, high self-reported anxiety was present in 34 % of patients [14], while after 2 years, 69 % still showed significant anxiety levels [15]. Similar results were reported in several other studies, which employed self-reported anxiety questionnaires (see Table 4.1). Moreover, a recent study by Poder and co-workers [16] conducted on a cohort of 251 patients found that 30.6 % had clinically significant social anxiety symptoms. A recent population-based study conducted in Canada detected the presence of anxiety disorders in 35.6 % of the MS population ($n=4,192$) using administrative data from sanitary records (i.e., ICD-9/10 codes). In summary, notwithstanding a shortage of robust epidemiologic studies regarding anxiety disorders, the current body of evidence shows that a large proportion of patients diagnosed with MS suffer from abnormal anxiety [17].

Table 4.1 Studies which assessed the presence of clinically significant anxiety in multiple sclerosis [7, 11, 13–28]

Study	Country	Population	Measures	% of patients with anxiety
Joffe et al. (1987) [18]	Canada	Clinic outpatients with MS ($n=100$)	SADS-L, RDC diagnosis	11 %
Minden et al. (1987) [19]	United Kingdom	50 MS patients	SADS	4 % prior to MS
				12 % since MS
				16 % lifetime (generalized anxiety)
Arias Bal et al. (1991) [20]	Spain	50 Patients with MS	CIS	12 %
Stenager et al. (1994) [21]	Denmark	94 MS outpatients	STAI	20.2 % high state score
				24.5 % high trait score
Diaz-Olavarrieta (1999) [13]	Mexico	MS outpatients ($n=44$), control subjects ($n=25$)	NPI, indirect evaluation	37 %
Smith and Young (2000) [22]	United Kingdom	88 patients with definite MS	HADS	34 %
Nicholl et al. (2001) [23]	United Kingdom	MS patients in contact with a rehabilitation consultant ($n=96$)	HAD anxiety	39 %
Mendes et al. (2003) [24]	Brazil	84 patients with relapsing-remitting MS	HADS (cutoff, 8)	34.5 %
Jannsens et al. (2003, 2006) [14, 15]	Netherlands	101 MS outpatients	HADS	34 % (8 months after diagnosis) of which 69 % had high anxiety after 2 years
Galeazzi et al. (2005) [11]	Italy	50 outpatients with definite MS diagnosis	SCID-I	36 %
Figved et al. (2005) [25]	Norway	Patients with MS (86), compared with 49 SLE controls	NPI	19.8 %
Korostil and Feinstein (2007) [7]	Canada	140 consecutive clinic attendees	SCID-I	35.7 %
Beiske et al. (2008) [26]	Norway	MS population-based study ($n=140$)	HSC-25	19.3 %

(continued)

Table 4.1 (continued)

Study	Country	Population	Measures	% of patients with anxiety
Dahl et al. (2009) [27]	Norway	172 MS patients	HADS	30.2 %
Poder et al. (2009) [16]	Canada	251 patients with MS	SPI	30.6 % (social anxiety)
Espinola-Nadurille et al. (2010) [28]	Mexico	37 outpatients with MS and 37 healthy controls	SCID-I	21.6 %
Marrie et al. (2013) [17]	Canada	MS population-based study ($n=4192$)	Case definition based on ICD-9/10 codes and physician-assigned diagnosis	35.6 %

SADS Schedule for Affective Disorders and Schizophrenia; *NPI* Neuropsychiatric Inventory; *SCID-I* Structural Clinical Interview for DSM Axis I Disorders; *CIS* Clinical Interview Scale; *HADS* Hospital Anxiety and Depression Scale; *ICD* International Classification of Diseases; *STAI* State-Trait Anxiety Inventory; *HSC* Hopkins Symptom Checklist; *SPI* Social Phobia Inventory

Clinical Presentation

Several aspects should be taken into account when considering the clinical features of anxiety in MS. In this regard, a common issue in the clinical assessment of psychiatric disorders such as anxiety and depression is the symptom overlap with somatic features of MS. Indeed, some of the somatic symptoms of anxiety such as unsteadiness, dizziness, fainting, and leg wobbliness can be often found among the somatic manifestations of MS. While this issue has been explored with regard to depression [29], the literature studying symptom overlap between anxiety and MS is scarce. Donnchadha et al. [30] indirectly explored this issue when validating the Beck Anxiety Inventory (BAI) in a group of patients with MS. With the use of hierarchical cluster analysis, they found three distinct symptom clusters in the BAI. Since all items of cluster one and some items of the second are also common somatic complaints in MS patients, they proposed to consider the development of a "trunk and branch" model for anxiety, a model originally conceptualized by Strober and Arnett for depression [29]: while "trunk" symptoms are shared between anxiety and MS, "branch" symptoms are specific for anxiety. However, as the authors point out, the evidence base for the development of a specific model for anxiety is insufficient. The symptom overlap between anxiety and MS has been also highlighted in a retrospective study by Brousseau et al. [31]. In their study, the authors sought to identify psychiatric diagnoses among 63 MS patients whose first clinical assessment suggested a primary psychiatric etiology for their symptoms. 92 % of patients in the Brousseau et al. study met diagnostic criteria for one or more psychiatric disorders including mood, somatoform, and anxiety disorders. In conclusion, clinicians

