

Review Paper:

# Depression and Anxiety in Patients With Multiple Sclerosis: A Systematic Review



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## ABSTRACT

**Background and Aim:** Multiple Sclerosis (MS) is among the most prevalent chronic and progressive neurological diseases with high simultaneity. MS is associated with some psychological conditions, such as depression and anxiety. Thus, we examined depression and anxiety in individuals with MS in this review study.

**Methods and Materials/Patients:** We conducted this study using a systematic review method relying on the search from January 2010 to December 2020. Accordingly, we searched the following keywords: "multiple sclerosis, MS, psychiatric issues, psychological disorders, psychological problems, anxiety, mental health, quality of life, and depression" in 4 online databases (PsycNET, PubMed, Scopus, and Magiran). Ultimately, we selected 14 comprehensive papers that quantitatively and qualitatively examined psychiatric disorders in patients with MS.

**Results:** A total of 14 studies were analyzed that included 27106 patients with MS. The results achieved by the analytical studies explained that depression and anxiety are significantly higher in patients with MS, compared with the healthy population. The prevalence of depression and anxiety in MS patients was reported to be heterogeneous.

**Conclusion:** Data related to a large number of patients with MS presented a high prevalence of depression and anxiety in them; however, not separating the symptoms from the disorder can be misleading. Consequently, it is recommended to conduct further research to precisely assess the prevalence of depression and anxiety in these patients. It is required that future studies consider the further use of clinical interviews instead of self-reported questionnaires, using sample selection methods, and providing a complete report of patients' demographic, and clinical information.

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## Highlights

- Patients with MS report a high prevalence of depression and anxiety.
- Different studies have presented conflicting information on the frequency of depressive and anxiety disorders.
- It is recommended to conduct further studies and eliminate heterogeneity barriers in precisely determining the frequency of depression and anxiety and implement therapeutic interventions.

## Plain Language Summary

Multiple Sclerosis (MS) is among the most prevalent chronic neurological diseases that might be related to psychiatric disorders. Anxiety disorders and depression can be considered the most prevalent conditions in these patients. However, there are no accurate statistics about them. This study examined the frequency of depression and anxiety in these patients using a systematic review method. A total of 14 studies were analyzed in which 27106 patients with MS were included. The relevant results explained that depression and anxiety are significantly higher in patients with MS, compared with the healthy population. It is recommended to conduct further studies to precisely determine the frequency of depressive and anxiety disorders in patients with MS.

### 1. Introduction

**M**ultiple Sclerosis (MS) is among the most prevalent neurological diseases. Moreover, this chronic disease involves multiple areas of the central nervous system as one of its main features. The disease is prevalent in 20- to 40-year-old individuals. It also continues for years by developing incapacitating symptoms; eventually, MS causes serious psychosocial health issues [1]. Patients with MS experience an all-inclusive range of movement limitations, pain, chronic fatigue, memory impairment, and concentration problems daily [2]. Consequently, MS influences all fields of a subject's life, including employment, relationships, leisure, and daily activities [3]. Accordingly, these limitations and disabilities might highly influence the experience of unpleasant emotions and the development of mood and anxiety disorders in them [4].

There is no remedy for MS and it is usually diagnosed early in life; thus, these patients live with these challenging symptoms for multiple years [5]. Patients with MS encounter higher levels of mental disorders, such as depression, stress, and anxiety, compared with the healthy population and those with other chronic conditions. These symptoms may directly result from the inflammation and demyelination of the nervous system [6]. The most valid study in a large sample using Magnetic Resonance Imaging (MRI) indicated that individuals with MS had "more hyperintense lesions in the left inferior medial frontal regions and greater atrophy of

the left anterior temporal regions". These two areas of the brain predict 42% of the variance in depression in individuals with MS [7]. The relationship between depressive symptoms and disease-modifying therapies, especially interferon- $\beta$ , remains contradictory [8]. However, a meta-analysis reported no significant relationship between depression and interferon- $\beta$  treatment in MS; a history of depression is an important risk factor for depressive syndrome in interferon- $\beta$  treatment [9]. Consequently, Major Depressive Disorder (MDD) has been reported in up to 50% of MS patients while it has been estimated to range from 10% to 15% in the general population [1, 10]. Studies have also revealed that patients with MS experience high levels of anxiety (about 36%-54%) and approximately 30% of patients with MS develop generalized anxiety disorder [11].

