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Review

Suicide risk in multiple sclerosis: A systematic review of current literature

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ABSTRACT

Background: Studies have shown that suicidal ideation is often revealed among patients suffering from Multiple Sclerosis (MS). Mental health assessment of physically ill patients should form part of routine clinical evaluation, particularly in chronic illness.

Objective: The aim of the present paper was to investigate whether there was a relationship between MS and suicidal behavior.

Methods: A systematic review of the literature was conducted to determine the potential association between MS and suicidal behavior. A total of 12 articles from peer-reviewed journals were considered and selected for this review.

Results: Most studies have documented a higher suicide rate in patients with MS compared to the general population, and suicide was associated with several risk factors: Depression severity, social isolation, younger age, progressive disease subtype, lower income, earlier disease course, higher levels of physical disability, and not driving.

Conclusions: Clinicians should be aware of the fact that suicidality may occur with higher frequency in MS patients, the available data suggest that the risk of self-harm is higher than expected in MS patients.

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Introduction: rationale and objectives

Multiple sclerosis (MS) is a chronic demyelinating central nervous system disease with time and space disseminated lesions that usually have a relapsing remitting course and affect the periventricular region, optical nerves, and spinal cord [1]. It affects around 2.5 million people worldwide and it is one of the most frequent neurological illnesses and cause of disability among young adults, especially in Europe and North America [2]. MS is a widespread autoimmune disorder that is associated with a series of symptoms that include sensory and motor loss, fatigue, blindness, difficulties with balance, pain, cognitive impairment, and depression [3–7]. The most common clinical signs and symptoms at presentation include sensory disturbance of the limbs (~30%), partial or complete visual loss (~16%), acute and subacute motor dysfunction of the limbs (~13%), diplopia (7%), and gait dysfunction (5%) [8]. These signs and symptoms may occur in isolation or in combination, and have to be present for a minimum of 24 h to be considered a “clinical attack.”

Further, psychiatric symptoms are frequent in MS patients. Patients often present with mood disorders, anxiety, cognitive deficits, delirium, and psychosis [9]. These symptoms could reflect the direct or indirect effect of the autoimmune disorder on the central nervous system, may be connected to medications used in the treatment, or may be a direct psychological impact from suffering with the disease [9]. Other autoimmune diseases that frequently co-occur with psychiatric symptoms are Systemic lupus erythematosus, Sjögren's syndrome, Addison's disease, Temporal arteritis, Sarcoidosis, Scleroderma, Polyarteritis nodosa, Hashimoto's thyroiditis, Myasthenia gravis [9].

Physical illness and mental disorders often co-occur [10,11]. Data from primary care and general medical settings have consistently documented high rates of suicide ideation among medical patients [12,13]. In fact suicidal ideation, considered to be a core symptom of major depression [14], is also observed among patients suffering from physical illnesses [15]. It has even been stated that suicidal thoughts, occurring in somatic patients, may arise from comorbid depression [16]. Iwasaki et al. [17] reported that depression, which is common in MS patients, contributes to cognitive dysfunction. High rates of anxiety, depression, and substance use disorders have been documented as risk factors for suicidal ideation in medical patient populations. The aim of the present paper was to investigate the relationship between Multiple sclerosis (MS) and suicidal behavior, and to determine whether or not people affected by MS are at an increased risk of suicide, attempted suicide, and/or suicidal ideation.

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Methods

In order to provide a new and timely systematic review, according to “The PRISMA statement for reporting systematic reviews” [18], about MS and suicidal behavior (suicide, suicide attempt or ideation), we performed a careful MedLine, Excerpta Medica, PsycLit and PsycInfo and Index Medicus search to identify all papers and book chapters in English for the period 1970 to 2011. The following search terms were used: (suicide OR suicide attempt OR ideation) AND (multiple sclerosis). Textbooks on psychiatry were also consulted. The selection of papers suitable for this review allowed for the inclusion of only those articles published in English peer-reviewed journals, including studies that added an original contribution to the literature. Where a title or abstract seemed to describe a study eligible for inclusion, the full article was obtained and examined to assess relevance based on the inclusion criteria. Any discrepancies between the two reviewers who, blind to each other, examined the studies for the possible inclusion were resolved by consultations with senior authors. In addition, we also examined reference lists and contacted experts in the field.

