WEGENKO, Cezary Michał, SITKA, Hanna, CZAJA, Magdalena, KUŹNIAR, Julia and KOZUBEK, Patrycja. Depression in patients with multiple sclerosis. The prevalence, diagnostic challenges and evidence-based treatment methods. Journal of Education, Health and Sport. 2024;72:57295. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2024.72.57295
https://apcz.umk.pl/JEHS/article/view/57295

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 20.11.2024. Revised: 23.12.2024. Accepted: 23.12.2024. Published: 25.12.2024.

Depression in patients with multiple sclerosis. The prevalence, diagnostic challenges and evidence-based treatment methods

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Abstract
Introduction and purpose: Gradual progression of cognitive and physical disability negatively affects personal, social and economic well-being of patients with multiple sclerosis. This particular group of people has a high risk of developing depressive disorders. This study reviews the prevalence, current diagnostic tools and evidence-based methods of treating depression in patients suffering from MS.
Material and Methods: This paper reviews various types of research documents with a special focus on sources from the past 10 years. Works from the 1980s and 1990s were also cited to outline the progress made in exploring the given topic. Its main aim is to indicate that MS poses a risk of developing depression and to emphasize that this disorder may be mistakenly attributed to the primary disease. It highlights the need for raising awareness about the topic to ensure interdisciplinary care.
Results: The study proved the connection between the prevalence of depression in MS. Characteristic somatic depressive symptoms such as chronic fatigue, sleep disturbances, can conclude either from MS or depression. Because of this, the prevalence of depression in MS patients is artificially altered.
Conclusion: The prevalence of depression is significantly greater in patients with multiple sclerosis compared to the general population. Many somatic symptoms caused directly by neurodegenerative changes pose difficulties in differential diagnosis. Multidisciplinary treatment, including both psycho- and pharmacotherapy, remains the most effective therapeutic approach. Nevertheless, the development of new, accurate diagnostic methods is necessary in order to screen for depression in this group of patients.

Keywords: Multiple Sclerosis, Depression, Epidemiology, Disability, Suicide

INTRODUCTION

Multiple sclerosis (MS) represents one of the leading causes of neurological dysfunction among young adults (in the age of 18-40) globally [1, 2]. The prevalence and incidence of this chronic, immune-mediated disease are rising worldwide in both developed and developing countries. These rates also differ depending on geographical location and the ethnicity of different populations [2, 3]. 2.8 million people around the world are affected with the diversified prevalence ranging from 5 per 100 000 in the WHO African region and Western Pacific region to over 100 per 100 000 in the WHO European region and region of the Americas, reaching nearly 300 per 100 000 in some of these areas [1]. There is also a correlation between the distance from the equator and increased prevalence of MS [4]. The disease affects women more frequently with the ratio approximately 3:1 in developed countries [3–5].

Although the direct cause of MS is often described as unknown, vitamin D levels, Epstein-Barr virus, birth season, smoking and genetic vulnerability have been recognized as important factors in the development of MS. New pathophysiological discoveries further emphasize the significance of the interaction between genetic and environmental factors [1, 4, 6].

Despite unclear etiology, interactions of above variables eventually lead to infiltration of the central nervous system by proinflammatory immune cells, causing the formation of

demyelinating plaques. These neurodegenerative changes have been associated with blood-brain barrier disruption and loss of its protective function [7, 8].
Taking the course of MS into consideration, we can classify the disease into relapsing–remitting (RR), secondary progressive (SP), or primary progressive (PP) phenotypes. RR phenotype is the most common, affecting 85–90% of patients, whereas PPMS occurs in 10-15% of cases [1]. As the disease progresses, RRMS may often evolve into SP phenotype with gradual progression of the symptoms, usually without relapses [9]. Initially, up to 85% patients with MS experience a single demyelinating attack that does not meet MS diagnostic criteria and is defined as clinically isolated syndrome [10].
Two main mechanisms by which people with MS acquire disability can be distinguished. The first one, called relapse-associated worsening, is related to inability to fully recover from a relapse. The second one, called progression independent of relapse activity, is associated with the continuous worsening of symptoms characteristic for PPMS and SPMS [11].
Chronic, gradual progression of cognitive and physical disability impacts not only the individual health of the patients but also their social and economic well-being [12]. From all the neuropsychiatric symptoms of MS, depression and anxiety are the most common [13]. Studies show that depressive disorders can affect nearly half of the people living with MS [14].

