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Brief communication

Psychopharmacology of patients with multiple sclerosis in Greece during the period 2017–2019

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ABSTRACT

Multiple Sclerosis (MS) is highly comorbid with mental disorders in any disease stage, while psychiatric manifestations may precede the onset of neurological symptoms as well as diagnosis. Neuropsychiatric comorbidities are associated with an elevated risk of MS disability progression, and therefore, people with multiple sclerosis (PwMS) with psychiatric comorbidities often experience a significantly lower functional status, perform worse in objective neuropsychological assessment, are less likely to adhere to pharmacological treatment, and exhibit higher levels of disruption of their supportive social environment as compared with "non-psychiatric" PwMS. The present study aims to estimate the nationwide use of psychopharmacological agents by PwMS in Greece. Prescription records of the nationwide digital prescription database were analyzed, in order to identify PwMS that have received prescriptions of an antipsychotic, an antidepressant, an anxiolytic or a psychostimulant during a 2-year study period. Pseudo-anonymized prescription records of PwMS (n=21218) were extracted from the Greek nationwide prescription database, dating from June 2017 to May 2019. According to this national level study, psychopharmacological agents are frequently prescribed in PwMS. Antidepressants were prescribed in 36.1% of the study sample, followed by anxiolytics (16.23%), psychostimulants (4.97%) and antipsychotics (3.76%). The proportion of patients under treatment with these agents was increasing with age. Selective serotonin reuptake inhibitors, second generation antipsychotics and benzodiazepines were the most often prescribed agents in each drug category and especially in younger age groups, possibly indicating a better efficacy/side-effect equilibrium, while modafinil was the only psychostimulant prescribed aiming to ameliorate levels of fatigue. A pharmacological preference for antidepressants and psychostimulants was observed in the 40-60 age group ($p = 0.02$), while antipsychotics and anxiolytics were more frequently prescribed in the >60 age group ($p<0.001$). Serotonin-norepinephrine reuptake inhibitors were mostly prescribed within the 40-60 age-group. Benzodiazepines were less favored among the >60 age-group. This study highlights the increased prevalence of mental disorders in this patient group. Adequate treatment and monitoring of psychiatric symptomatology, may improve long-term outcomes of the disease, however caution is needed regarding potential drug interactions and side effects.

KEYWORDS: Multiple sclerosis, psychopharmacology, benzodiazepines, antidepressants, antipsychotics, psychostimulants.

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Introduction

Multiple Sclerosis (MS) is highly comorbid with mental disorders.[1] Psychiatric manifestations are occasionally noted to precede the onset of neurological symptoms and MS diagnosis,[2,3] while acute psychiatric symptoms have been reported as signs of MS-related inflammatory events.[4,5] Psychiatric symptomatology may be present in any disease stage and negatively affects daily functioning of people with MS (PwMS).[6]

Whether psychiatric manifestations in MS are directly attributed to autoimmune mechanisms or constitute common comorbidities is still a matter of debate. Various researchers suggest an association between depression, anxiety and MS related brain inflammation. Possible pathogenesis involves the localized production of cytokines in the brain, which contribute to neuronal and oligodendral damage, modulate the serotonergic and noradrenergic circuits and activate responses of the neuroendocrine system.[7] Similarly, an autoimmune driven alteration of synaptic transmission within dopaminergic and glutamatergic pathways, leading to a disequilibrium between inhibitory-excitatory mechanisms, has been proposed as a mechanism of psychotic symptoms in MS.[8] Furthermore, hypothalamic-pituitary-adrenal (HPA) axis dysfunction evident by increased cerebrospinal fluid (CSF) levels is common in multiple sclerosis and associated with increased severity of MS.[9,10] Leukocyte-induced neuronal damage to the hypothalamus or a secondary effect of a global stress response to disease are suspected, but its exact underlying mechanism has not yet been confirmed.[9,10] In addition, the biopsychosocial medical model is being considered for pathogenesis, development, symptomatology and exacerbations in the course of MS.[11] Neuroimmunological studies have detected alterations of clinical significance in lymphocytes and cytokines of PwMS under different pressures, while most evidence-based studies have indicated that chronic psychosocial pressures such as interpersonal conflicts, lack of social support, grief, anxiety and depression are closely intertwined with relapses of MS and have been also identified as risk factors for clinical worsening including psychiatric symptomatology. Therefore, all in all, autoimmunity, dysfunction of the hypothalamic–pituitary–adrenal axis and perceived psychosocial stressors have been suggested as possible underlying mechanisms triggering MS related psychiatric manifestations.[9–11] Fatigue, a commonly reported symptom among PwMS, is also attributed to autoimmune mechanisms. The proposed fatigue generation model includes the effect of pro-inflammatory cytokines in homeostatic and interoperable centers within cortico-striato-thalamo-cortical networks, resulting in their dysfunction.[12]