There is a complicated relationship between mental disorders and MS; its frequency can be a reaction to several factors. Moreover, physical symptoms such as fatigue, disability, the experience of family problems, work, and social life result in the recurrence of psychological symptoms; consequently, it leads to an increase in the pressure of chronic disease [12]. The relationship between depressed mood and the prevalent symptoms of MS was supported by several studies. Studies almost revealed a mutual relationship between depression and MS symptoms worldwide [13]. Some researchers have assigned the prevalence of depressive disorders in MS patients to the symptoms of chronic fatigue, cognitive disorders, and pain experience; it is assumed that perceived fatigue and disability, as well as pain,

can expedite depression [14]. It was determined that nearly half of MS patients experience cognitive disorders. The speed to process the information, attention and concentration, memory, and executive function is considered as the most significant cognitive disorders experienced by MS patients. The symptoms of cognitive disorders can cause extensive difficulties in individual and social functioning that might cause depression [15]. Furthermore, depression and anxiety in patients with MS cause different psychosocial risk factors including inadequate coping or poor social support or MS-related biological processes such as changes in brain structure or immunological and inflammatory pathways [16]. The most concerning issue in this field indicates a high risk of suicide in patients with MS and comorbid depressive symptoms. Evidence implies that the risk of suicide in depressed patients with MS is between 1.6 and 2.3 times higher than that in the general population. Additionally, approximately a quarter of patients with MS permanently contemplate suicide [17].

MDD is highly significant in patients with MS; however, anxiety has been less considered in this disease. Several studies have been conducted in this field and suggested that approximately 25%-41% of patients with MS are anxious. The clinical interview structure was applied only in two studies to evaluate the diagnosis of anxiety; consequently, both investigations reached the rate of 36% in patients. Generally, an anxiety score of up to 18.6% is normal in MS patients. Those patients who develop anxiety are frequently women with depression who contemplate suicide [18].

Examining the conducted studies revealed that the quality of life in depressed patients with MS is extremely lower than that in patients who are not depressed; even if nervous disabilities and fatigue are controlled. Depression unpleasantly affects MS patients. Depressed patients with MS experience the bewilderment of social and family support. Besides, there is even evidence that depression stops self-management behaviors in these patients [19]. Furthermore, depression and anxiety in patients with MS are associated with poor quality of life, cognitive dysfunction, increased risk of suicide, and occupational problems [18]. Depression and anxiety in MS appear to become more serious over time. It can be frequently treated at the beginning, i.e., significant to diagnose the disease early. Moreover, precisely examining and identifying psychological disorders, such as anxiety and depression in patients with MS play an effective role in developing treatment programs to reduce these disorders. Accordingly, this review study examined depression and anxiety in patients with MS.

## 2. Methods and Materials/Patients

This was a systematic review. We searched 4 online databases (PsycNET, PubMed, Scopus, and Magiran). Searches were performed applying the following keywords: “multiple sclerosis, MS, psychiatric issues, psychological disorders, psychological problems, anxiety, mental health, quality of life, and depression”. The search was performed in each database after conducting specific filters (publication date, title/abstract, and article type). For example, the search was conducted based on the Medical Subject Heading (MeSH) in the PubMed database. We first searched the keyword “multiple sclerosis” by applying restrictions (all time from 2010 to 2020 and title/abstract). There was no limitation in the research design of the studies and quantitative and qualitative studies were analyzed. We removed duplicates after identifying the studies and examined the results based on titles and abstracts. Full texts were examined for the qualified studies of retrieval and additional inclusion and exclusion criteria.

If these studies reported experiences or psychological consequences (anxiety & depression) observed in patients with MS, they could be the inclusion criteria. The exclusion criteria were as follows: studies which had evaluated psychological consequences in patients with other disorders (Not MS), non-original studies (systematic review, etc.), studies based on clinical intervention, studies written in languages other than English or Persian, studies which aimed at developing and validating scales, studies which had examined acute stress, studies which only had examined the linear relationships between the variables and studies which did not report the frequency of disorders. The two arbitrators evaluated the papers according to the inclusion criteria. The second arbitrator examined and approved the papers and the disputes were resolved through discussion. Figure 1 shows the search process. The critical appraisal was performed by two psychologists based on 3 indicators; evaluating the validity of selected articles, interpreting the results, and applying the results to clinical situations.

