MOOD DISORDER AND COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS – COMPLEX STUDY OF EVALUATION AND TREATMENT

Summary of Phd Thesis

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IASI - 2017 –
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PhD thesis is illustrated with 55 tables and 47 figures. Summary selectively restores iconography and references in the text respecting numbering and the thesis content in extenso. The bibliographic references presented are identical to those in the thesis.
Introduction

Multiple sclerosis is a multifaceted neurological disorder, with so many manifestations throughout the whole body that it came to be known as the disease with a thousand faces. The dramatic aspect of this disease is the impact it has on the young and adults of working age, preventing them to carry on their professional activities affecting their family life, bringing up in this way many questions and fears.

Against this background of vulnerability, amplified by the structural changes in the brain, emotional imbalances can install themselves in even from the beginnings of multiple sclerosis, fueled by those of neuro-bio-chemical nature. These imbalances are manifesting in the form of depression, anxiety, panic attacks, sleep disorders, and, in some cases, delusional or psychotic disorders in the spectrum of schizophrenia may occur. In almost half of the patients with multiple sclerosis, cognitive dysfunctions do occur in the early stages of the disease. All these issues from the psychic scope require attention and adequate medical care.

Multiple sclerosis can become a disabling condition and then, the overlapping of affective or cognitive disorders emphasize that this cumulation of symptoms and afections having common cerebral origin, certainly decreases the quality of life and the ability to self-conduct and self care. Therefore the mental disorders in multiple sclerosis are a public health problem and it is necessary to represent a continuous concern for professionals involved in health caring these patients.

The complications of mental afections are serious and may endanger the life of the sick or their integrity. These are: psychoactive substance abuse, severe stages of dementia, suicide attempts and the actual suicide act. Direct and indirect costs of care of psychiatric disorders in multiple sclerosis along with the costs for therapy of the underlying disease amount to significant sums that challenge the health budgets of countries with high incidence of this neurological disorder.

This work comes to bring clarification on some controversial aspects from the causal association of multiple sclerosis with the psychiatric disorders. As shown in the general part of this work, OMS data shows that depression will become in the coming years the main cause of morbidity and disability worldwide, its level if incidence surpassing even the frequency of cardio-vascular diseases. Multiple sclerosis, being the neurological disorder that affects primarily young adults, is also a potential cause of disability. The overlap of these pathologies in this age group often force these people out of workforce and brings an unfavorable outlook on life as a whole.

Depression, anxiety and cognitive disorders in multiple sclerosis were a concern in recent years, for several branches of medicine in an attempt to establish consistent and concrete data for specialists directly involved in care to work with for remission of symptoms and reducing the negative impact on quality of life. Neurology, psychology, psychiatry, ophthalmology, brain neuroimaging and other branches of traditional medicine developed tests, techniques and methods for quantifying and studied multiple drug therapies having a curative tendency or one towards changing the evolution of the disease.

Neuropsychological testing of depression, anxiety and cognitive dysfunction applies to almost all medical pathology, since any chronic or debilitating disease may be associated or may cause one or more disorders in the emotional or cognitive scope, in the course of the affection. So they can be recognized and quantified as diseases ranging from those as well known as hypertension, diabetes, rheumatoid arthritis and musculoskeletal disorders involving chronic pain, degenerative diseases and the full oncologic pathology, to the rare or orphan diseases.

Thus, the more understandable becomes the occurrence of psychiatric pathology in neurological diseases, having the same system as organic support: the brain and the central
and peripheral nervous system. The stroke, Parkinson's disease and epilepsy associate increased prevalence of depression, anxiety and disorders of cognitive functions. Multiple sclerosis is not an exception, but falls on the same line of epidemiological data with figures much higher than in the general population of mental disorders.

Neuropsychological testing of these disorders provides a clearer picture and a measurable one for the affective and cognitive disorders in multiple sclerosis, and drug treatments come in order for the purpose of symptoms improvement, achieving and maintaining remission for a time interval as large as possible the ultimate goal being the curative one.

In anticipation of this doctoral work and aiming to build on specific and up to date data, I carried out a pilot study in which I highlighted the high frequency of depression, anxiety and cognitive dysfunction in multiple sclerosis and the necessity of appropriate therapies adapted to these pathologies. The study was conducted over a period of 12 months and included a total of 65 patients and took place at Clinica de Neurologie a Spitalului de Recuparare, Iaşi.

The data and conclusions of the study were presented in the form of a scientific paper entitled “Diversitatea tulburărilor afective și cognitive în scleroza multiplă” (“Diversity of the affective and cognitive disorders in multiple sclerosis”) as part of the 5th National Conference of multiple sclerosis with international participation, Iaşi, 18 to 20 November 2010.