The principal reviewer (MP) inspected all reports. Then, three reviewers (AL, MP, GS) independently inspected all citations of studies identified by the search and grouped them according to topic of the papers. Reviewers acquired the full article for all papers located. Where disagreement occurred, this was resolved by discussion with GS who also with double-blind features inspected all articles located and grouped them following the major areas of interest identified by all authors. If doubt remained, the study was put on the list of those awaiting assessment, pending acquisition of more information. We excluded from our analysis any studies vaguely reporting on the subject. Results of this search are presented in the paragraphs regarding suicide in multiple sclerosis. By reviewing selected articles we identified some specific fields of interest. We also consulted a number of international experts in the field to determine whether studies selected were relevant for discussing the subject matter. The authors and experts that were consulted performed a careful analysis of the literature data and agreed on a number of key subjects relevant to the aim of this paper. We will therefore offer an overview of studies dealing with MS and suicide risk.

Results

Search strategy

The combined search strategies yielded a total of 126 records screened, of which the most relevant articles were selected for this review. After a complete analysis of the abstracts, 30 full-text articles were reviewed and 18 were excluded. Abstracts that did not explicitly mention suicide and MS were excluded. We excluded 9 studies that included data related to suicide but were not clear about follow-up times, 5 studies were excluded because the method of statistical analysis was not specified, 4 studies because diagnostic criteria or the number of patients studied were not clear. Finally, 12 studies met our inclusion criteria and were included in the present review (Fig. 1).

Study design and quality assessment

A quality assessment was performed as shown in Table 1. Studies were rated for the quality assessment using the following criteria: I) representativeness of the sample than the general population (1 point) II) presence of a control group (1 or 2 points) III) $n > 1000$ subjects /treatment group (1 or 2 points); IV) duration > 1 year/follow up group (1 or 2 points). V) evidence based measures of assessment (1 or 2 points) VI) Data Presentation (1 or 2 points) VII) evidence-based measures assessing suicide or suicide attempts (1 or 2 points). Quality ratings reported 13 as maximum score for each study.

The 12 included studies have comprised four cohort studies, five retrospective studies and two observational studies. Most of the studies are characterized by good data presentation and evidenced based measures for the assessment of MS. Retrospective studies and cohort studies included are characterized by large sample sizes and representativeness of the sample than the general population; 8 studies have a sample size of more than 1000 subjects. On the other hand quality of studies was often compromised by the absence of evidence-based measures assessing suicide or suicide attempts. One of the retrospective studies is compromised by unrepresentative sample size. The two observational studies

are characterized by good data presentation and evidence based measures assessing suicide or suicide attempts, however, a small sample sizes limited the quality of these studies.

Study outcomes

Several studies have reported an increased suicide risk in patients with MS. Kahana [19] found that 3% of 295 patients with MS died by suicide over a 6-year period, which is 14 times the suicide rate in the general population. A subsequent epidemiological study of more than 5000 patients with MS found almost twice the number of suicides as would be expected (53 vs. 29) [20]. The cumulative lifetime risk of suicide from the time of onset of MS was nearly 2%, while the Standard Mortality Ratio (SMR) was 1.83. Male patients with onset of MS < 30 years were at the highest relative risk of suicide (SMR = 2.73). Further, it was found that the lowest relative risk of suicide was in females with an onset age < 30 years (SMR = 1.28, *ns*) and males > 30 years (SMR = 1.66, $p = .05$). The SMR for suicide was found to be the highest in males and females < 40 . These authors concluded that the suicide risk was highest among patients under 30, males, and within the first 5 years of a MS diagnosis.