The development of such symptoms worsens the prognosis, leads to higher suicide rates and adversely affects the compliance of patients taking disease-modifying drugs [15]. Diagnosing and treating depression in people suffering from MS poses a challenge for clinicians, as some of the symptoms characteristic of depression may derive directly from neuronal damage [15].

AIM

The purpose of this paper is to provide an up-to-date overview of the connection between MS and depression. This article focuses on analysing increased prevalence of this affective disorder in people living with MS and emphasizes the diagnostic difficulties in this group of patients. Furthermore, evidence-based treatment methods have been discussed.

MATERIALS AND METHODS

In order to select appropriate references for this article, a bibliographic research was conducted in November 2024 and updated in December 2024. Papers were identified using the PubMed search engine with the key terms: “Multiple Sclerosis”, “Depression” “Epidemiology”, “Disability”, “Prevalence”, “Suicide”. Articles’ publication dates range from 1983 until 2024, with a focus on those published during the past 10 years.
Some articles were selected from the references of the searched publications. Only papers published in English were included into the final reference list.

CURRENT STATE OF KNOWLEDGE

Epidemiology

Multiple sclerosis (MS) is a primary, inflammatory-demyelinating, chronic disease of the central nervous system (CNS), with its basis in autoimmune processes. From a neuropathological perspective, it involves an inflammatory process, demyelination, axonopathy, and damage to oligodendrocytes, which are responsible for the production of the myelin sheath. This leads to neuron loss and astrocytic gliosis. The term gliosis refers to the hypertrophy and proliferation of glial cells, as a response to CNS damage. The destruction is

caused by immunogenic T cells that produce cytokines. These cells promote an inflammatory response from T helper (Th1) cells, which are the main initiators of myelin destruction in MS [4]. Initial contact with yet unknown antigen leads to the production of cytokines, interferon IFN-γ, interleukin-1. Further regulation of Th cells and the production of metalloproteinases results in damage to the blood-brain barrier (BBB), allowing Th cells to infiltrate the CNS [16].

The disease affects approximately 2.3 million people worldwide, with the most common age of diagnosis occurring between 20 and 50 years old. The highest risk of developing the disease has been observed among individuals of Northern Europe and of Caucasian race [4]. The global median prevalence of MS is 33 per 100,000 people, although this varies between countries. The highest prevalence is found in North America and Europe, with rates of 140 (North America) and 108 (Europe) per 100,000 people. The lowest median prevalence is found in Asia (2.2 per 100,000) and Africa (2.1 per 100,000) [17]. Black individuals or those of Asian descent, however, may experience more severe disability associated with the disease [18].

The cause of multiple sclerosis is not fully understood, but it is suggested that factors such as the Epstein-Barr virus (EBV), smoking, low vitamin D levels, and even childhood obesity may play a significant role in its development. Symptomatic infectious mononucleosis can double the risk of developing MS [3]. The risk associated with smoking is stronger in men and increases with the duration and intensity of smoking. Childhood obesity may lead to lower vitamin D levels, contributing to an increased risk of developing MS [19].

The disease is now more commonly diagnosed in females, although studies show that this relationship has not always been observed. At the beginning of the 20th century, the gender ratio was nearly equal, but since then, it has shifted to the disadvantage of women, reaching about 3:1 (F:M) [3]. Some authors suggest that studies conducted at that time may not have accurately reflected reality, as men, seen as the breadwinners of the family, may have received more frequent testing and diagnoses than women [20]. Over time, with advancements in science and increased awareness of the disease, a wealth of epidemiological data has been gathered regarding changes in the incidence of multiple sclerosis and the progression of the disease. The prevalence of MS has increased over the past decades, but the nature of the disease has become milder, especially since the introduction of the first disease-modifying therapies (DMTs) [21].

Clinical manifestation - what MS patients experience on a daily basis?

There are many forms of the disease, with the most common being RRMS. Neurological symptoms appear suddenly, which is called a relapse, followed by periods of complete or almost complete recovery, known as remission. Over time, these episodes may occur less frequently, but patients gradually develop worsening disability – this is SPMS [22]. In less than 10% of patients, disease progression is observed from the very beginning, which is classified as PPMS [23].