**Objectives of paper**
- evaluation of casuistic distribution by gender, age, provenance in order to discovery of certain features related to these parameters for depression, anxiety and dementia in multiple sclerosis
- establishing the severity of depression, anxiety and cognitive impairment through specific neuropsychological tests
- the relation between depression, anxiety, and dementia and multiple sclerosis
- assessment specific symptoms of depressive syndrome (suicidal thoughts, panic attacks, psycho somatization, insomnia)
- the relationship between specific antidepressant, anxiolytic and dementia medication and evolution of multiple sclerosis
- study and achievement of correlations between antidepressant and anxiolytic treatment and therapy of multiple sclerosis
- comparing and establishing of correlations between antidepressant and anxiolytic therapy and clinical and demographic data
- assessing the specific evolution features of psychiatric treatment

**Material and methods**

The study group consisted of 17 multiple sclerosis patients, hospitalized in the Clinica de Neurologie a Spitalului Clinic de Recuperare Iaşi and the psychiatric cabinet of the policlinic adjacent to the hospital, during the period May 2013 - July 2016.

Parameters included in the files of patients in the study group were the ones below:
- Epidemiological characteristics: age, gender, area of origin, living environment
- The level of intellectual preparation and integration into employment
- Associated pathologies: hypertension, other cardiac and vascular disorders, gastrointestinal pathology, degenerative disorders of osteoarticular, metabolic or algesic nature, epilepsy
- Immunomodulatory treatment
- EDSS values
- The clinical forms of multiple sclerosis
- The duration of development of multiple sclerosis
- In my study I have made use of:
  - two rating scales for depression: the Hamilton rating scale for depression (HAM-D) and Montgomery-Asberg Depression Rating Scale (MADRS)
  - a scale for evaluating anxiety: the Hamilton rating scale for anxiety (HAM-A)
  - and one for evaluating cognitive dysfunctions: Mini-Mental State Examination (MMSE)
- The pharmaceutical preparations which I have used in the study are:
  - antidepressants: tianeptine, duloxetine, escitalopram, trazodone, mirtazapine, agomelatine
  - anxiolytics: lorazepam, alprazolam, bromazepam, nitrazepam, clonazepam
  - antidemential: donepezil, memantine

The following were determined: the clinical form of multiple sclerosis, the degree of disability of the patients, the type of immunomodulatory treatment, the duration of the development of multiple sclerosis, the number of flare-ups. And evaluated were the severity of mental disorders by applying neuropsychological tests for depression, anxiety and cognitive dysfunction. Antidepressant, anxiolytic and antidemential medication was administered.

Neuropsychological evaluation tests confirm the depression in multiple sclerosis, associated with disorders in the anxiety spectrum, and cognitive impairment in multiple sclerosis. Neuropsychological tests used are used in most studies that research affective and cognitive disorders.

The administered treatment enabled specific tracking of mental disorders in therapy in relation to multiple sclerosis.

For the realization of this study, the following were used: the Hamilton rating scale for depression, the MADRS scale for depression, the Hamilton rating scale for anxiety, the MMSE scale for dementia, antidepressant, anxiolytic and antidemential psychiatric medication.

**Results and discussions**

Regarding epidemiological data about multiple sclerosis, the study group complies with known demographic characteristics.

Thus, the study group include more women than men, with a ratio women:men of 4:1, being known that the disease is 2-3 times more frequent in women than in men (Băjenaru et al, 2011).

![Fig. 8.2. Structure of lot by age groups](image-url)
Also, in terms of age parameter, on the studied cases, the age of onset of the disease, between 20-40 years, corresponds to 47.1%, i.e. almost half the subjects, consistent with the data in the specialised literature. Women in the study group are slightly younger than the men just because multiple sclerosis is more common in women (Băjenaru et al, 2011).

More than 60% of patients with multiple sclerosis and depression show pathological conditions. In the study group we observe that cardiovascular affections and the algetic pathology are the most common. Metabolic, osteo-articular, gastrointestinal and epileptic affections are also associated with multiple sclerosis and depression patients, but in much smaller percentages.

Cardiovascular affections are correlated statistically significant with age (p = 0.037), which are present only in patients over 40 years, the aspect being consistent with the data in the specialised literature on age of onset of cardiovascular diseases and their association with mental affections such as depression and anxiety. Given that all patients in the study were diagnosed with depressive syndrome, this association confirms the presence of depression in chronic diseases.