In a 16 year longitudinal study of 3126 patients in Canada, it was reported that the proportion of deaths by suicide was 7.5 times higher than that of the general population and 15.1% of all patients deaths were attributed to suicide [21]. Bronnum, Stenager, and Koch-Henriksen [22] demonstrated that among 10,174 Danish citizens with MS, the suicide risk was more than twice that of the general population. Specifically, the researchers found that the expected number of suicides in a matched general population was 54.2 (29.1 males, 25.1 females), while 115 MS patients died by suicide (63 males, 52 females). They also demonstrated that the increased risk was particularly high during the first year following diagnosis, although it remained elevated for many years after diagnosis. The excess suicide rate during the first 15 years following diagnosis was relatively stable for men (SMR varying between 2.18 and 2.76). The SMR for age < 30 was 2.55, whereas for age > 40 , it was found to be 1.52. Moreover, the suicide risk among Danes in general was found to be higher for men than for women, and this was also true for Danes with MS. Furthermore, the researchers reported that men with MS were more likely to report previous suicidal behavior, previous mental disorders, depression, recent deterioration of health resulting from MS, and moderate disability, whereas, the characteristics of women with MS were less apparent. Finally, they identified several predictors of suicidal ideation including social isolation, major depression, and alcohol abuse, and they assessed for the possibility that brain lesions caused by MS may contribute to personality alterations leading to suicide. On the contrary, a previous large scale study [23] of MS patients found no relationship between global physical disability and suicidal ideation.

Koch-Henriksen et al. [24] also confirmed that patients with multiple sclerosis are at increased risk. In a sample taken from the nationwide Danish Multiple Sclerosis Registry and the National Registry of Causes of Death, they compared causes of death in patients with multiple sclerosis with the background population, and they analyzed Standardised mortality ratios (SMRs). Completed suicides were more frequent in patients with multiple sclerosis, and the SMR was higher than for cardiac and vascular diseases. They reported that the SMR from suicide was 1.62.

In a large study of Swedish hospital patients ($N > 12,000$) with a diagnosis of MS [25], the researchers found an elevated suicide risk of 2.3 times the expected rate. Among the 5,052 deaths, the authors found 90 cases of suicide (1.8%). The suicide rate was higher ($p < .001$) in males (114) than in females (47), with an odds ratio of 2.4 (95% CI: 1.6–3.8). The mean period between the initial admission date with a MS diagnosis at discharge and the date of suicide was 5.8 years, which was significantly shorter ($p = .002$) than the mean of 7.9 years for MS cases who died due to other causes. Furthermore, the highest suicide risk was found in the first year following discharge and 58% of the suicides occurred within 5 years after the first admission.

Brønnum-Hansen et al. [26] analyzed trends in survival and causes of death in a sample of MS patients and compared these patients with the general population. In a sample of 4053 subjects affected by MS, 183 (4.5%) died from accident and suicide. They concluded that since 1950 there was an improved survival in MS patients but the risk for death due to accidents or suicide remained stable during the 10 year observation period. They found that this improved survival was due to lower death rates from all diseases, with the exception of cancer and cardiovascular diseases for females, and from accidents and suicide for both males and females.

Lalmohamed et al. [27] recently conducted a population-based cohort study on the General Practice Research Database, and national death certificates. The sample consisted of 1270 MS patients and a control group of subjects without MS matched by age, gender, and practice. In order to estimate mortality rate ratios (Hrs), the authors used Cox proportional hazards models. They found that the most common cause of death was infectious or respiratory diseases (58.0%) in the MS patients group. This study failed to show any significant differences in HR between the MS group when compared to the general population regarding fatal accident and suicide.

Fisk et al. [28] examined the prevalence of bipolar disorder, depression, and attempted suicide among patients who utilized hospital-based psychiatric services in Nova Scotia and compared these characteristics between individuals with MS and a non-MS population. The results indicated that 1.97% of hospitalized MS patients were diagnosed with bipolar disorder and 4.27% were clinically depressed. These prevalence rates were significantly higher than those reported for the patients without MS. Moreover, the estimated frequency of suicide attempts in the total MS population was more than three times that of the general population.