## 3. Results

Table 1 explains the results of analyzing 14 studies. A total of 27106 patients with MS participated in these studies. Văcăraș et al. [10] reported that depressive syndrome' prevalence equals 30.1%. Karimi et al. [12] measured the prevalence of moderate depression and anxiety as 47.1% and 39.1%, respectively. Stojanov et al. [20] explained that patients with MS achieved higher scores on anxiety and depression scales, compared

with healthy individuals. Saadat et al. [21], in a qualitative study using exploratory interviews, suggested that anxiety and depression are highly prevalent in patients with MS. Taail et al. [16] argued that 34% of patients with MS presented MDD symptoms. McKay et al. [22] reported a prevalence of mood disorders or depression as 35.8%, depression 37%, and anxiety as 22.1%. According to Rossi et al. [23], 33.5% of patients had state anxiety, 28.1% had trait anxiety, and 11.6% of patients encountered a severe depressive disorder. Nasir et al. [24] found that  $\geq 46.9\%$  of patients with MS reported at least one psychiatric disorder.

Based on Marrie et al. [25], 19.1% of patients with MS had depression, 11.1% had anxiety, and 3.15% had bipolar disorder. Alsaadi et al. [19] explained that 17.50% of patients with MS had MDD and 20% had anxiety disorders. Dehghan et al. [26] found that 19.2% of patients had severe anxiety and 29.2% had severe depression. Sarisoy et al. [27] reported that depressive and anxiety disorders were significantly more prevalent in patients with MS, compared with healthy individuals. Bruce et al. [28] revealed that anxiety was significantly higher in patients with MS, compared with healthy individuals. Goretti et al. [29] stated that mood disorders are more

prevalent in adolescents suffering from MS compared with the general population.

#### 4. Discussion

The data of the current review revealed that anxiety and depression are more prevalent in patients with MS, compared with healthy subjects. Perhaps, the comorbid depression and anxiety in these patients is a natural reaction to the unpredictable course of an incapacitating and chronic disease. Depression and anxiety can also negatively affect health status, treatment adherence, or provide direct pathophysiological effects on immunity by increasing the severity of symptoms [30].

Moreover, the risk of depression in MS varies from 11% to 35% [16-25]. These differences can be caused by multiple methodological issues such as differences in used definitions, measurement instruments, diagnostic criteria, sample size, and nature of the studied population [31]. Most studies measured and reported depression and anxiety using self-report questionnaires; consequently, using different tools can be among the reasons for heterogeneity in various statistics that have different cutting points [32]. Furthermore, it is impossible to apply these scales to formally diagnose psychiatric disorders; they tend to overestimate the prevalence, compared with diagnostic interviews [31]. The symptoms of depression and anxiety in MS have been frequently assessed in small samples of MS in the related treatment centers, which fail to represent all MS patients [17-19]. Increasing the risk of developing anxiety in MS varies from 11% to 33% [16-25]. Numerous studies revealed a significant relationship between high levels of anxiety and depression in patients with MS. One study explained that depression was identified as the most significant factor related to anxiety [33]. A prospective study conducted in two years revealed that depression is the most significant predictor of anxiety in these patients [34]. Women included the majority of participants in many studies. Gender imbalance plays a significant role in the frequency and prevalence of anxiety; in general, women are more anxious compared with men [35].

Comorbid anxiety and depression can present unpleasant consequences on disease claims and quality of life among MS patients [33]. Treatment interventions to simultaneously decrease depression and anxiety in the research background were ignored for MS patients; however, transcendental interventions which apply fundamental principles concerning mental disorders were beneficial for individuals with comorbid anxiety and