![Correlation between age and associated pathology](image)

In terms of the level of intellectual preparation, most subjects, more than a third, have completed vocational school. Persons with higher education and high school are less present, but in relatively equal proportions, and subjects with a low level of education (1-8 grades) are the fewest.

Most patients in the study group are medically retired or are receiving medical disability allowance, together representing over 70% of the total. Fewest are the employees and students.

These data show that multiple sclerosis and depression negatively affect the ability of patients to cope with the workplace or with the intellectual requirements to complete their education level.
The percentage of patients receiving immunomodulatory treatment is slightly increased compared to that of patients not receiving therapy for modifying the development of multiple sclerosis, which is more than 50%.

Most patients in the study group present the clinical form of relapsing-remitting multiple sclerosis, which is consistent with the data in the specialised literature, data confirming that this clinical form of the disease is the most common.

More than 70% of the subjects in the study present a disease development with a duration of between 1 and 10 years, the remaining patients having a disease duration of more than 10 or even 15 years. These percentages can be explained by the rise in recent years of the addressability of patients to specialized medical services, the establishing of clearer criteria and easier to use in diagnostic (McDonald criteria) and evolution of methods of brain investigation through imaging (MRI), including increased accessibility to these methods of investigation.
As assessed by the Hamilton rating scale for depression (HAM-D), depression severity was identified as severe in all subjects in the study group. The score obtained by these persons was higher than 26 points. Age appears to influence statistically significant the score on the HAM-D scale, so that the values closer to the limit of moderate depression are found in younger ages and higher scores are associated with persons over 30 years. A possible explanation for these findings may be that young people find inner resources and coping methods to diagnosis and neurological disease, thus reducing the severity of depressive symptoms.

Moderate and severe anxiety is encountered in almost 50% of subjects in the study. The total of people with any form of anxiety is about 70%. These data are consistent with those in the specialised literature which reported similar data on the prevalence of anxiety in people with multiple sclerosis (Chwastiak, Ehde, 2007 Korostil, Feinstein, 2007).
Nearly 60% of patients experience cognitive disorders of light and medium type with a MMSE score between 19 and 29 points, and 90% have mild cognitive dysfunction. These data are consistent with those in the literature on the epidemiology of cognitive impairment in multiple sclerosis, that shows percentages of 45% - 60% for multiple sclerosis patients with cognitive problems (Guimarães, José Sá, 2012).

A similar percentage of patients maintained the treatment for short periods of 1-2 months but also for periods of time exceeding 2 years. These data show that there are relatively equal percentages of those who decide to undergo treatment to achieve remission and of those who renounce antidepressant medication shortly after the symptoms improve.

When initiating antidepressant therapy, Duloxetine and Tianepetine were the most used drugs at a rate of more than 70% of patients. Following are Trazodone and then Mirtazapine, Escitalopram and Agomelatine, the last two having equal percentages.

During the course of the study, the administration of antidepressant treatment was found to show a distinctive dynamic, meaning changes occurring in therapeutic regimens for some patients. Duloxetine remains at the forefront of therapeutic choice, but with an increase in people where it was used. Tianepetine is the second choice for therapy of depression in multiple sclerosis, being used for the same number of patients as in the beginning of the study. Escitalopram surpasses trazodone as frequency of use and becomes in order the third.
drug chosen in therapy. For mirtazapine the percentage of its use remains the same. Agomelatine does not appear anymore as a treatment option at the end of the study. The novelty at the end of the study is the requirement of drug combination for achieving remission in three patients.

These data show differences when compared with data from specialised literature.

![Fig. 8.21. Dynamics of antidepressant therapy during the study](image)

**Fig. 8.21. Dynamics of antidepressant therapy during the study**

► Escitalopram – SSRI- they are the most widely used class of antidepressants for treatment of depression in multiple sclerosis (Pérez et al., 2015, Bayas et al., 2016); the safety and efficacy in major depression;
   – in my study ranks third in use
► Duloxetine – studied mainly for the antalgic effect in multiple sclerosis (Brown, Slee, 2013, Bayas et al., 2016)
   – the first therapeutic choice: multireceptorial profile, for the positive effects on depression symptoms and those of multiple sclerosis that often overlap with the depressive symptoms, such as fatigue and algical complaints. Its frequency of use in the study increased overall precisely because of its effectiveness in achieving remission and safety of administration.
► Tianeptine – the second therapeutic choice; the share of administration remained constant until the end of the study;
   – It is used successfully in therapy since 1960 (Racagni, 2008). However, the data from literature regarding the use of tianeptine in depression in multiple sclerosis, is scarce (Spedding, Gressens, 2008).
► Trazodone, mirtazapine and agomelatine – first study with them as efficient therapeutic options; the literature offers very little information
► Combinations of antidepressants – improvement/remission
   – first study; specialised literature lacks information

In terms of flare-ups during antidepressant treatment, the percentage of patients without flare-ups was higher than 80%. The antidepressant treatment does not correlate with an
increased number of flare-ups, on the contrary, it seems to have a protective role, as only 11.8% of patients manifested flare-ups.