should be cautious in the identification of psychiatric conditions producing pseudo-neurological and nonspecific symptoms (such as anxiety), and they should pay special attention when assessing anxiety exclusively with screening measures, as this symptom overlap could inflate scale scores and require further assessment with a clinical interview.

The largest study that assessed the prevalence of specific anxiety disorders with a clinical interview found that GAD is the most common among MS patients [7]. GAD is characterized by uncontrollable worry accompanied by several physical symptoms such as headaches, nausea, muscle tension, and swallowing difficulty. The presence of generalized worry and health anxiety in MS patients has been underlined in several studies [32–34], and it is no surprise given the unpredictable nature of MS. As distinctly described by Bruce and Arnett [33], "Some MS patients must awaken each morning not knowing whether a restaurant will be wheelchair accessible, whether an exacerbation will prevent a vacation, or whether sudden onset visual disturbances will make a trip to the grocery store nearly impossible." Patients with MS have several reasons to be constantly worried and anxious about their health complications. In this connection, Janssens and colleagues [35] found an association between the perception of prognostic risk and anxiety in MS patients. Patients who thought that they would become dependent from a wheelchair within 2 years had high levels of anxiety and depression. Notably, in the same study, patients were inclined to overestimate their short-term risk of wheelchair dependence. Another study conducted by Jopson et al. [36] showed an association between illness identity and anxiety, explained by the authors with the fact that the tendency to attribute unpredictable symptoms (such as headache and sore throat) to MS could make patients anxious if they interpret that as a signal of disease progression. Excessive health anxiety results in greater medical care [37] and increased physical disability [38]. Kehler and Hadjistavropoulos [34] found that MS patients with elevated health anxiety are less likely to use problem-focused coping, preferring emotional preoccupation and social support as main coping strategies. They also showed how MS individuals with high levels of health anxiety experience greater disability and GAD. These results are in line with a study conducted by Feinstein et al. [39], which showed that comorbid anxiety and depression in MS patients result in increased somatic preoccupations and social dysfunction. The authors also found that suicidal thoughts in MS patients are the result of comorbid anxiety and depression and not depression alone.

As highlighted by these studies, the clinical manifestations of anxiety in MS patients could be interpreted as a reaction to the disease. While this view is sustained by a neuroimaging study that found no evidence of a cerebral correlate of anxiety in MS [40], it should be noted that two recent studies have found an association between inflammatory processes in the central nervous system and anxiety in animal models of MS [41, 42] and one MRI study found an association between gray matter atrophy in the superior and middle gyri of the right frontal lobe and anxiety scores [43]. Further investigations are needed in order to understand whether elevated anxiety in MS could be linked to specific features of the disease.

Relationships of Anxiety with Other Aspects of MS

As previously reported, a consistent percentage of MS patients show anxiety symptoms. However, it is undeniable that not all MS patients are affected by clinically relevant anxiety. This means that one or more factors can facilitate or protect a MS patient by developing an anxious state.

Many of the possible candidate factors have been examined, but a fundamental question remains unanswered about the direction of the causality between anxiety and these other aspects.

About the relationships between anxiety and other clinical aspects of MS, in some cases, the reasoning that has informed the research is that anxiety can influence another clinical feature of the disease; in other cases, a reversed direction has been hypothesized. We shall examine the details about these points case by case.

Anxiety and MS Phases, Course, Relapses, and Induced Disability

Anxiety and MS Diagnosis

A first aspect to be examined is the relationship between anxiety and the phases of the disease. Notwithstanding the possible interest of the topic, few studies have specifically addressed the issue. The diffusion of the intuitive belief that anxiety is given by a reaction to the disease and by its course over time is a possible explanation of this scarcity.

Already in 1994, it was found that the level of anxiety was influenced by the uncertainty of the diagnosis following the appearance of neurological disturbances resembling the picture of MS; after MS was confirmed or disconfirmed, anxiety more likely decreased even in the subjects which received a diagnosis of MS; subjects with no definite diagnosis tend to be more anxious [44, 45]. To be noted, the above reported studies were conducted when immune-modulating drugs were not available.