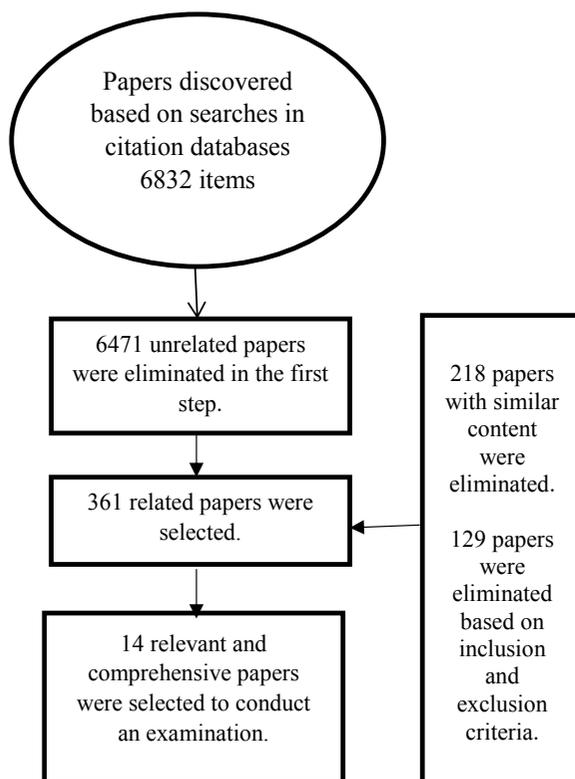


Figure 1. Steps to select the study papers



**Table 1.** The characteristics of the included articles

Authors & Publication, Year	Country	Study Design	MS Type	Sample Size	Age (M)	Sex (Female%)	Assessment Tool/s	Observed Consequences
Văcăraș et al., 2020 [10]	Romania	Cross-sectional study	RRMS SPMS CIS	146	40.8	71.92	BDI-II	depression symptoms (30.1%)
Karimi et al., 2020 [12]	Iran	Cross-sectional study	Not available	87	35.5	70.1	DASS-21	41 (47.1%) had moderate depression and 34 (39.1%) had moderate anxiety.
Stojanov et al., 2020 [20]	Serbia	Cross-sectional study	RRMS	95	43.4	67.6	HAM-A HAM-D	Anxiety was higher in MS patients than HC. Depression was higher in MS patients than HC.
Saadat et al., 2020 [21]	Iran	Qualitative study	RRMS PPMS	24	34.5	83.3	Exploratory interview	Depression and anxiety disorders were the most frequent in MS patients, respectively.
Tauil et al., 2018 [16]	Brazil	Cross-sectional study	RRMS	132	35	78	BDI-II	34% of MS patients had depression disorder.
McKay et al., 2018 [22]	Canada	Retrospective cohort study	RRMS PPMS	2312	36.9	75.7	Clinical criteria	Mood or anxiety disorder (35.8%), Depression (37.0%), and Anxiety (22.1%)
Rossi et al., 2017 [23]	Italy	Cross-sectional study	RRMS	405	Not available	Not available	BDI-II STAI-Y	Clinically, state anxiety was 33.5% and the prevalence of trait anxiety was 28.1%. The BDI-II score indicated clinical depression in 11.6 of the patients.
Nasir et al., 2016 [24]	Iran	Cross-sectional study	Not available	113	35.46	70.8	SCID-I	37.2% had depression disorder and 11.5% had some kind of anxiety disorder. Overall, 46.9% of the subjects had at least one psychiatric disorder.
Marrie et al., 2016 [25]	Canada	Retrospective cohort study (Final results)	RRMS PPMS SPMS	23382	44	71.9	Population-based administrative data	19.1% of MS patients had depression and 11.1% had anxiety.
Alsaadi et al., 2015 [19]	United Arab Emirates	Cross-sectional study	Not available	80	35	65	PHQ-9 GAD-7	17.50% had major depression and 20% had anxiety disorders.
Dehghan et al., 2013 [26]	Iran	Cross-sectional study	Not available	110	Not available	68.2	DASS-21	46.4% had severe stress, 19.2% had severe anxiety and 29.2% had severe depression.
Sarisoy et al., 2013 [27]	Turkey	Cross-sectional study	RRMS PPMS SPMS	76	37.84	73.7	SCL-90-R BDI-II	Symptoms of depression and anxiety were higher in MS patients than in healthy people.
Bruce et al., 2011 [28]	USA	Cross-sectional study	RRMS PPMS SPMS	85	47.12	87.05	Structured psychiatric interview	Anxiety was significantly higher in MS patients than in healthy people.
Goretti et al., 2010 [29]	Italy	Cohort study (Final results)	RRMS PPMS	56	17.2	50.0	Clinical criteria	Twelve out of 39 patients who underwent clinical interviews received an official diagnosis of a mood disorder.