Immunomodulatory agents and immunosuppressants commonly used to treat PwMS do not have an impact on psychiatric manifestations; therefore, treatment of such symptoms includes non-pharmacological approaches and psychopharmacological agents (PAs).[13] Throughout literature it is reported that the use of psychiatric medications specifically in this population is poorly studied, and therefore, no high-quality data exists from this particular population. General principles are often reported, such as avoiding strong sedatives, anticholinergics, or drugs that may cause orthostatic hypotension.[14] Interestingly, various studies have suggested a potential neuroprotective and anti-inflammatory role of some antidepressants.[15,16] Treatment for the range of mood disorders has been reported to include primarily selective serotonin reuptake inhibitors (SSRIs), as most well-tolerated antidepressants, as first-line therapy, while tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are intended for second-line therapies.[17] Regarding fatigue, off-label treatments, including the psychostimulant modafinil, are often prescribed to PwMS in order to ameliorate subjective feeling of tiredness and exhaustion, although their effectiveness is still questionable.[18]

In this study, we aimed to investigate frequency and trends regarding the prescribed PAs in Greek PwMS, using administrative data of the nationwide digital prescription database and to enlighten which psychopharmacological substances seem to be mostly used in the treatment of PwMS psychiatric symptoms. The study was performed according to the ethical standards of the Declaration of Helsinki and was approved by the Greek Ministry of Health, in accordance with the national legislation on Data Protection (32129/24-04-2019).

Material and Method

Data collection

Pseudo anonymized prescription records of PwMS (n=21218; F:M ratio 1.93:1; 65.8% female PwMS) were extracted from the Greek nationwide prescription database, dating from June 1, 2017, to May 31, 2019. The identification of PwMS and the methodology used have been previously described.[19] In this study, we extended the analysis, in order to identify those PwMS who have received prescriptions of an antidepressant, anxiolytic, antipsychotic or psychostimulant, using the same methodology, during this study period. According to the national legislation on Data Protection, participants informed consent was not applicable for this study.

Limitations

According to the studied database, analysis was performed in relation to pharmacological substances. In the majority of instances, the only ICD-10 classification code used in the electronic prescription system is code "G35," standing for MS, and thus, it may not always be clear why each separate medication is prescribed (symptomatically). Specifically, antiepileptic drugs may be prescribed to help PwMS as for the symptoms of neuropathic pain, trigeminal neuralgia, epilepsy, migraine, anxiety and/or affective disorders as mood stabilizers. Therefore, an analysis based on ICD-10 codes would be uncertain and inaccurate. Due to all aforementioned reasons, antiepileptics were also excluded from the analysis.

Other qualitative variables, such as the degree of disability, the type and the duration of the disease, are data that cannot be extracted from the prescribing system. Furthermore, the analysis was not performed on the basis of gender as it was based on primary data extracted from the initial MS prevalence study for northern Greece not including the gender of each anonymized patient.

Statistical analysis

Relationships between the use of specific psychotropic drug classes and age variables of PwMS were examined, classified both in terms of symptomatic use and distinct pharmacological action. Statistical significance was tested with Fisher's exact test and Mann-Whitney U test. All tests were performed in IBM SPSS software 25.0, were two-tailed, and the significance level was set at $p<0.05$.