Moreover, Turner et al. [29] demonstrated that suicidal ideation is common among patients diagnosed with MS and is associated with several suicide risk factors. Depression

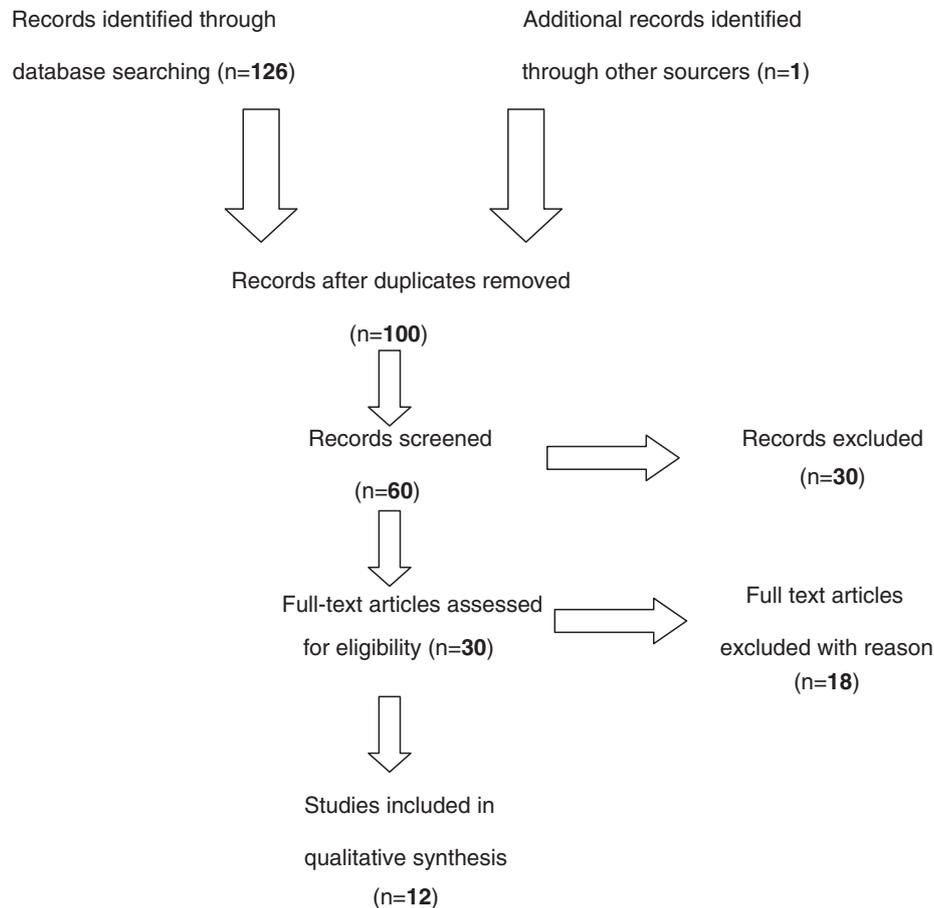


Fig. 1.

severity is one of the most well-established risk markers for suicide, but suicidal ideation is also associated with social isolation, younger age, progressive disease subtype, lower income, earlier disease course, higher levels of physical disability, and not driving. Among 445 respondents, 131 (29.4%; 95% CI: 25.4%–33.9%) reported suicidal ideation and 35 (7.9%; 95% CI: 5.7%–10.8%) showed persistent suicidal ideation during the previous 2 weeks. Suicidal ideation was significantly more likely among people who had: low income (OR = 2.27; 95% CI: 1.48–3.48), progressive disease (OR = 1.67; 95% CI: 1.08–2.57); more physical disability in the domains of mobility (OR = 1.14; 95% CI: 1.02–1.28), bowel function (OR = 1.46; 95% CI: 1.26–1.71), and bladder function (OR = 1.35; 95% CI: 1.18–1.54).

Another [30] study based on a small sample was unable to demonstrate an increased risk of suicide attempts in MS patients as compared to the general population in the county of Funen in Denmark. Among 404 MS patients, 15 suicide attempts were recorded and no statistical difference was found between observed and expected numbers of suicide attempts. They also examined the relation between interferon-beta (INF-beta) therapy and depression in MS patients. The researchers did not find a difference in number of suicide attempts between patients treated with INF-beta and untreated patients; however, these findings are contradictory as to what would be expected and conclusions cannot be made regarding the effectiveness of INF-beta therapy in MS patients until new studies emerge, and these findings are either replicated or refuted. In a sample of 11 subjects, Frangoso et al. [31] documented an association between INF-beta and severe depression among MS patients without a previous psychiatric history in addition to the widely accepted finding of a relation between INF-beta and severe depression in those patients who were previously depressed. They observed phobic, aggressive, behavioral, psychotic, and manic symptoms in these severely depressed patients, underlying the possible existence of a particular mood-behavior disorder associated with INF-beta treatment. Although uncommon, severe depression with suicide ideation or attempts may be observed during treatment of MS with INF-beta; however, the authors did not exclude the use of this drug, but suggested that physicians should be aware of the possible adverse effects of INF-beta therapy.