The disease typically manifests in young individuals and presents as sensory disturbances, unilateral optic neuritis, or partial spinal cord inflammation [24]. The first episode of the disease, suggesting a demyelinating disorder of the nervous system, is called a clinically isolated syndrome (CIS). These symptoms develop acutely or subacutely over a period of days or weeks, are usually monocentric, and involve structures such as the spinal cord, brainstem, cerebellum, and optic nerve. Such an attack should last at least 24 hours, and the presence of fever or infection must be excluded. CIS is not sufficient for a definitive diagnosis, but it carries the risk of developing multiple sclerosis in the future [18].

In advanced stages, the disease may manifest as difficulty in moving, coordination problems, and issues with maintaining balance. Motor disorders in the form of tremors can affect one-

third to even half of those with the disease. These tremors are usually bilateral, more often affecting the upper limbs than the lower limbs, and can also impact the neck, head, or vocal cords [25]. The tremors are typically postural or intentional, with postural tremor being significantly more common than intentional tremor (44% compared to 6%, respectively). In rare cases, palatal tremor has also been described [26].

One of the most common symptoms of MS is optic neuritis, which makes 25% of CIS cases. It is estimated that around 50-70% of patients will experience optic neuritis at some point during the course of the disease. It manifests as sudden, unilateral vision loss, with retro-orbital pain and pain during eye movements. Examination of these patients often reveals reduced visual acuity and a reduced visual field [27]. Abnormalities in the cerebellum, vestibular pathways or in the connections between afferent visual pathways and the brainstem can manifest as nystagmus [28]. Patients may also experience loss of stereopsis, blurred vision and diplopia [29].

Patients with multiple sclerosis also experience progressive cognitive deficits. Learning processes and memory are also impaired. These symptoms are most strongly associated with regional atrophy of the brain's gray matter and disruptions in neuronal connections. It has been shown that patients with MS who have an onset in childhood have difficulties developing language skills, which affects their later academic performance [30].

Another issue that patients may face is trigeminal neuralgia, which poses a challenge for pain management. It manifests as paroxysmal, severe facial pain that significantly impairs daily functioning. The pain is unilateral, short in duration, with a sudden onset and offset. It is restricted to the distribution of one or more branches of the trigeminal nerve. Neuralgia is recurrent and can be triggered by harmless stimuli [31].

How does MS influence patients' quality of life?

Multiple sclerosis is a disease that affects not only physical aspects, followed by cognitive deficits, but can also impact patient's mental health. The affective symptoms that emerge during the course of the disease can negatively influence family and social life and are also factors that worsen the progression of MS. The lifetime prevalence of affective symptoms such as anxiety disorders and severe depression can be as high as 50%, which shows that the risk of their occurrence is higher than in the general population (20%) [32].

The progression of the disease and the associated disability force some patients to quit their jobs, which, as studies show, also impacts the course of MS. When comparing groups of MS patients, a higher percentage of those with a more severe disease course, were unemployed rather than employed, with no differences observed in terms of age, education, or gender. Cognitive tests revealed significant differences between employed and unemployed individuals in areas such as learning speed, information processing, and memory [33].

The quality of life for patients can be significantly impacted by various sensory and motor disturbances in the facial region, such as cranial nerve neuralgias, paresthesias, tremors, facial muscle paralysis, dysphagia, dysarthria, temporomandibular joint disorders, and painful tonic spasms of the mimic muscles. These symptoms contribute to significant difficulties in eating, speech, and maintaining oral hygiene, further compounded by deteriorating manual dexterity. All of these issues affect not only physical but also mental aspect, worsening the overall life satisfaction of patients [34]. Daily functioning is also greatly hindered by chronic fatigue and a constant feeling of low energy [35]. Men with multiple sclerosis may also experience sexual health issues, which not only impact their quality of life but also pose challenges to reproduction. These problems mainly include decreased libido, erectile and ejaculatory dysfunction, reduced sperm quality, and consequently, fertility issues [36].

Can depression be the major reason of suicides in group of MS patients?

The mortality rate among patients with multiple sclerosis is higher compared to the general population and there is an increasing focus not only on the physical health impairments caused by the disease but also on its impact on mental health, developing depression, and consequently, the increased incidence of suicides. Studies have shown a link between significant physical difficulties, bladder, bowel, and speech disorders, and the emergence of suicidal thoughts. These issues were also associated with the inability to drive, loss of employment or lower income and being single [37].