Di Legge et al. [46] reported that subjects with a clinically isolated syndrome that can be considered as the first manifestation of a possible MS showed trait anxiety scores higher than controls at the baseline evaluation; at follow-up performed on average 33 ± 6 months later, no more difference appeared. This result is at odd with what could be expected, as trait anxiety should be stable over time.

A recent (0–24 months) diagnosis of MS has a significant impact in terms of anxiety on both patients and their partners: 34 % of MS patients and 40 % of partners showed significantly higher levels of anxiety than those observed in healthy individuals from a population sample; patients (36 %) were more frequently distressed than partners. A higher EDSS (≥ 3) score corresponded to higher levels of anxiety in patients, but disability levels did not influence anxiety in partners [35].

Anxiety seems to decrease as the time since diagnosis elapses as demonstrated by a 1-month [47], 6-month [48], 24-month [49], and 30-month [50] follow-up. In the Bianchi et al. study, anxiety scores were related to "accepting responsibility" and "seeking social support" coping, and at 24-month follow-up a reduction in "seeking social support" coping and an increase in "planful problem solving" was detected. The changes in anxiety were strongly related to those in depression at follow-up.

An increase of anxiety is among the changes perceived by close relatives in MS patients in relationship with MS appearance [51]. In this study, the behavioral changes perceived in MS patients were similar to those found in subjects with other inflammatory diseases not involving the CNS: this does not support an MS-specific behavioral profile or the connection with the damage caused by MS pathology, even if behavioral changes were associated with dysexecutive and cognitive dysfunctions in MS patients.

Anxiety and MS Exacerbations

The influence of exacerbations on the mood state has been explored by Warren et al. [52], McCabe [53], and Burns et al. [54]. Warren et al. [52] found that the experience of exacerbation increases the level of emotional disturbance in comparison with the remission phase. In the McCabe [53] study, MS patients who experienced an exacerbation in 6 months before the start of the study had anxiety levels higher than both MS patients without exacerbation and control subjects; the anxiety level registered at baseline remained stable over the 18-month observation period.

Burns et al. [54] have prospectively examined the relations of anxiety and depression to exacerbations and pseudo-exacerbations: increase in anxiety symptoms relative to baseline has predictive value for subsequent pseudo-exacerbation, while increased somatic depressive symptoms predicted confirmed exacerbation.

Warren et al. [52] and McCabe [53] have obtained different results about the use of coping strategies by MS patients in relation to exacerbations, but the differences in timing relative to exacerbation (Warren et al.'s patients were having an exacerbation when tested, while McCabe's patients experienced the exacerbation in the previous 6 months) can explain the discrepant results [52].

The relationship between anxiety and first stages of MS or relapses can be examined from a reverse point of view, that is, the possibility that anxiety, as well as other emotional disturbances, could precipitate MS onset and increase the relapse occurrence risk.

Actually, MS patients report frequently that in the period of time preceding the onset of symptoms, later diagnosed as the debut of MS, or before relapses, important stressful events happened. Some MS patients report also the experience of unusual and incomprehensible feelings preceding relapse symptoms.

Systematic observations [55–59] have shown that stressful events are associated with an increase occurrence of exacerbation, independently from infections, and psychosocial factors (negative familiar and social events related to anxiety) are associated with MS onset. Trait and state anxiety per se were not correlated with the occurrence of relapses in the Brown et al. [57] study.

Anxiety and Disability

The association between anxiety and disability levels is an issue difficult to examine. So many variables (e.g., gender, education, time since diagnosis, disease course and exacerbation number, concomitant medications, measurement of both disability and anxiety) can play a role in the relationship between the measured or perceived disability and anxiety that a single study cannot consider all of them. The cross-sectional nature of many studies makes it difficult to derive firm conclusions.

Colombo et al. [60] were the first to investigate the relationship between anxiety (using the Symptom Rating Scale), disease severity, disease duration, and age and did not find any significant association.

The studies reporting data on the association between the objective measure of disability represented by the EDSS and anxiety can be summarized with the conclusions of the Tsivgoulis et al. [61] study that "disability status is an independent but moderate determinant of depression and anxiety in MS patients."

Anxiety does not seem to influence the perception of disability in MS patients [22].

A partial conclusion that could be derived by the data on the impact of discovering of being affected by MS or of experiencing a disease exacerbation is that anxiety levels increase in a substantial percentage of these patients and that this increase seems due to reactive psychological mechanisms. However, these studies suggest something that can be underlined for many of the studies we have considered: it is very difficult to establish the direction of the causality when exploring the relations between anxiety and other aspects, e.g., is the coping strategy influencing the increase of anxiety? Or is anxiety increasing the use of a certain coping strategy?