Discussion

Data from primary care and general medicine has documented high rates of suicidal ideation among medical patients [12,13]. Several studies, as we have shown, demonstrated that MS is associated with

an increased risk of suicide. Studies have documented an increased suicide rate in patients with MS, and reported that the frequency of suicide in MS patients was found to be higher than that of the general population [19–23,25]. We also found studies that did not support these findings, and reported that the suicide rate was not higher than that of the general population [27]. These findings taken together should address the need of more effective suicide prevention strategies in patients affected by MS, and suicide assessment should be part of the clinical evaluation. We also focused on risk factors associated with suicide risk in MS. Evidence suggests that suicide risk among MS patients is higher for men than for women, and social isolation, major depression, and alcohol abuse can be considered predictors of suicidal ideation [22]. Depressive symptoms as all other psychiatric manifestations, in subjects with MS, should be considered by primary care physicians. Suicidal ideation in MS is associated with several risk factors such as: depression severity, which is considered to be one of the most potent risk markers, social isolation, younger age, progressive disease subtype, lower income, earlier disease course, higher levels of physical disability, and not driving [29]. Long and Miller suggested that family support could be considered very useful in predicting suicidal tendencies in people with multiple sclerosis [32]. Some researchers have found that the first year after diagnosis presents the highest risk, especially in younger patients [25], and this addresses the importance of an early suicide assessment and prevention efforts. The age of onset of the disease is an important risk factor; the risk was demonstrated to be higher among younger patients and especially among males [20,22]. Gender differences should also be taken into account when assessing suicide risk. As reported by Bronnum et al. [22] in a Danish sample, it was found that suicide risk was higher among men than among women with multiple sclerosis in the first year after diagnosis. The relation between interferon-beta (INF-beta) therapy and suicidal behavior remains unclear.

Table 1

Most relevant studies about multiple sclerosis and suicide risk, attempted suicide, and/or suicidal ideation.