Depressive symptoms occur in patients with MS four times more often than in the general population. However, due to the difficulty in distinguishing them from typical symptoms of the disease — such as chronic fatigue and cognitive disturbances — these symptoms are often attributed to MS rather than depression [38]. This complicates the identification of individuals who require psychiatric help and support. Studies have shown that multiple sclerosis increases the risk of developing depression, and depression, in turn, has a direct impact on the occurrence of suicidal thoughts and the risk of suicide [39].

How to diagnose depression in MS?

Diagnosing depression in MS is especially difficult, because many somatic symptoms characteristic for depression (such as sleep or work difficulties, chronic fatigue) may conclude from MS itself [40]. Nyenhuis et al. suggested in their study that inclusion of somatic symptoms in self-report depression scales may artificially raise the number of diagnoses and severity of depression. Therefore, most significant factor that should be taken into consideration should be mood disorders [40]. The best way to diagnose depression in MS patient seems to be structured clinical interview, in context of DSM V [41]. The problem although is time and qualified personel required to conduct such examination [42].

There were attempts in the past to picture whether there is a correlation between depression in MS patients and lesions in their nervous system. Few studies were conducted, but the number of examined patients was rather low, e.g. Honer et al in an old study (1987) used magnetic resonance imaging to analyse eight MS patients suffering from any psychiatric disorders and compared the results with MRI images of non-psychiatric MS patients [43]. The study concluded that psychiatric disorders were correlated with temporal lobe lesions. However, it was a small study and it included patients with any kind of psychiatric disorder. There are also some more current studies, in which researchers look for connection between MS and depression in brain morphology. Van Geest et al. in their study from 2018 tried to explore structural and functional fronto-limbic changes in two groups of patients, with and without depression. They based their study upon previous reports about potential link between major depressive disorder and fronto-limbic disconnection [44]. Researchers analysed 22 moderate-to-severe depressed MS patients, 21 patients not suffering from depression and 12 healthy controls. All patients included in study underwent neuropsychological testing and magnetic resonance imaging (MRI), in which researchers analysed brain volumes (white and gray matter, amygdala, hippocampus, thalamus), lesion load, fractional anisotropy of fronto-limbic tracts and resting-state functional connectivity between limbic and frontal areas. They performed regression analysis to relate MRI measures to the severity of depression. Depressed MS patients presented more distinct structural and functional lesions in temporo-frontal regions than not depressed patients with MS, which was suggestive of fronto-limbic disconnection [44].

Another not so inapparent variable that could be considered as predictive for depression development in MS patients is treatment used in MS pharmacotherapy, precisely interferon beta. This has been the concern of clinicians since interferon was introduced to treatment. It was speculated if patients can develop depression or their previously existing depression can get exacerbated, due to interferon [45]. Patten et al. conducted an analysis of data collected

in PRISMS and SPECTRIMS clinical trials [46, 47]. The results of the analysis of both trials were unambiguous; no evidence of depression as the effect of interferon beta was established [46, 47]. The conclusion of this consideration should be perhaps that patients and their mental state must be under close monitoring during interferon beta therapy, but regardless of present or past depression episodes, patients must not be excluded from interferon beta treatment programs [48].

One symptom that depression and MS have in common is cognitive impairment. It could seem as if one's impaired cognitive functioning was enough reason to start suspecting coexisting depression. In the past many analyses regarding this problem were conducted. In a 1998 study Brassington and Marsch summarised 10 papers concerning the association between cognitive impairment and depression in SM [49]. At that time, the conclusion was clear; no correlation between those two could be established. But since then new studies ascertained that, indeed, there is a connection and it is quite significant. Bogaardt et al. in 2023 tested a group of MS patients with a computerized test battery that assessed cognitive impairment and Beck Depression Inventory [50]. The main purpose of this study was to distinguish disability level of patients with MS and with benign MS. 38% of patients with benign and 66% of patients with MS expressed signs of cognitive impairment [50]. They concluded that depression and cognitive impairment is common among patients with MS. Whitehouse et al. searched for association between depression, anxiety and cognition in MS and other immunomediated inflamatory inflammatory diseases [51]. They tested participants of the study with Hospital Anxiety and Depression Scale and cognitive tests, including the Symbol Digit Modalities Test, the California Verbal Learning Test, and Letter Number Sequencing test. Moreover, every patient completed a structured psychiatric interview. Researchers presented results of collected and analysed data as follows: all patients experienced higher rates of impairment, especially in processing speed, verbal learning and delayed recall memory, relative to general population norms [51]. They also noted that higher depression levels were associated with slower processing speed. The conclusion of the study was that in order to efficiently alleviate effects that MS has on the organism, symptoms of depression must be considered and treated.