The cross-sectional nature of some of the above reported studies does not help to derive a firm conclusion; even an observation period of 18 months seems not sufficient to clarify the point, due to the apparent stability of anxiety levels.

We shall see that data derived by different approaches concur on the idea that anxiety increase is related to reactive psychological mechanisms.

Anxiety and Worry

Worries and concerns are two topics strongly connected with anxiety: following Bruce and Arnett [33], excessive, uncontrollable worry is the hallmark of GAD, and GAD has resulted in the most common anxiety-related disorders in MS patients [7].

The study performed by Bruce and Arnett [33] on the relationships between worry and anxiety in MS patients has confirmed that, notwithstanding the strong relation with anxiety, worry can be considered as a separable and unitary construct. The relevance of worry and concerns for MS patients and their peculiarities in these patients have prompted the development of an assessment scale suitable for testing MS patients [32].

Anxiety and Cognitive Functioning

The possible correlation of anxiety, as well as of other affective symptoms, with cognitive dysfunctions has attracted the interest of various researchers. Impairment of some cognitive function affects a high percentage of MS patients (see the specific chapter in this volume), and it is therefore relevant to identify all the possible determinants.

Following a study of Simioni et al. [62], anxiety typically found at an early stage of MS seems also related to the presence of cognitive impairment; however, after adjustment for QoL levels, the relation between cognitive deficits and mood state was no longer significant; this could mean that QoL summarizes the effects of other factors influencing the same QoL.

Stenager et al. [21] have reported that the only cognitive test showing significant correlation with both trait and state anxiety was the Trail Making Test.

Summers et al. [63] found that high anxiety levels were associated with poor performance in the working memory, information processing speed, attention, and memory scores in a sample of MS patients evaluated 7 years after a clinically isolated syndrome onset.

By means of regression analyses, Julian and Arnett [64] evidenced that state, but not trait, anxiety contributed, independently from depression, to the variance of an executive function index.

On the other hand, state anxiety seems a predictor of cognitive changes over a 1-year observation period together with other negative affects [65].

The relationships between anxiety/depression and the objective performances in cognitive tests of executive functions were confirmed even in a study by Bol et al. [66]; this study has also registered that anxiety (and depression) was a significant contributor to the levels of cognitive complaints by MS patients. Unfortunately, the authors have taken into account the cumulative score of the HADS and have not separated anxiety and depression scores.

The significant relationship between anxiety and perceived cognitive functioning has been confirmed by a subsequent research by Middleton et al. [67]. However, the authors did not evaluate the influence of anxiety on objective cognitive functioning.

On the contrary, in the Karadayi et al. [68] study, retrieval from long-term memory and psychomotor speed was not related to anxiety or depression, but to other clinical variables.

Goretti et al. [69] showed that state anxiety was related to a worse performance in the SDMT; the relation with the performances in the PASAT-3 and with the presence of cognitive impairment was almost significant.

Bruce et al. [70] reported that trait anxiety was associated with self-reported memory problems. This study suggests also that normative dissociation (i.e., the disruption of an individual's usually integrated cognitive processes, such as consciousness, memory, identity, or perception) partially mediated the relationship between emotional problems and perceived memory difficulties.

Other studies support the role of anxiety in the perception or self-evaluation of cognitive functioning in MS patients: anxiety, together with other variables, was a significant predictor of the scores in the patient report of the Multiple Sclerosis Neuropsychological Questionnaire [71]; the perception of cognitive slowing was related to trait anxiety, as well as to motor speed, impulsivity, and increased introversion, more than to real performances of processing speed [72]; in the van der Hiele et al. [73] study, MS patients underestimating their executive performances showed higher levels of anxiety, as well as of depression and psychosocial stress, and used a different coping style with respect to accurate estimators and overestimators; the underestimators' awareness of some objective cognitive impairment in processing speed and cognitive flexibility might lead to psychological distress and negative report bias.

Lastly, in the study of Lester et al. [74], the relationship between anxiety and self-reported cognitive impairment was evaluated by a reverse angle, that is, the possibility that the estimate of cognitive functioning level could influence anxiety levels. Perceived cognitive impairment accounted for a 17 % of the variance in anxiety, added to the 21 % accounted for by the MS physical impact subscale. MS physical impact and perceived cognitive impairment produce, in the authors' opinion, a sense of helplessness or a feeling of lack of control.

Anxiety and Other Psychiatric Disturbances

The relationship between anxiety and other psychiatric disturbances in MS patients is obviously of interest both from a clinical and a theoretical perspective, but even this topic has not received great attention by researchers.