Study	Quality score*	Aim and study design	Sample	Follow-up	Method	Results	Risk or protective factors – SMR	Conclusion
<i>Multiple sclerosis</i> Kahana et al., 1971 [19]	I=1 II=0 III=0 IV=2 V=1 VI=1 VII=1 Total score=6	Examine clinical factors and increased risk of suicide Observational study	295	6 years	Diagnosis of MS: Allison and Millar's clinical criteria. Degree of disability assessed according to Hyllested's criteria.	Euphoria:16 patients (5%). Depression: 18 patients (6%). Suicide: 8 patients (3%).	Not reported	Suicide rate 14 times higher than suicide rate in the general population
Sadovnick et al., 1991 [21]	I=1 II=0 III=2 IV=0 V=1 VI=1 VII=1 Total score=6	Analyze causes of death Retrospective study	3126	No	Patients from two different clinics in Western Ontario and Brithis Colombia, Canada. Notification of deaths in several ways.	63 deaths, 18 (28.6%) suicides, (9.5%) miscellaneous causes, of which two may have been suicides.	Not reported	The proportion of suicides: 7.5 times that for general population.
Stenager et al., 1992 [20]	I=1 II=1 III=2 IV=2 V=1 VI=2 VII=1 Total score=10	Assess the risk of death by suicide Retrospective study	5525	No	Based on entries recorded at the Danish Multiple Sclerosis Registry (DMSR)	Cumulative lifetime risk of suicide from the time of onset: nearly 2%. Total number of expected suicides: 28–9. SMR was 1–83	Male with onset of MS<30 years were at highest relative risk of suicide (SMR=2.73). Lowest relative risk of suicide: females with an onset age<30 years (SMR=1–28, ns) and males>30 years (SMR=1–66), p=005). SMR for suicide was highest in males and females<40.	Risk was highest among the youngest patients and especially among males.
FisK et al., 1998 [28]	I=1 II=2 III=2 IV=2 V=1 VI=1 VII=1 Total score=10	Examine the prevalence of bipolar disorder, depression, and attempted suicide Retrospective study	3099	No	Data regarding diagnosis and utilization were extracted from two linked databases which included all hospital separation records over a 3 year period	Prevalence in hospitalized MS patients: 1.97% bipolar disorder, 4.27% depression. These rates were significantly higher than the non-MS.	Estimated frequency of suicide attempts in the total MS population was more than three times that of the general population	Bipolar disorder and depression rates were higher in MS patients than in the general population. Estimated frequency of suicide attempts was at least three times greater.
Koch-Henriksen et al., 1998 [24]	I=1 II=2 III=2 IV=2 V=2 VI=2 VII=2 Total score=13	determine the underlying causes of death in a large population based register Retrospective and cohort study	6068	Yes	based on the nationwide Danish Multiple Sclerosis Registry and the National Registry of Causes of Death. In the cohort based part of the study SMRs were computed	the SMRs for causes of death other than multiple sclerosis were highest for infectious or pulmonary diseases. Suicides were also more common in patients with multiple sclerosis	SMR from suicide was 1.62	This study confirm the increased risk of suicides in patients with multiple sclerosis
Feinstein et al., 2002 [23]	I=0 II=2 III=0 IV=0 V=1 VI=1 VII=2 Total score=6	Examine neurologic and psychiatric correlates of suicidal intent Observational study	140	No	Major depression and anxiety disorders: Structured Clinical Interview for DSM-IV Axis 1 disorders (SCID-IV) Psychological stressors: Social Stress and Support Interview. Suicidal intent: SCID-IV and Beck Suicide Scale	Suicidal patients were more likely: to live alone, family history of mental illness, more social stress, and lifetime diagnoses of major depression, anxiety disorder, comorbid depression-anxiety disorder, and alcohol abuse disorder.	Logistic regression analysis: severity of major depression, alcohol abuse, and living alone had an 85% predictive accuracy for suicidal intent.	Suicidal intent is common in MS and is strongly associated with: major depression, alcohol abuse, and social isolation.
Fredrikson et al., 2003 [25]	I=1 II=1 III=2 IV=1 V=1 VI=2 VII=1 Total score=9	Investigate suicide risk Retrospective study	12,83	Yes	MS was a primary or secondary diagnosis at discharge. The mean follow-up time for the whole cohort was 9.9 years. Data linked to the Swedish Causes of Death Register	90 suicides (1.8%). Suicide risk higher in the first year and among younger male. Mean age at the time of suicide: 44.5 years. 58% of the suicides were committed within 5 years after the first admission.	Suicide rate higher (p<.001) in males (114) than in females (47), with an odds ratio of 2.4 (95% CI: 1.6–3.8).	These findings have implications for suicide preventive measures in neurological practice.

Table 1 (continued)