Are there any tools that could facilitate detection of depression in MS patients and enable screening in this group?

Because of the high prevalence of depression in MS patients, it could be beneficial to perform some noncomplex depression tests to initially either exclude depression or refer patient to further diagnostic and therapeutic process [52]. As it has been pictured in a study from Marck et al., clinicians dealing with MS on a daily basis (nurses and neurologists) admit that they don't test patients routinely for depression, but when they do and result is positive, they lack competences and time to deal with it [53]. Screening tests should be simple and evidence-based, what participants of the study also pointed out [53].

Many MS services utilise patient reported outcome measures (PROMs), such as the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) [44]. This scale, created in 1983 by Zigmond and Snaith [54] is still one of the most commonly used in medical conditions scales assessing probability of depression and anxiety, as it skips the somatic ailments [55]. It should not be used to make a diagnosis, but rather to routinely screen patients for depression and anxiety and indicate the need of treatment [55]. It includes such items as worrying, feeling of relaxation, panic attacks etc., described in a very straightforward way [54].

Another useful tool could be the Multiple Sclerosis Impact Scale (MSIS-29), created by Hobart et al. in 2001 [56]. It measures physical and psychological impact of MS in one questionnaire with questions about patient's problems generated by MS in the last two weeks (e.g. spasms in limbs, urgent need to use toilet, limitations in social and leisure activities, problems with sleeping, lack of confidence, problems concentrating).
Both scales can be useful in the preliminary process of ruling out depression in MS patients, but more precise and problem-oriented tools are still required, thus further studies on this topic is still essential.
What kind of treatment (pharmacological and non-pharmacological) can be offered to MS patients suffering from depression?
Treatment of depression in MS should be multidimensional and include psycho- and pharmacotherapy, with emphasis on cognitive-behavioral therapy [57, 58]. As for pharmacotherapy, desipramine is one of the most analysed drugs used to treat depression in MS [57, 59, 60]. In clinical trials, it showed a trend toward efficacy [60]. Other antidepressants used in treatment are sertraline, fluoxetine, fluvoxamine, moclobemide, all of which have documented efficacy in open-label studies [56].
According to the study from Young et al., depression affects 25,3% patients suffering from MS and almost 50% of them are untreated or undertreated [44]. There is a need to formulate clear guidelines for treating depression in MS, because of its common prevalence and impact on patients' everyday life [53]. This necessity is also pointed out by clinicians who deal with MS patients every day [52].

CONCLUSIONS

Studies show that the prevalence of affective symptoms is significantly greater in patients with MS compared to the general population. As the first clinical manifestations of the disease often occur in young individuals, MS can have a devastating impact on patients' lives from early adulthood until death. From initial sensory disturbances or optic neuritis to advanced motor disorders, cognitive deficits and chronic pain, MS affects not only people's physical and mental health but also their families and social lives.
Significant worsening of the quality of life eventually leads to the development of depression, which in turn can worsen the progression of MS itself. It should also be emphasized that crucial physical difficulties have been associated with the emergence of suicidal thoughts.
The similarities between symptoms caused primarily by depression and those originating from direct neurodegenerative changes in MS pose difficulties in estimating precise prevalence, as well as diagnosing and providing proper support. As many somatic symptoms may arise both from affective disorder and MS, including them into depression diagnostic scales may lead to false positive results and artificially raise the severity of the condition. Therefore, authors suggest that mood disorders should have more diagnostic value in MS patients. Structured clinical interview, in the context of DSM V, seems to remain the best way to diagnose depression in those individuals. Although initial depression tests could be beneficial to either exclude the condition or consult the patient with a psychiatrist, clini- cians report lack of competence and time to cope with them. The depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) and the Multiple Sclerosis Impact Scale (MSIS-29) can be useful diagnostic tools in screening for depression in MS patients. Nevertheless, further research is necessary in order to develop more problem-oriented and accurate diagnostic methods.
Multidisciplinary treatment that includes both psycho- and pharmacotherapy appears to be the most effective therapeutic approach for treating depression in patients suffering from MS. It is crucial to emphasize that a large group of those people remains untreated or

undertreated. In order to provide them with essential support, further studies and the development of clear guidelines are necessary.