MS: Multiple Sclerosis; M: Mean; RRMS: Relapsing-Remitting Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis; CIS: Clinically Isolated Syndrome; BDI-II: Beck Depression Inventory-II; EMAS-S: Endler Multidimensional Anxiety Scales-State; DASS-21: Depression, Anxiety and Stress Scale-21; HAM-A: Hamilton scales for the assessment of anxiety; HAM-D: Hamilton scales for the assessment of depression; PPMS: Primary Progressive Multiple Sclerosis; STAI-Y: State/Trait Anxiety Inventory; SCID-I: Structured Clinical Interview for DSM-IV Axis I Disorders; PHQ-9: Patient Health Questionnaire nine-item; GAD-7: Generalized Anxiety Disorder-7; SCL-90-R: Symptom Checklist-90-R.

depression [36]. These interventions apply the fundamental principles and techniques regarding cognitive behavioral therapy, like exposure and cognitive restructuring. They target the common processes of anxiety and depression. Besides, a systematic review on these interventions for depression and anxiety disorders in adults indicated a considerable reduction in anxiety and depression and enhanced average quality of life [37]. Selective Serotonin Reuptake Inhibitors (SSRIs) are also regarded as the initial treatment line for depression and anxiety disorders [38]. Moreover, combining benzodiazepines with SSRI can result in faster control of anxiety and enhance the control of episodic or situational anxiety [39]. Tricyclic Antidepressants (TCAs) such as amitriptyline were also highly effective on relieving depressive symptoms [40], though there is no credible evidence of clinical trials in MS patients. Urinary incontinence is one of the most common problems in these patients; thus, using TCAs for improving urinary incontinence and mood syndrome was suggested [41]. There exists little evidence considering the drug treatment of depression and anxiety specifically for MS patients. In general, clinical trials are required for drug treatment in MS to make strong evidence of their efficacy for depression and anxiety.

One of the causes for the heterogeneity of statistics about the frequency of anxiety and depression in MS patients addresses various definitions of anxiety and depression. Accordingly, in some research, anxiety, and depression were assessed as a disorder based on accurate clinical criteria and in others as a trait of the patients. Thus, it is required to assess anxiety as a disorder applying clinical interviews in future studies. In surveying the frequency of depression and anxiety, the clinical and demographic status of these patients must be regarded. Therefore, some research indicated that anxiety is higher in patients with recurrent MS. There is also a relationship between early age and depression and anxiety. Therefore, age can be a confounding variable in reporting the frequency of depression and anxiety. Furthermore, employment status influenced the severity of anxiety and depression in these patients [42].

A research discovered that depression, regardless of other factors, is associated with fatigue and aging [43]. Generally, the prevalence of anxiety and depression in MS patients is very high; the relationship between economic and clinical status and psychological symptoms of depression and anxiety is significant [12]. Based on findings of another study, the prevalence of depression was high during relapse and gradually decreased after relapse [44]. Based on these data, in reporting the fre-

quency of psychological disorders in MS patients, the role of demographic and clinical factors of these patients must be considered. These factors can be among the reasons for heterogeneous statistics on the frequency of psychological disorders in these patients.

## 5. Conclusion

Generally, anxiety and depression, whether as traits and symptoms or disorders, are more prevalent in MS patients, compared with the general population. Further research is required on the prevalence of depression and anxiety in MS patients to provide more accurate information considering the mentioned limitations. For the sake of practical use, it is proposed that MS patients be constantly assessed by psychiatric specialists via the course of the disease to inhibit the recurrence of symptoms with early diagnosis. The effects of disease-modifying therapies, like interferon- $\beta$  on depression in MS patients remains unclear. However, medication should be used more carefully in MS patients with depressive symptoms. It is recommended that pharmacological and psychotherapeutic interventions be applied to improve the psychological conditions of MS patients based on their clinical symptoms.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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### Authors' contributions

All authors contributed equally in performing the project and preparing the manuscript.

### Conflict of interest

The authors declared no conflicts of interest.

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