Study	Quality score*	Aim and study design	Sample	Follow-up	Method	Results	Risk or protective factors – SMR	Conclusion
Brønnum-Hansen et al., 2004 [26]	I=1 II=0 III=2 IV=0 V=1 VI=2 VII=2 Total score=8	Analyze trends in survival and causes of death Cohort study	9881 (3954 m, 5927 f)	Yes	Data based on Danish Multiple Sclerosis Registry	4.5% died from accidents or suicide	Not reported	More than half (56.4%) of the patients had died from multiple sclerosis. They also had excess mortality rates from accidents and suicide.
Brønnum-Hansen et al., 2005 [22]	I=1 II=2 III=2 IV=2 V=1 VI=2 VII=2 Total score=12	Compare suicide risk with that of the general population, evaluate changes over 45 years. Retrospective study	10,174	Yes	Linkage between the Danish Multiple Sclerosis Registry and the Cause of Death Registry.	115 MS subject (63 m, 52 f) committed suicide; expected number of suicides in a matched general population was 54.2 (29.1 m, 25.1 f).	Excess suicide rate during the first 15 years after diagnosis was relatively stable for men (SMR varying between 2.18 and 2.76). SMR: age < 30 = 2.55, age > 40 = 1.52	Suicide risk among is higher for men than for women. The risk is still high many years after diagnosis. Suicide risk in MS was twice that of the general population.
Turner et al., 2006 [29]	I=1 II=0 III=2 IV=2 V=1 VI=2 VII=2 Total score=10	Examine risk factors for suicidal ideation Cohort study	1090	Yes	9-item depression module from the Patient Health Questionnaire (PHQ), USPSTF minimal screen	131 (29.4%; 95% CI, 25.4%–33.9%) reported suicidal ideation and 35 persistent suicidal ideation. SI was more likely if: low income, progressive disease; more physical disability in the domains of mobility, bowel function, and bladder function.	Multivariate model: bowel-functioning disability and depression severity remained the only variables independently associated with suicidal ideation.	Suicidal ideation is associated most significantly with depression but also with younger age, earlier disease course, progressive disease subtype, lower income, social isolation, not driving, and higher levels of physical disability.
Fragoso et al., 2010 [31]	I=0 II=0 III=0 IV=0 V=1 VI=1 VII=1 Total score=3	Assessment of patients who were using IFN-beta with suicide attempts or ideation Retrospective study	11 cases of severe depression With suicide attempts or ideation	No	Inclusion criteria were established to collect clinical data on 11 patients with relapsing-remitting who presented severe depression with suicide ideation and attempts during the use of ifn-beta.	12 cases of severe depression with suicide ideation and/or suicide attempt. Severe depression associated with IFN-beta may present with significant psychotic or manic behavior.	Not reported	Depression in a patient with MS is not drug related at all, but the possibility that there may be such a relationship must be taken into consideration.
Stenager et al., 2011 [11]	I=0 II=0 III=0 IV=2 V=1 VI=2 VII=1 Total score=6	1) Estimate the risk of suicide attempts, 2) estimate the risk of suicide attempts in patients receiving immunomodulating therapy compared with untreated Cohort study	404	Yes	Danish MS Register, established in 1956 and based on a nationwide prevalence study of MS. The standard incidence ratios (SIRs) for suicide attempt were calculated.	15 suicide attempts. No statistical difference between observed and expected numbers of suicide attempts.	Not reported	This study has not been able to demonstrate an increased risk of suicide attempts in MS patients compared with the background Danish population.
Lalmohamed et al., 2012 [27]	I=1 II=2 III=2 IV=1 V=0 VI=2 VII=2 Total score=10	Estimate mortality rates compared with the general population Population-based cohort study	1270	Yes	General Practice Research Database, Hospital Episode Statistics, and national death certificates. Cox proportional hazards models were used to estimate mortality rate ratios (HRs)	Accidents and suicide are reported on death certificates in 2.9% of the deceased patients with MS vs. 8.5% amongst deceased referent subjects.	Not reported	This study was not able to detect any increased suicide related mortality rate in patients with MS

* Studies were rated for the quality assessment using the following criteria as specified below:

- I) representativeness of the sample than the general population (1 point).
- II) presence of a control group (1 or 2 points).
- III) n > 1000 subjects /treatment group (1 or 2 points).
- IV) duration > 1 year/follow up group (1 or 2 points).
- V) evidence based measures of assessment (1 or 2 points).
- VI) Data Presentation (1 or 2 points).
- VII) evidence-based measures assessing suicide or suicide attempts (1 or 2 points). Quality ratings reported 13 as maximum score.

Fragoso et al. [31] documented an association between INF-beta and severe depression, but as reported in our results other studies did not find a clear difference in number of suicide attempts between patients treated

with INF-beta and untreated patients. Also, Patten and Metz [33] reported that patients treated with INF have no more depressive symptoms than controls undergoing other treatments. Although the role of INF-beta is

unclear, clinicians should consider it as a potential risk factor for depression and suicidal behavior. Moreover, the patient's level of hopelessness should always be assessed, as some authors reported high hopelessness levels in MS patients [34]. Recognizing the psychiatric symptoms of MS and generating a differential diagnosis is a complex task for physicians. Treatment of the psychiatric component of the disorder should be considered when addressing steroid induced side effects, psychotropic medications, psychotherapy, patient and family education, and a strong physician-patient relationship [9].