First, we are going to examine the connection between anxiety and depression: this association is statistically significant in all the studies that have examined both matters. But, as far as it has been reported in the existing literature, not all MS patients showing clinically significant anxiety have been classified as depressed and vice versa [7, 39, 48, 75].

A longitudinal assessment of anxiety, together with depression and fatigue, over a 2-year period was performed by Brown et al. [76]. Even if also unhealthy behaviors and psychological factors predicted psychological distress and immunotherapy status predicted state anxiety, depression at baseline was the stronger predictor of anxiety and fatigue, and anxiety and fatigue at baseline were the stronger predictors of depression. In the authors' opinion, co-morbidity of anxiety, depression, and fatigue and the overlap of their symptoms are the most suitable explanation of their results. The anxiety-lowering effect exerted by being on immunotherapy can be interpreted as a reaction of feeling safe from the disease pathological process.

Gay et al. [75] applied statistics based on causal path analysis models looking for predictors of depression in MS patients; functional status (measured by EDSS), trait anxiety, alexithymia, and social support satisfaction were the predicting factors of depression. Trait anxiety and functional status were independent and simultaneous

predictors of depression; trait anxiety played a predominant role, and alexithymia and social support play as mediators for trait anxiety.

The influence of anxiety on self-harm, the degree of somatic complaints, and the functioning at social level have been examined by the above reported study of Feinstein et al. [39]: the association of depression and anxiety represents a more relevant risk than anxiety or depression alone.

Bruce and Lynch [77] have explored the relationship between personality traits and mood and anxiety disorders: anxious MS patients showed more neuroticism and were less extroverted, open, agreeable, and conscientious than both healthy controls and MS patients without an anxiety disorder. The authors suggest that MS patients with Axis I mood or anxiety disturbances are likely to experience concomitant personality changes and that suffering from MS does not mean experiencing a personality change.

No study has specifically explored the relationship between fundamental emotions and anxiety: indirect information can be derived by the lack of a significant correlation between both state and trait anxiety and the type of anger expression reported in a study devoted to anger phenomenology in a cohort of MS patients [78].

Relationship Between Anxiety and Health-Related Quality of Life

There is extensive evidence showing how anxiety is associated with low health-related quality of life (HRQoL) in MS. The first study to explore this relationship, conducted by Fruehwald et al. [79], found highly significant correlations between the majority of the scales of the Functional Status Questionnaire (FSQ) and anxiety levels measured with the Zung Anxiety Rating Scale. Benito-Leòn et al. [80] obtained very similar results using the Functional Assessment of Multiple Sclerosis (FAMS) and the Hamilton Rating Scale for Anxiety (HRSA). It has to be noted that these first studies only used bivariate correlations in order to assess the association between anxiety and HRQoL and did not control demographic data or other confounding variables such as depression or EDSS.

Spain and co-workers [81] studied the relationship between HRQoL and illness perception using multivariate models in order to predict the Short Form Health Survey (SF-36) scales. They found that anxiety was a significant predictor of all the SF-36 scores except the Physical Function Scale after controlling for age, disease duration, processing speed, fatigue, pain, and depression. Goretti and co-workers [69] obtained similar results. In their study, they tried to predict Multiple Sclerosis Quality of Life-54 (MSQoL-54) Mental and Physical Health domains accounting for anxiety (STAI-Y), mood (measured with the BDI), disability (EDSS), personality (Eysenck Personality Questionnaire, EPQ), coping (Coping Orientation for Problem Experiences, COPE), and fatigue (Fatigue Severity Scale) using multivariate regression analysis and found a significant association between lower anxiety and the mental health summary score of the MSQoL-54. Similarly, Dubayova and

colleagues [82] found an association between anxiety and lower scores in the mental health composite scores of the MsQoL-54 after controlling for demographical variables and disability measured with EDSS.

Interestingly, the relationship between quality of life and clinical variables in MS patients has also been explored using path analysis in two studies [83, 84]. Salehpoor et al. [83] report an indirect relationship between anxiety and fatigue, mediated by the physical components of quality of life. Using their model obtained through path analysis, they hypothesize that an increase of fatigue levels could be a consequence of the heightened stress and tension originated from physical impairments. Using structural equation modeling, Kikuchi et al. [84] found a twofold influence of anxiety and depression on FAMS thinking and fatigue scores if compared to the EDSS.