The percentage of patients with depression receiving immunomodulatory therapy based on interferon represents a majority of 70%. The risk of depression in people receiving glatiramer acetate is reduced. These data are consistent with the literature which shows higher risk of psychiatric affections in people receiving treatment based on interferon beta (Feinstein et al, 2002, Chwastiak, Ehde, 2007 Hersh, Fox, 2014).

![Fig. 8.23. Structure of lot by administered immunomodulatory pharmaceutical product](image)

About 40% of studied patients with normal cognitive status have lower scores on the EDSS, from 1 to 4. The subjects with mild or medium cognitive dysfunction have an impairment level of absent to very serious.

![Fig. 8.21. Correlation between anxiety and the degree of disability](image)

Higher EDSS values are associated with a worsening degree of anxiety, although the cases studied are not sufficient to achieve statistical validation. The ways to adapt to the conditions created by the neurological illness progressively decrease together with an increase in the levels of anxiety and of development of various anxiety spectrum disorders (Sandford et al, 2000, Chwastiak, Ehde, 2007 Goleman, 2008).
Fig. 8.28. Structure of lot by associated psychiatric symptoms

- insomnia - present in about half of patients
< 20% of patients - symptoms such as hallucinations and delusions
~12% of all subjects manifest suicidal ideation; which figures lower than the data from literature, 22% (Feinstein, 1997, Kanner, 2005)
- panic attacks - present in approximately 35% of patients; prevalence of panic disorder in multiple sclerosis: 10% (Korostil, 2007)

Fig. 8.29. Correlation between age intervals and associated psychiatric symptoms

- a statistically significant correlation between age and panic attacks, which are present only in patients over 40 years (Chi-squared = 8.461, p = 0.037); the psychotic symptoms, insomnia and psychosomatisation are not influenced by age.
- the duration of development of multiple sclerosis affects in a statistically significant way insomnia, the panic attacks and the psychosomatisation
- insomnia installs itself in over 75% of patients having more than 5 years of multiple sclerosis development
- the risk of panic attacks is higher with increasing number of years of evolution of multiple sclerosis (Chi-squared = 8.461, p = 0.037)
- psychosomatisation (Chi-squared = 11.266, p = 0.010) - much more present in the first years after onset (1-5 years), and then after a longer duration of the disease, meaning more than 15 years.

Influence of antidepressant treatment on multiple sclerosis
- lower degree of disability, EDSS < 3, the most commonly used drugs are duloxetine and tianeptine. In patients with a higher degree of disability most frequently used = duloxetine, followed by escitalopram. Duloxetine = used regardless of the degree of disability.
- flare-ups – on reduced disability, EDSS < 3, no statistically significant correlation between flare-ups and EDSS
- flare-ups along antidepressant treatment with tianeptine and respectively, trazodone, no statistical correlation
- the absence of flare-ups - all drugs used in the study

Antidepressant therapy and demographics
Duloxetine is the most widely used pharmacological product in both social backgrounds of subjects, but more in the case of urban environment, for half of these patients. The second in dosing for people from both rural and urban areas is tianeptine, but twice the percentage for patients in rural areas. Trazodone was more frequently used in rural areas. Escitalopram and agomelatine were exclusively used in therapy for people residing in urban environment and mirtazapine was administered only to people in rural areas. Although these differences are obvious, no statistically significance was obtained.

![Fig. 8.33. Correlation between antidepressant treatment and the living environment](image)

Patients receiving therapy based on interferon (Avonex, Rebif, Betaferon), known for its potential to develop depressive symptoms, received the whole range of drugs used in the study as antidepressant therapy, but not agomelatine.

Individuals treated with Copaxone for multiple sclerosis received duloxetine and agomelatine as therapy for depression.
Lorazepam and alprazolam = the anxiolytics most used in association as antidepressive therapy, lorazepam = first place with a percentage of 35.3%. Following in frequency of administration are: bromazepam, nitrazepam and clonazepam, in similar percentages. Noticeable, the 23.5% representing associations of two anxiolytics.