The first step in the assessment of a patient at risk should include the evaluation of current suicidal behavior and the past history of suicide attempts. From a clinical point of view, clinicians may consider the presence of suicidal ideation in their patients with MS, as our results suggest that the risk of self-harm may be higher than expected. This is particularly relevant when treating patients with multiple physical illnesses, because there could also be a "dose-response relationship" between number of medical problems and the risk of self-harm [35,36]. Results from the literature also address the key role of primary care physicians; depression comorbidity and suicide risk factors might be carefully examined by general practitioners. Given the association between MS and suicide, it is of great importance to prevent suicide in these high-risk patients. Preventive strategies should include a routine screening for suicidal ideation by general practitioners and other specialists and referral to psychiatrists for treatment [16]; mental health assessment should be part of the clinical evaluation. Further work is needed to understand the potential mechanisms underlying the association between MS and the likelihood of suicide attempt and also to identify a demographic, physical and psychosocial profile that could predict patients at high risk.

Limitations

The present review should be considered in the light of some limitations. First, we did not carry out a meta-analysis because data from most of the studies that were focused on the main topic did not permit it. Specifically, samples included different measurements and different outcomes, and they assessed patients at different time points.

Although, the current review adequately summarizes the research in this field, focusing on relevant issues related to the phenomenon, and attempts to present key topics in order to offer an easy tool when facing suicide risk in MS patients, the inclusion and exclusion of papers cited in this paper may reflect the authors' choice, both on the basis of their expertise and the consultations that they engaged with experts in the field.

The studies attempting to identify risk factors for suicide in MS have a number of shortcomings. First, some studies had small sample sizes and small numbers of suicides that reduces the power of the research. Second, a number of methodological problems often made the results difficult to interpret (e.g., not all studies included specific follow-up periods and, additionally, not all studies mention the exact number of suicide attempts and completions so that the rate of suicide among subjects cannot be calculated). Some of the studies included in the present review were retrospective designs, and the absence of strategies to ensure both inter-rater reliability and the validity of the data need to be considered.

The present review includes only suicides explicitly reported, excluding accidental deaths and other deaths of uncertain causes. Excluding these ambiguous cases of death may result in an under-estimation of suicide rates. In addition, although the samples usually met the diagnostic criteria for the inclusion in the studies, the diagnostic criteria differ in the different samples.

Most of the studies investigated a mixture of age groups, and future research should take the age of MS patients into account. Most of the studies were carried out in heterogeneous samples, mixing patients at different stages of their illness. This did not permit clarification of whether there is an association between age of onset of MS and the age at suicide.

A relatively younger age of onset may expose subjects to a longer period of higher suicidal risk?

Although most of the studies analyzed were based on retrospective data, risk factors such as age, gender, marital status and employment status can be assessed reliably. If the information, collected retrospectively, is reliable, a retrospective design is adequate and not hampered by recall bias. On the other hand, clinical variables are not easily measured reliably in retrospective designs. Some studies considered only inpatients, studied only a few variables, and did not include a control group.

Conclusions

Taken together, results from this review suggest that the risk of self-harm is higher than expected in MS patients; these findings support the supposition that the mental health assessment of patients with MS should form part of the routine clinical evaluation. As demonstrated in many studies, some risk factors should be evaluated during the suicide risk assessment. Depression severity was found to be one of the most potent risk factors. Other risk markers are social isolation, younger age, progressive disease subtype, lower income, earlier disease course, higher levels of physical disability, and not driving. People who are separated, divorced, widowed, or have experienced another significant interpersonal loss are at higher risk of suicide. These patients should be assessed for suicidality on an ongoing regular basis given their elevated risk for suicide. Similarly, premorbid suicidal ideation should be considered a very important risk factor, especially during the early period of diagnosis when patients are living in hospitals.

Conflict of interest

There is no conflict of interest.

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The first two authors contributed equally to this work.

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