Lifestyle and Anxiety

The interest for lifestyle in MS patients has more and more increased in the last years as a consequence of the possible causal relationships between some habits and disease course or progression. Unfortunately, as for the actual topic, the interest of researchers up to now has been limited to the relationships of mood disorders with alcohol or drug abuse. The few published studies have obtained conflicting results, with Bombardier et al. [85], Quesnel and Feinstein [86], and Korostil and Feinstein [7] reporting an increased prevalence of anxiety and depression in excessive drinkers and Turner et al. [87] and Beier et al. [88] finding no significant association. The different results can be explained by differences in applied methodologies, e.g., use of clinical interviews vs. standardized scales.

In the Quesnel and Feinstein [86] study, high anxiety levels and a family history of mental illness represent warning signals for suspecting the drinking problem which appears to be also associated with suicidal ideation and abuse of other substances.

In the Korostil and Feinstein [7] study, the association disappears when a different level of statistical significance is applied.

Beier et al. [88] also reported that an increase in drug use was associated with lower self-reported anxiety, but with greater disability and depression.

Other Aspects Related to Anxiety in MS

Anxiety seems to be related to other relevant aspects of MS or MS patients' behavior, but as these relations emerge by sparse evidences, further confirmations should be welcomed.

Bruce et al. [89] have reported that in MS patients, problems adhering to disease-modifying schedules are connected to the presence of anxiety disorders.

Anxiety has been found to be related with fatigue, mainly with mental fatigue, but even in this case the literature shows scarce and conflicting results [66].

The relationship between anxiety and employment has been examined by Krokavcova et al. [90] and by Glanz et al. [91]. Krokavcova et al. reported that MS patients without anxiety had a 2.64 greater chance of being employed, while in the study by Glanz et al., exploring work productivity in a sample of MS patients, various parameters of work and daily activities have been taken into account; among these parameters, they have also examined presenteeism (impairment while working) that was the main cause of work productivity losses and was related to some other factors, anxiety included. Even overall work productivity and activity impairment (working plus not working subjects) were related to the same factors.

As already reported in a previous section, anxiety can be related to performances on neuropsychological tests. A particular aspect of mental activity, that is, social cognition, does not seem related to anxiety levels [92].

Trait anxiety is also associated with the disability level due to comorbid migraine in MS patients [93]. In MS female patients, chronic pain was significantly related to anxiety (and depression) [94].

Anxiety and Neuroimaging

Actually, only few studies explored the possible associations between neuroimaging data and anxiety levels: Zorzon et al. [40] have reported that MRI parameters (brain volume, regional and total lesion loads) did not correlate with anxiety, while some interesting data emerged about the relationship of depression and right frontal lesion load and right temporal volume; in this study, anxiety did not correlate with any other clinical parameter, and MS patients were not more anxious than patients with rheumatoid diseases. Considering the overall obtained results, the authors conclude that "anxiety is a reactive response to the psychosocial pressure put on the patients."

Diaz-Olavarrieta et al. [13] explored the prevalence of neuropsychiatric symptoms in a sample of MS patients and their relationship with MRI results, and once more, they could not find any significant association for anxiety, measured by the Neuropsychiatric Inventory.

Also Di Legge et al. [46] did not find any correlation between state and trait anxiety and any MRI parameters, regional lesion load included.

On the contrary, an association between some MRI data and anxiety levels has been found by a study of Fassbender et al. [95], aimed at studying the relationship between mood disorders and dysfunction of the hypothalamic-pituitary-adrenal axis in MS. The authors report that 8 out of 23 enrolled MS patients that showed active lesions had significantly higher levels of depression and anxiety. The relationship of anxiety levels with inflammatory phenomena was confirmed also by the correlation with higher cell counts in cerebrospinal fluid. Furthermore, the increase of cortisol production after corticotropin stimulation correlated with anxiety scales scores (the corticotropin effect was maintained elevated in MS patients even after the suppression of HPA axis by dexamethasone).

A more recent study [43] has applied the voxel-based morphometry in studying the relationship of cognitive and mood disorders with gray matter atrophy and has found that atrophy in the gray matter of superior and middle gyri of the right frontal lobe correlated with the scores in the Hamilton Anxiety Rating Scale.

Therapeutic Interventions

As underlined thus far, although anxiety represents a common psychiatric comorbidity in MS patients, researchers in the psychiatric field have overlooked it. Not surprisingly, the literature that explores the efficacy of pharmacologic and non-pharmacologic treatments for anxiety disorders is scarce and produced inconsistent results. In their comprehensive guideline, Minden et al. [96] reviewed several studies, which concerned the assessment and management of psychiatric disorders in MS patients. Despite pharmacologic and non-pharmacologic therapies are often used for the treatment of anxiety in MS, the authors found little evidence supporting their efficacy. Indeed, few specific studies assessed the efficacy of these treatments for anxiety disorders in MS.