Results

The study sample consisted of 21218 PwMS (65.8% females, mean age 46.6±13.5). PAs prescribed to PwMS were mainly agents commonly used for disorders of the affective rather than psychotic spectrum (ratio 15.3:1, $p<0.001$). Antidepressants were the most common PAs administered (36.10%) and were prescribed 2.22 times more frequently than anxiolytics (16.23%), which in turn were prescribed 3.27 times more frequently than psychostimulants (4.97%), which were in turn prescribed 1.32 times more frequently than antipsychotics (3.76%). A statistically significant difference occurred in the comparison of all classes of PAs with each other (Fisher's exact; $p<0.01$) with respect to the overall frequency of use in the sample group of PwMS (table 1).

Identified cases were further divided into 4 age groups (under 18, 18–39, 40–60, over 60). Although antidepressants were the most common PAs administered followed by anxiolytics, psychostimulants, and antipsychotics across all age groups (figure 1), certain pharmacological concentration shifts were noted by age-group, and thus, significant differences emerged between PAs in relation to age. Among PwMS under 18 years of age, although at very low levels as expected, and among PwMS between 18-39 years of age, all prescriptions of PAs followed equivalent patterns without significant differences. Higher concentrations were noted for psychostimulants and antidepressants in the 40-60 age group, as compared to the other psychopharmacological agents (psychostimulants: antipsychotics ratio

Table 1. Number and percentage of people with multiple sclerosis under treatment with psychopharmacological agents in Greece.

	Age group				
Drug classification	<18 n: 133	18-39 n: 6,342	40–60 n: 11,244	>60 n: 3,499	Overall n: 21,218
Antipsychotics					
Typical	0	11	42	26	79
Atypical	0	105	400	214	719
Total	0	116	442	240	798
Antidepressants					
SSRIs	4	707	2800	1058	4569
SNRIs	0	215	1208	447	1870
Other	2	173	740	306	1221
Total	6	1095	4748	1811	7660
Anxiolytics					
Benzodiazepines	1	396	1758	737	2892
Other	0	75	300	177	552
Total	1	471	2058	914	3444
Psychostimulants	0	147	671	237	1055

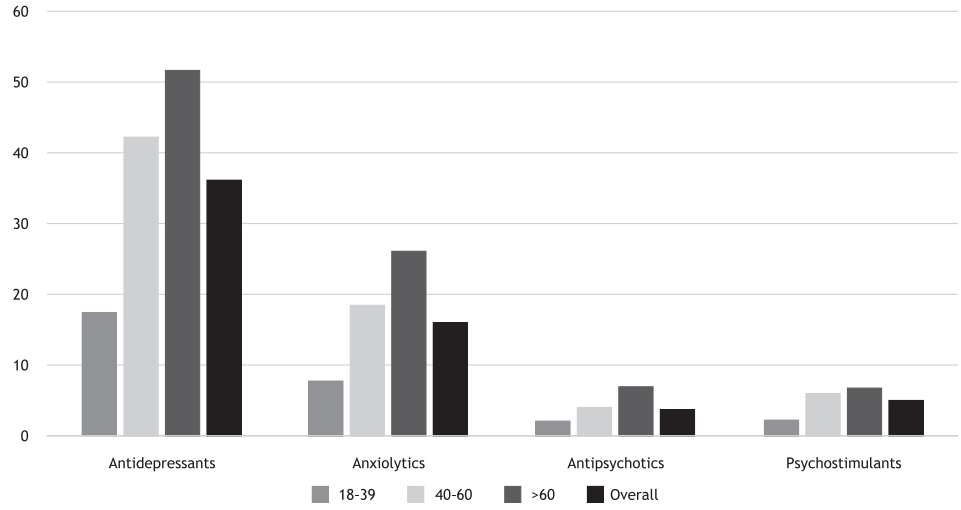

Figure 1. Percentage of Greek people with multiple sclerosis under treatment with psychopharmacological agents, by age group.

1.15:1, p<0.001; antidepressants: antipsychotics ratio 1.12:1, p<0.001; anxiolytics: antipsychotics ratio 1.08:1, p=0.02). On the contrary, among patients of the >60 age-group, a pharmacological spectrum shift was noted towards antipsychotics and anxiolytics (antipsychotics: psychostimulants ratio 1.34:1, p<0.001; anxiolytics: psychostimulants ratio 1.18:1, p<0.01).