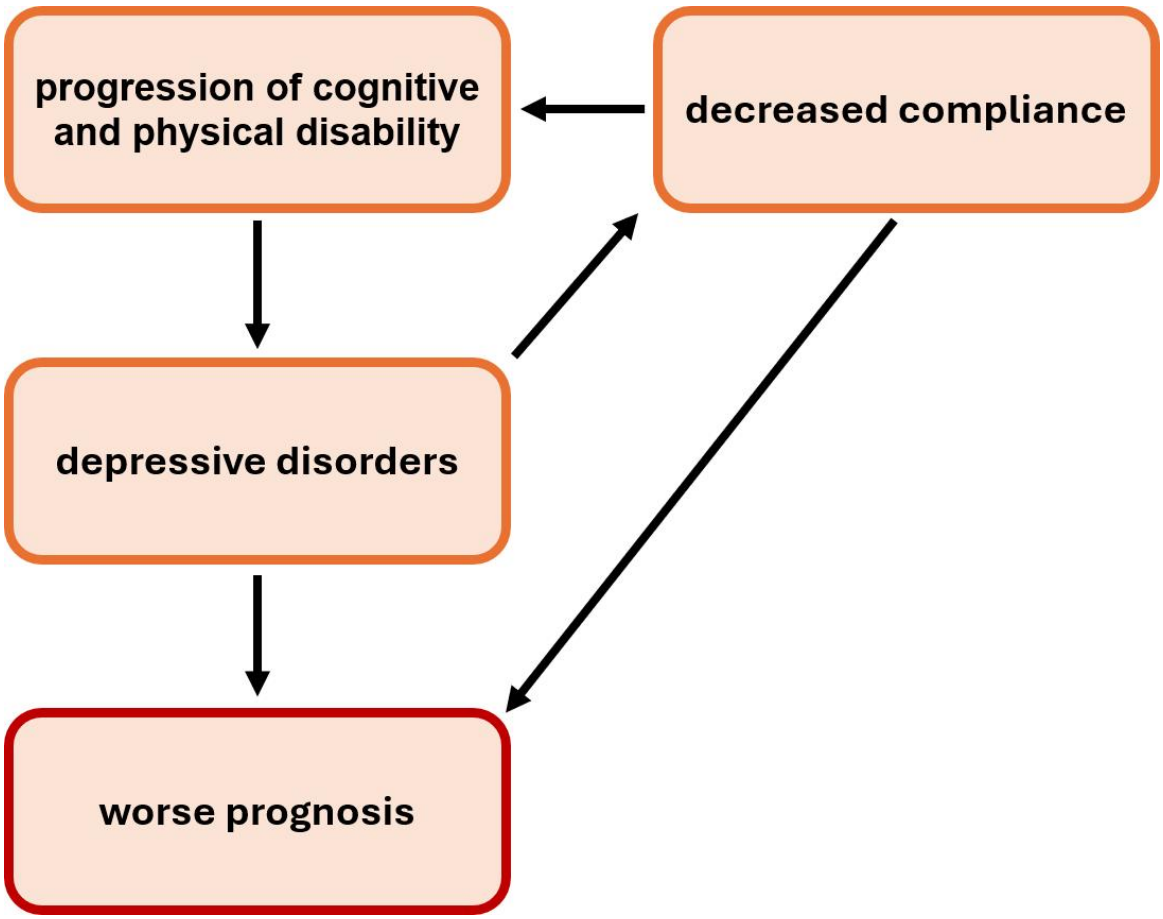

Figure 1. Relationship between the symptoms of MS, depressive disorders, prognosis and compliance.

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Visualization: Magdalena Czaja, Hanna Sitka, Cezary Wegenko Supervision: Cezary Wegenko

All authors have read and agreed with the published version of the manuscript.

Funding statement:
No financial support was received.
Institutional Review Board Statement:
Not applicable.
Informed Consent Statement:
Our work did not involve direct human subject or obtaining their consent for participation in the study.
Data Availability Statement:
Since this is a review paper, our work does not contain new data or analyses.
Conflict Of Interest:
The authors declare no conflict of interest.

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