Non-pharmacologic Treatments for Anxiety Disorders

The majority of the research regarding psychological therapies for anxiety in MS is based on manualized cognitive behavioral interventions, and the results supporting their efficacy are conflicting [96]. A randomized controlled trial (RCT) comparing the efficacy of a short-term protocol mixing cognitive behavioral therapy (CBT) and relaxation training with two sessions of supportive psychotherapy (namely, the "stress inoculation training" or SIT) found a reduction of the STAI scores after treatment for the SIT group [97]. Another RCT found that a treatment based on relaxation and imagery is more effective than no treatment in reducing high anxiety levels measured with the STAI [98]. However, in the same study, anxiety symptoms measured at baseline with the Profile of Mood Scales (POMS) were low, thus questioning the generalizability of the results. Another study assessing the efficacy of CBT-based group therapy on a group of 20 patients with MS showing elevated anxiety and depression found no significant difference in anxiety levels between the pre- and post treatment conditions [99]. More recently, a RCT comparing a CBT self-management program (MS Invigor8) with standard care found significant improvements in anxiety and depression in the treatment group [100].

Given the inconsistency in the literature, it has to be underlined that when evaluating non-pharmacologic and psychotherapeutic interventions for psychological disorders in MS, clinicians should be well aware that despite a growing body of evidence supporting the efficacy of "empirically supported treatments" for specific disorders, there is just as much evidence showing that the majority of the variance

in the outcome of a therapeutic intervention is explained by nonspecific factors [101, 102]. As already established by solid research, the most important predictor of the success of psychotherapy is the working alliance between the therapist and the patient [103, 104]. In other words, the quality of the relationship between a healthcare professional and the patient (e.g., the agreement of both on therapeutic tasks and goals) is crucial for the success of the intervention, regardless of the diagnosis. For this reason, clinicians cannot disregard that the singularity of the patient is far more important than the specificity of the treatment to the diagnosis. As stated by the conclusions and recommendations of the interdivisional task force on evidence-based therapy relationships of the American Psychological Association, "efforts to promulgate best practices or evidence-based practices (EBPs) without including the relationship are seriously incomplete and potentially misleading" [101]. Therefore, further qualitative and quantitative studies are needed in order to widen the range of therapeutic interventions (i.e., including interpersonal, psychodynamic, and humanistic interventions) together with special focus on effective ways in which clinicians could tailor their work on the specificity of the problems faced by patients with MS.

Pharmacologic Therapy

There is no trial having considered a pharmacologic therapy of anxiety in MS patients. The absence of such trials in the literature is confirmed by a very recent and already cited report [96]. Therefore, we cannot advance any suggestion based on controlled data. The experience of the single specialist remains valid, based on the efficacy of various drugs in anxious patients in the general population, with some important warnings: benzodiazepines that could be used for acute anxious symptoms can cause excessive somnolence, mental slowing, and diffuse muscle relaxation, which could be problematic for MS patients; drugs in the categories of selective serotonin reuptake inhibitors or selective norepinephrine reuptake inhibitors are suitable for long-term treatment of some chronic anxiety disorders: they are more manageable than older drugs, like tricyclic antidepressants, but they can nevertheless have important side effects (e.g., sexual dysfunctions, weight increase, sedation, feelings of fatigue). Even a more recently introduced drug, mirtazapine, which does not impair sexual function, causes sedation and weight gain. These drugs are frequently abandoned by MS patients under treatment for depression, and therefore, they could appear even less acceptable to patients for treating isolated anxiety disorders. Patients affected by GAD from the general population have taken advantage by treatments based on pregabalin, a calcium channel modulator, or quetiapine, an atypical neuroleptic, both drugs at medium-high doses; this second drug can be charged by relevant side effects. The only suggestion that can be advanced, hoping in some well-conducted drug trial, is a case-by-case evaluation of a pharmacologic therapy for an anxiety disorder and to rely on the practice with non-MS patients.

Conclusion

Anxiety levels and anxiety disorders are more frequent in MS patients than in general population; pathological increase of anxiety levels is reported in the literature as more frequent than depression, when the two disorders have been examined in the same MS patient sample. While normal anxiety and fear are largely adaptive, pervading anxiety is considered maladaptive, and in its various forms, it can characterize clinical disorders. However, anxiety in MS is overlooked and undertreated.

The increase of anxiety seems mainly related to the diagnostic work-up period (in this case also connected to diagnostic uncertainties), after the diagnosis has been advanced and after an exacerbation. Anxiety tends to decrease as time elapses after diagnosis and exacerbations; however, the "longitudinal" studies that have been conducted till now have covered a maximum of 30-month period and have regarded the RR phase of the disease. Information is not available about patients in the SP phase or with PP course. Anxiety seems to increase more frequently in women than in men. While stressors resulted to increase the risk of relapses and have been also connected to MS onset, anxiety per se does not seem to influence those risks.