Regarding antidepressants, most patients in all age groups were treated with selective serotonin reuptake inhibitors (SSRIs, 21.53%), followed by serotonin–norepinephrine reuptake inhibitors (SNRIs, 8.81%, SSRIs: SNRIs ratio 2.44: 1, p<0.001), followed by other antidepressants such as tricyclic antidepressants and noradrenergic and specific serotonergic antidepressants (SSRIs: "Others" ratio, 3.74: 1, p<0.001; SNRI: "Others" ratio, 1.53: 1, p<0.001). With respect to anxiolytic treatment, the majority of PwMS regardless of age group were treated with benzodiazepines (13.63%) as compared to other anxiolytics such as buspirone (2.60%; ratio 5.24:1, p<0.001). Regarding antipsychotic medications, second generation antipsychotics (SGAs) were more frequently prescribed than first-generation antipsychotics (3.39% vs 0.37%; ratio 2.57:1, p<0.001). About 5% of PwMS in this study were prescribed a neurostimulant (modafinil), with occurrence rates increasing with age.

Supplementary material is available in the present article, within which the reader has the opportunity to view a table representation of statistical data extracted from all variable comparisons, the percentage representing each numerical value within the sample, the ratio of the compared sets and the statistical significance of each comparison.

Discussion

The present study has yielded a considerable rate of PwMS treated with PAs, increasing proportionally with age, a finding consistent with the relevant literature.[18] Antidepressants and anxiolytics were the most common PAs, confirming previous studies.[13,20,21] In the 40–60 age group, a pharmacological preference was noted for treatments with excitatory action aiming more at mobilization, improvement of mood and functionality, indicating that the majority of PwMS in this group may experience psychomotor retardation (depressive symptoms). Conversely, in the over-60 age group, a shift to treatments with more sedative, hypnogogic and anxiolytic action was observed, aiming to treat psychomotor anxiety, irritability or agitation. SSRIs, benzodiazepines, and SGAs were preferred in each PA category respectively, possibly indicating a better efficacy – side-effect equilibrium.[22–24] According to this study results, psychostimulants are prescribed by Greek physicians in a small though considerable amount of PwMS (in comparison to the other pharmacological categories), as an attempt to ameliorate levels of fatigue.

Neuropsychiatric comorbidities are associated with elevated risk of MS disability progression, while they may implicate the results of clinical trials.[25] PwMS with psychiatric comorbidities perform worse in objective neuropsychological assessment[26] and are less likely to adhere to pharmacological treatment.[3] They often experience a significantly lower functional status and higher levels of disruption of their supportive social environment[27] as compared with "non-psychiatric" PwMS. Consequently, their employment status is worse[28] and

the overall quality of life is significantly lower,[29] even when factors such as levels of disability and fatigue are controlled. In addition, high levels of stress and anxiety have been associated with increased occurrence of relapses and infections in PwMS.[30] Therefore, a multidimensional approach and adequate pharmacological treatment of psychiatric symptomatology is suggested, in order to improve long term disease outcomes and patients' overall quality of life.[6]

PAs are widely used in order to treat effectively psychiatric disturbances of PwMS. Although generally safe, caution may be needed, when they are administered in PwMS under immunomodulatory treatment. For instance, teriflunomide used as a first-line treatment in MS may reduce the exposure of agents metabolized by CYP1A2 such as duloxetine.[31] Clinicians' alertness may be needed when PAs that potentially induce QT interval prolongation are administered with concomitant immunomodulators, such as fingolimod, that may also disturb heart rhythm.[32] Furthermore, benzodiazepines, anticholinergics and antiepileptics may induce or exacerbate cognitive impairment often seen in MS,[33] while interferons and corticosteroid therapies have been linked with a possible worsening of a pre-existing affective disorder.[34,35] Therefore, monitoring and dose adjustments may be needed when prescribing PAs in PwMS.