- more patients in urban areas needed anxiolytics associated with the antidepressant therapy than those in rural areas
- all of the youngest patients required the antidepressant therapy to be associated with anxiolytics
- in the case of patients with therapy for modifying the evolution of the neurological disease, it was necessary to associate anxiolytics in a higher percentage than in the case for those with no treatment

Antidepressant therapy and remission
In the studied cases, the following are distinguished:
- 11 patients – complete remission of depressive symptoms (HAM-D < 7p)
- 4 patients – mild depression (HAM-D = 8 - 17p)
- 2 patients – moderate depression (HAM-D = 18- 25p)

Fig. 8.46. Structure of lot with regard to obtaining remission

- moderate depression - age between 31 and 40 years.
- half of people with mild depression are either young people between 31-40 years or older, over 50 years.
- complete remission was obtained for subjects in all age groups, mostly by people between 41 and 50 years, with a percentage of 36.4%.

Fig. 8.45. Correlation of age with remission

- antidepressant therapy for more than 2 years = complete remission
- moderate depression - the shortest duration of treatment for depression, 1-2 months
- mild depression - people with treatment under 24 months
- the duration of antidepressant therapy certainly has an influence on obtaining and maintaining complete remission
Fig. 8.47. Correlation of duration of antidepressant therapy with remission

The limitations of the study are caused by the reduced size of the available study group and therefore between certain parameters a statistically significant correlation could not be established, although the number and percentage differences were objectified. However, the data obtained in the study provides valuable information for both the clinician and medical research.

Conclusions

- the most common psychiatric disorders in multiple sclerosis depression, anxiety and cognitive impairment / dementia
- a higher proportion of patients with multiple sclerosis and depression come from urban areas
- depression in multiple sclerosis was found in greater proportion of patients aged over 30 years in rural areas
- lack of social and family support is a risk factor for depression and anxiety in multiple sclerosis
- Cardiovascular diseases are present only in persons with multiple sclerosis depression over 40 years
- depression in multiple sclerosis reduces intellectual and professional skills
- depression is more frequent in patients with multiple sclerosis at onset
- interferon-based immunomodulatory therapy can be a risk factor for development of depressive symptoms
- depression occurs more frequently in people with multiple sclerosis with lower invalidity score
- severity of depression is more emphasized in patients with multiple sclerosis for over 30 years
- age over 40 years is a risk factor for the occurrence of panic attacks
- evolution of multiple sclerosis for over 5 years increases the frequency of insomnia
the most used treatment for depression in multiple sclerosis is represented by duloxetine (serotonin and noradrenaline re-uptake inhibitor), tianeptine (modulator of serotonin release) and escitalopram (selective serotonin reuptake inhibitor)

efficient for remission of depressive symptoms are also trazodone, mirtazapine, tianeptine and agomelatine

duration of antidepressant therapy longer than one year is optimal for complete remission of depression symptoms

associations of two different classes of antidepressant showed greater efficiency to achieve remission than maintaining of therapy with a single drug

lorazepam and alprazolam are the most used anxiolytic in treatment of anxiety associated with depression in multiple sclerosis

antidepressant treatment may be a protective factor against attacks

therapy with memantine has proven effective in improving cognitive status and slowing deterioration

treatment options for depression, associated anxiety and cognitive disorders in multiple sclerosis are more varied and a far wider range of antidepressants, anxiolytics and pharmacological products for dementia can be used in medical practice

Selective Bibliography


Bartzokis G. Acetylcholinesterase inhibitors may improve myelin integrity. Biol Psychiatry 2007; 62: 294-301


Guimarães J., José Sá M. Cognitive Dysfunction in Multiple Sclerosis. Front Neurol. 2012; 3:74

Jones SM, Amtmann D. The relationship of age, function, and psychological distress in
Kanner AM. Depression in Neurological Disorders. Lundbeck Institute Cambridge Medical Communication Ltd, 2005


**ANNEX. LIST OF PUBLISHED WORKS**


**Communications at scientific events:**

- **Pavăl L.**, Achiţei G., Cognitive Impairment and Dementia in Multiple Sclerosis. World Psychiatric Association Congress, with the theme “Primary Care Mental Health: Innovation and Transdisciplinarity”, Bucharest, 24-27 june, 2015
- **Pavăl L.**, Tescu Grigorovici C., Management of Depression in Multiple Sclerosis. Congress "Innovation and excellence" of World Psychiatric Association, with theme "Primary health care, mental health and public health integration: the catalytic role of information and communication technology", Bucharest, 10-13 april, 2013
- **Pavăl L.**, Tescu Grigorovici C., Clinical features and therapeutic management in post-stroke depression, National Conference of Psychiatry with international participation "Records and values in contemporary psychiatry", Iaşi, 4-7 octombrie, 2012