Assessment of anxiety has been mainly performed by standardized self-reported scales, being the Hospital Anxiety and Depression Scale the most extensively used. Rarely, a clinical interview (e.g., SCID) suitable for diagnosing also the presence of a specific anxiety disorder has been used. A moderate interest has been as well devoted to the identification of trait or state anxiety.

When specific anxiety disorders have been searched for, GAD, panic disorder, and obsessive-compulsive disorder showed to be the most frequently present. To be noted, however, obsessive-compulsive disorder is no longer considered in the classification of anxiety disorders in the DSM-V and described in a dedicated chapter with other obsessive-compulsive-related disorders, as substantial evidence suggests that obsessive-compulsive spectrum disorders are distinct from anxiety disorders both in their behavioral and phenomenological appearance [105].

Anxiety levels have been studied in connection with many other variables of interest in MS patients. Apart from the abovementioned relation with disease fundamental clinical features, the most frequently studied relationships were those with cognitive functioning and health-related quality of life (HRQoL): about cognitive functioning, even taking into account conflicting results, anxiety seems to influence complex attention and executive functioning; by a reverse angle, perceived cognitive dysfunctions seem to increase anxiety. HRQoL is clearly related to anxiety levels or severity.

Apart from anxiety and depression that have been evaluated in almost every study aimed at exploring MS patients' psycho-emotional state, the relationship between anxiety and other psychiatric dysfunctions, personality traits, or emotion expression has been largely ignored.

The relative neglect for anxiety and its relationships has probably its motivation in the diffuse belief, among clinicians, that increase of anxiety has a purely reactive nature and that an anxious reaction is unavoidable, especially in some occurrences like diagnosis disclosure or relapses.

The available data seem to confirm this position, as the few studies devoted to search for a connection between the various aspects of brain damage (lesion load and/or atrophy, both global and/or regional) and anxiety parameters have achieved mainly negative results. Together with the clinical data, these results support the "reactive" interpretation of anxiety.

Therefore, anxiety could be explained by the ineffectiveness of "buffer" mechanisms or the exhaustion of energies in response to an intense distress caused by the perspective connected to a serious and unpredictable disease. Anxiety in MS patients appears to be related to the beliefs concerning the pathology, such as the prognostic risk and the likelihood of being wheelchair dependent.

The role of coping strategies in moderating or favoring anxious reactions and the relationship between normative dissociation (defined as the disruption of usually integrated cognitive processes) and anxiety are of support to the reactive nature of pathological anxiety.

After this brief summary of the most interesting results, it's time to spend some words on the weaknesses and limitations of the available studies.

The cross-sectional nature of some studies and the relatively short length of the longitudinal ones do not allow inferring the real meaning of the reported relationships. Furthermore, it is not easy to establish the direction of the relationship between anxiety and other aspects, from both the conceptual and observational point of view. The hypothesis that anxiety and the other aspects are both a consequence of a third factor is worth being explored in many cases.

Some of the available studies have important limitations (e.g., small samples, retrospective collection of data, lack of important data, exclusion of some subjects). One of the most important points, the "reactive" vs. "organic" nature of anxiety disorders, not considering the complexity and uncertainty of the theme in general, has never been explored through functional neuroimaging studies.

The second most disappointing aspect appears from a very recent statement made in the framework of the report on evidence-based guidelines for the assessment and management of psychiatric disorders in individuals with MS [96]: not a single instrument among those used in the published studies for evaluating anxiety has obtained even the lower level of recommendation. We would like to point out that, even if the instruments that have been taken into account in our treatise are not completely satisfactory, the obtained data have some reliability, as in most cases they have been validated in MS samples. Otherwise, all results and considerations reported in this chapter have scarce meaning.

The main disappointment arises from the awareness that anxiety disorders are under-identified and, consequently, undertreated: these aspects are in reciprocal relation with the lack or paucity of clinical trials on the treatment of anxiety, both pharmacologic and non-pharmacologic.

A possible list of recommendations for future research in this field can be found in the abovementioned report [96]. For clinical practice, waiting for further information by the research side, we credit MS specialists for their capacity to suggest anxiety treatments when needed, relying on the knowledge deriving from their experiences about the same disturbances in the general population, with all the

cautions requested by the peculiarities of MS patients. As a first step, we wish to recommend that a good-quality communication between healthcare providers and patients is crucial in order to prevent excessive anxiety.

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