This study was performed on the basis of administrative data of a nationwide prescription database, since, up to now, to the authors' knowledge, a nationwide registry for PwMS in Greece does not exist. Consequently, correlations between the use of PAs and levels of MS related disability, disease type and duration could not be performed. Comorbid disease coding misclassifications by physicians may lead to inaccurate results, when administrative data are used for epidemiological studies.[36] Thus, in this study, we did not use the ICD-10 classification in order to explore psychiatric comorbidities of PwMS. Instead, we performed our analysis on the basis of the active substances prescribed. Still, the findings of this study are in accordance with previous published studies regarding comorbid conditions in MS, where neuropsychiatric conditions such as depression and anxiety, are frequently observed amongst PwMS. Antiepileptics that are also used as mood stabilizers were excluded from the analysis, since it is not always clear whether they are prescribed for epileptiform abnormalities or affective episodes through this particular database (due to the lack of clear diagnosis recording). Antiepileptics are often prescribed in PwMS as symptomatic treatments for multiple sclerosis for numbness, atypical headache, neuropathic pain, trigeminal neuralgia, and mood disorders. It is worth noting that epilepsy is 3.5% and bipolar disorder (BD) 8.4% co-morbid with MS. In addition, BD and epilepsy also show a comorbidity of 6.2%.[37–39]

Conclusion

The present national level study highlights the frequent use of PAs in PwMS. psychiatric disorders seem to commonly occur during this chronic disease. Despite numerous studies, the pathogenesis of these disorders remains unclear and has not yet been identified as an indicator of disease, comorbidity or both. Nevertheless, their diagnosis and adequate treatment may contribute to an optimal disease course.

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References

1. Ghaffar O, Feinstein A. The neuropsychiatry of multiple sclerosis: a review of recent developments. *Curr Opin Psychiatry* 2007, 20:278–285, doi: 10.1097/YCO.0b013e3280eb10d7
2. Yusuf FLA, Ng BC, Wijnands JMA, Kingwell E, Marrie RA, Tremlett H. A systematic review of morbidities suggestive of the multiple sclerosis prodrome. *Expert Rev Neurother* 2020,20:799–819, doi: 10.1080/14737175.2020.1746645
3. Labiano-Fontcuberta A, Aladro Y, Martínez-Ginés ML, Ayuso L, Mitchell AJ, Puertas V et al. Psychiatric disturbances in radiologically isolated syndrome. *J Psychiatr Res* 2015, 68:309–315, doi: 10.1016/j.jpsychires.2015.05.008
4. Nandy A, Nielsen M, Hilt C, Mogensen PH, Yavarian Y. A case report revealing acute onset psychosis and cognitive impairment as primary manifestation in relapsing-remitting multiple sclerosis. *Clin Case Rep* 2020, 8:833–836, https://doi.org/10.1002/ccr3.2781
5. Hotier S, Maltete D, Bourre B, Jegouzo X, Bourgeois V, Guillin O. A manic episode with psychotic features improved by methylprednisolone in a patient with multiple sclerosis. *Gen Hosp Psychiatry* 201,37: 621.e1–2, doi: 10.1016/j.genhosppsych.2015.07.002
6. Haussleiter IS, Brüne M, Juckel G. Psychopathology in multiple sclerosis: diagnosis, prevalence and treatment. *Ther Adv Neurol Disord* 2009, 2:13–29, doi: 10.1177/1756285608100325
7. Pucak ML, Carroll KA, Kerr DA, Kaplin AI. Neuropsychiatric manifestations of depression in multiple sclerosis: neuroinflammatory, neuroendocrine, and neurotrophic mechanisms in the pathogenesis of immune-mediated depression. *Dialogues Clin Neurosci* 2007, 9:125–139, doi: 10.31887/DCNS.2007.9.2/mpucak.
8. Jeppesen R, Benros ME. Autoimmune Diseases and Psychotic Disorders. *Front Psychiatry* 2019, 10:131, doi: 10.3389/fpsyt.2019.00131
9. Paparrigopoulos T, Ferentinos P, Kouzoupis A, Koutsis G, Papadimitriou GN. The neuropsychiatry of multiple sclerosis: focus on disorders of mood, affect and behaviour. *Int Rev Psychiatry* 2010, 22:14–21, doi: 10.3109/09540261003589323

10. Burfeind KG, Yadav V, Marks DL. Hypothalamic Dysfunction and Multiple Sclerosis: Implications for Fatigue and Weight Dysregulation. *Curr Neurol Neurosci Rep* 2016, 16:98, doi:10.1007/s11910-016-0700-3
11. Liu XJ, Ye HX, Li WP, Dai R, Chen D, Jin M. Relationship between psychosocial factors and onset of multiple sclerosis. *Eur Neurol* 2009, 62:130–136, doi: 10.1159/000226428
12. Hanken K, Eling P, Hildebrandt H. The representation of inflammatory signals in the brain - a model for subjective fatigue in multiple sclerosis. *Front Neurol* 2014, 5:264, doi: 10.3389/fneur.2014.00264
13. Murphy R, O'Donoghue S, Counihan T, McDonald C, Calabresi PA, Ahmed MA et al. Neuropsychiatric syndromes of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2017, 88:697–708, doi: 10.1136/jnnp-2016-315367
14. Patten SB. Psychopharmacology of multiple sclerosis. *Handb Clin Neurol* 2019,165:309–315, doi: 10.1016/B978-0-444-64012-3.00018-6
15. Sales MC, Kasahara TM, Sacramento PM, Rossi ÁD, Cafasso MOSD, Oyamada HAA et al. Selective serotonin reuptake inhibitor attenuates the hyperresponsiveness of TLR2+ and TLR4+ Th17/Tc17-like cells in multiple sclerosis patients with major depression. *Immunology* 2020, doi: 10.1111/imm.13281
16. Grech LB, Butler E, Stuckey S, Hester R. Neuroprotective Benefits of Antidepressants in Multiple Sclerosis: Are We Missing the Mark? *J Neuropsychiatry Clin Neurosci* 2019, 31:289–297, doi: 10.1176/appi.neuropsych.18070164
17. Pérez LP, González RS, Lázaro EB. Treatment of mood disorders in multiple sclerosis. *Curr Treat Options Neurol* 2015, 17:323, doi: 10.1007/s11940-014-0323-4
18. Yang TT, Wang L, Deng XY, Yu G. Pharmacological treatments for fatigue in patients with multiple sclerosis: A systematic review and meta-analysis. *J Neurol Sci* 2017, 380:256–261, doi: 10.1016/j.jns.2017.07.042
19. Bakirtzis C, Grigoriadou E, Boziki MK, Kesidou E, Siafis S, Moysiadis T, et al. The Administrative Prevalence of Multiple Sclerosis in Greece on the Basis of a Nationwide Prescription Database. *Front Neurol* 2020, 11:1012, doi: 10.3389/fneur.2020.01012
20. Marrie RA. Comorbidity in multiple sclerosis: implications for patient care. *Nat Rev Neurol* 2017, 13:375-382, doi: 10.1038/nrneurol.2017.33
21. Panda SP, Das RC, Srivastava K, Ratnam A, Sharma N. Psychiatric comorbidity in multiple sclerosis. *Neurol Neurochir Pol* 2018, 52:704–709, doi: 10.1016/j.pjnns.2018.09.003
22. Zhang JP, Gallego JA, Robinson DG, Malhotra AK, Kane JM, Correll CU. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. *Int J Neuropsychopharmacol* 2013, 16:1205–2018, doi: 10.1017/S1461145712001277
23. Santarsieri D, Schwartz TL. Antidepressant efficacy and side-effect burden: a quick guide for clinicians. *Drugs Context* 2015, 4:212290, doi: 10.7573/dic.212290
24. Guina J, Merrill B. Benzodiazepines I: Upping the Care on Downers: The Evidence of Risks, Benefits and Alternatives. *J Clin Med* 2018, 7:17, doi: 10.7573/dic.212290
25. McKay KA, Tremlett H, Fisk JD, Zhang T, Patten SB, Kastrukoff L, Campbell T, Marrie RA; CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis. Psychiatric comorbidity is associated with disability progression in multiple sclerosis. *Neurology* 2018, 90:e1316–e1323, doi: 10.1212/WNL.0000000000005302
26. Julian L, Merluzzi NM, Mohr DC. The relationship among depression, subjective cognitive impairment, and neuropsychological performance in MS. *Mult Scler* 2007, 13:81–86, doi: 10.1177/1352458506070255
27. Gilchrist AC, Creed FH. Depression, cognitive impairment and social stress in multiple sclerosis. *J Psychosom Res* 1994, 38:193–201, doi: 10.1016/ 0022-3999(94)90115-5
28. Smith MM, Arnett PA. Factors related to employment status changes in individuals with multiple sclerosis. *Mult Scler* 2005, 11:602–609, doi: 10.1191/1352458505ms1204oa
29. Amato MP, Ponziani G, Rossi F, Liedl CL, Stefanile C, Rossi L. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Mult Scler* 2001, 7:340-4, doi: 10.1177/135245850100700511
30. Potagas C, Mitsonis C, Watier L, Dellatolas G, Retziou A, Mitropoulos P et al. Influence of anxiety and reported stressful life events on relapses in multiple sclerosis: a prospective study. *Mult Scler* 2008, 14:1262–1268, doi: 10.1177/1352458508095331
31. Aubagio, INN – teriflunomide. Summary of product characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/aubagio-epar-product-information_en.pdf
32. Gilenya, INN – fingolimod Summary of product characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/gilenya-epar-product-information_en.pdf
33. Bakirtzis C, Ioannidis P, Messinis L, Nasios G, Konstantinopoulou E, Papathanasopoulos P et al. The Rationale for Monitoring Cognitive Function in Multiple Sclerosis: Practical Issues for Clinicians. *Open Neurol J* 2018, 12:31–40, doi: 10.2174/1874205X01812010031
34. Pinto EF, Andrade C. Interferon-Related Depression: A Primer on Mechanisms, Treatment, and Prevention of a Common Clinical Problem. *Curr Neuropharmacol* 2016,14:743–748, doi: 10.2174/1570159X14666160106155129
35. Patten SB. Exogenous corticosteroids and major depression in the general population. *J Psychosom Res* 2000, 49:447–449, doi: 10.1016/s0022-3999(00)00187-2
36. Högg T, Zhao Y, Gustafson P, Petkau J, Fisk J, Marrie RA et al. Adjusting for differential misclassification in matched case-control studies utilizing health administrative data. *Stat Med* 2019, 38:3669–3681, https://doi.org/10.1002/sim.8203
37. Burman J, Zelano J. Epilepsy in multiple sclerosis: A nationwide population-based register study. *Neurology* 2017, 89:2462–2468, doi: 10.1212/WNL.0000000000004740.
38. Joseph B, Nandakumar AL, Ahmed AT, Gopal N, Murad MH, Frye MA et al. Prevalence of bipolar disorder in multiple sclerosis: a systematic review and meta-analysis. Evid Based
39. Lu E, Pyatka N, Burant CJ, Sajatovic M. Systematic Literature Review of Psychiatric Comorbidities in Adults with Epilepsy. *J Clin Neurol* 2021, 17:176–186, doi: 10.3988/jcn.2021.17.2.176

Σύντομο άρθρο

Ψυχοφαρμακολογία των ασθενών με πολλαπλή σκλήρυνση στην Ελλάδα κατά την περίοδο 2017–2019

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ΙΣΤΟΡΙΚΟ ΑΡΘΡΟΥ: Παραλήφθηκε 13 Μαΐου 2021/Αναθεωρήθηκε 9 Αυγούστου 2021/Δημοσιεύθηκε Διαδικτυακά 21 Φεβρουαρίου 2022

ΠΕΡΙΛΗΨΗ

Η πολλαπλή σκλήρυνση παρουσιάζει υψηλή συννοσηρότητα με ψυχικές διαταραχές σε οποιοδήποτε στάδιο της νόσου, ενώ οι ψυχιατρικές εκδηλώσεις μπορεί ακόμη και να προηγούνται της εμφάνισης οποιασδήποτε νευρολογικής συμπτωματολογίας και συνεπακόλουθα και της διάγνωσης. Τα νευροψυχιατρικά συνοδά νοσήματα παρουσιάζουν, επίσης, συσχέτιση με αυξημένο κίνδυνο εξέλιξης της αναπηρίας, και ως εκ τούτου, τα άτομα αυτά συχνά παρουσιάζουν σημαντικά χαμηλότερο επίπεδο λειτουργικότητας, έχουν χαμηλότερη απόδοση στη νευροψυχολογική κλινική αξιολόγηση, είναι λιγότερο πιθανό να συμμορφώνονται με τη φαρμακοθεραπεία και επιπλέον παρουσιάζουν σημαντικά υψηλότερα επίπεδα διαταραχής του υποστηρικτικού τους κοινωνικού περιβάλλοντος σε σύγκριση με τους «μη ψυχιατρικούς» ανθρώπους με πολλαπλή σκλήρυνση. Η μελέτη στοχεύει στην εκτίμηση της εθνικής χρήσης ψυχοφαρμακολογικών παραγόντων από άτομα με πολλαπλή σκλήρυνση στον ελληνικό πληθυσμό. Αναλύθηκαν τα αρχεία της εθνικής ψηφιακής βάσης δεδομένων συνταγογράφησης, προκειμένου να εντοπιστούν άτομα με σκλήρυνση κατά πλάκας που έχουν συνταγογραφηθεί αντιψυχωσικές, αντικαταθλιπτικές, αγχολυτικές ή ψυχοδιεγερτικές θεραπείες κατά τη διετή διάρκεια της μελέτης. Ανωνυμοποιημένα αρχεία ηλετρονικής συνταγογράφησης ασθενών με πολλαπλή σκλήρυνση (n=21218) εξήχθησαν από τη βάση δεδομένων ΗΔΙΚΑ σε εθνικό επίπεδο, από τον Ιούνιο του 2017 έως τον Μάιο του 2019. Σύμφωνα με αυτήν τη μελέτη σε εθνικό επίπεδο, οι ψυχοφαρμακολογικοί παράγοντες συνταγογραφούνται συχνά σε άτομα με σκλήρυνση κατά πλάκας. Αντικαταθλιπτική αγωγή συνταγογραφήθηκε στο 36,1% του δείγματος μελέτης, ακολουθούμενο από αγχολυτικά (16,23%), ψυχοδιεγερτικά (4,97%) και αντιψυχωσικά (3,76%). Το ποσοστό των ασθενών που έλαβαν θεραπεία με αυτούς τους παράγοντες παρουσίασε αύξηση ανάλογη με την ηλικία. Οι εκλεκτικοί αναστολείς επαναπρόσληψης σεροτονίνης, τα αντιψυχωσικά δεύτερης γενιάς και οι βενζοδιαζεπίνες ήταν οι πιο συχνά συνταγογραφούμενοι παράγοντες σε κάθε κατηγορία φαρμάκων, και ειδικά σε νεότερες ηλικιακές ομάδες, υποδεικνύοντας πιθανώς καλύτερη ισορροπία αποτελεσματικότητας / ανεπιθύμητων δράσεων, ενώ η μονταφινίλη ήταν το μόνο ψυχοδιεγερτικό που συνταγογραφήθηκε στοχεύοντας τη βελτίωση των επιπέδων αισθήματος κόπωσης. Μια φαρμακολογική προτίμηση για αντικαταθλιπτικά και ψυχοδιεγερτικά παρατηρήθηκε στην ηλικιακή ομάδα 40-60 ($p = 0,02$), ενώ τα αντιψυχωσικά και τα αγχολυτικά έδειξαν υψηλότερη προτίμηση στην ηλικιακή ομάδα > 60 ($p <0,001$). Αυτή η μελέτη υπογραμμίζει τον αυξημένο επιπολασμό ψυχικών διαταραχών σε αυτήν την ομάδα ασθενών. Η επαρκής θεραπεία και παρακολούθηση της ψυχιατρικής συμπτωματολογίας, μπορεί να βελτιώσει τα μακροπρόθεσμα αποτελέσματα της νόσου, ωστόσο απαιτείται προσοχή όσον αφορά στις πιθανές αλληλεπιδράσεις και ανεπιθύμητες δράσεις.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Σκλήρυνση κατά πλάκας, πολλαπλή σκλήρυνση, ψυχοφαρμακολογία, βενζοδιαζεπίνες, αντικαταθλιπτικά, αντιψυχωσικά, ψυχοδιεγερτικά.

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