Procognitive Effects of Immunomodulatory, Anticholinergic and Glutamatergic Medication in Multiple Sclerosis

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Multiple sclerosis is the most common neurological disorder present in young population, with neurological and psychiatric disabilities. Cognitive dysfunction can occur with the onset of multiple sclerosis. Therefore, these disorders are difficult to detect early, especially when neurological disability therapy outweigh the mental state. Various pharmacological agents have been studied in order to control the cognitive impairment in multiple sclerosis. Chemical substances with immunomodulatory effect such as interferon-beta and glatiramer acetate are the first indicated in therapy. Their purpose is to reduce organic brain damage by modulating the immune response. Specific pharmacological agents with procognitive action, used in dementia treatment, correct the neuro-bio-chemical deficit that is the consequence of neuronal dysfunction and degradation that appears in multiple sclerosis evolution. Procognitive effect of these medicines stems from the anticholinergic and glutamatergic action which increases levels of acetylcholine in the brain and moderates glutamate activity reducing oxidative stress. This paper presents an analysis of studies that highlight the procognitive effects of immunomodulatory, anticholinergic and glutamatergic pharmacological agents in multiple sclerosis.

Keywords: interferon-beta, glatiramer acetate, acetylcholine, procognitive effect, multiple sclerosis

Pharmacological products with procognitive effect represented constantly a challenge for researchers, chemists and clinical physician. Neuro-bio chemical mechanisms of dementia have been less studied and are incompletely understood. However, in the recent years, they have been developed and used in medical practice several chemical substances with role of preservation and improvement of cognitive status.

The importance of these pharmacological products is revealed by the population burden of dementia that show an increase from 76 million people in 2030 and 145 million in 2015, while in 2015, 47 million people had a type of dementia, as evidenced the WHO statistics [1].

Cognitive dysfunction in people with multiple sclerosis generates a potential of disability, and pharmacological substances useful in therapy is an area of study recently entered in specialists attention [2].

The severity of this early onset dementia is highlighted by epidemiological data: between 45 - 60% of people with multiple sclerosis have cognitive problems [3]. This pathology represents 4.3% of all dementias and 1.4% of all cases of dementia in young age [4,5].

The biochemical substrate of cognitive impairment in multiple sclerosis is represented by a deficit of acetylcholine and glutamate pathway hyperactivation, along with an autoimmune mechanism. At organic cerebral level, they are utmost the consequence of primary lesions of axonal degeneration and neuronal loss, features itself disease progression [6]. As a consequence of the decrease of brain volume is ascertained cerebral atrophy that can develop up to severe stage of dementia multisclerotica [6,7].

Immunomodulatory pharmacological agents represents the first line of intervention and therapy of cognitive disorders in multiple sclerosis. Then intervenes dementia with specific chemical products in order to correct and to modulate the neuro-bio-chemical deficit.

Interferon beta and glatiramer acetate

The pharmaceutical products of interferon beta or glatiramer acetate represent the disease-modifying therapy in multiple sclerosis. Reducing the action of inflammation and development of demyelinating and of degenerative lesions at cerebral level can improve cognitive function [6].

Interferon beta

Medications for multiple sclerosis based on interferon beta represent recombinant product containing an amino acid sequence identical to that of interferon beta-1a. The action mechanism of interferon beta is less known. A possible effect is the one mediated by adenosine which has anti-inflammatory and neuroprotective activity. Thus, interferon beta delays neuronal damage and keeps longer the optimal level of brain acetylcholine preserving cognitive function [8,9].

The effects of interferon beta-1b on cognitive performance was evaluated in the course of time, in several studies [2]. Worldwide, these are few as number and with small lots of patients, being a niche area biochemical, pharmacological and medical.

Pliskin NH. Investigates interferon beta in 1996, in a study with 30 patients diagnosed with relapsing-remitting multiple sclerosis. Final results have revealed an improvement of some cognitive parameters such as visual memory and reading words in all patients who received immunomodulatory therapy [10].

Gerschlager W. established that interferon beta-1b administered subcutaneously determine cognitive improvement in all patients with relapsing-remitting multiple sclerosis and receiving treatment. His study was...
conducted without a group of patients without immunomodulatory treatment, so the researchers could not perform a comparative analysis to In 2000, Fischer J. states that interferon beta-1a significantly improves memory and processing information ability. The study group included a large number of subjects, 276 people, of which approximately half of them received intramuscular interferon beta-1a and the other half received placebo [12].

Glatiramer acetate
Glatiramer acetate is a polypeptide based on amino acid sequence of a myelin protein. The action mechanism of glatiramer acetate is to modulate the immune response by affecting the properties of antigen presenting cells, such as monocytes and dendritic cells. These cells suppress brain inflammatory process. Glatiramer acetate increases the synthesis of neurotrophic factors and anti-inflammatory cytokines. This pharmacological product preserves the integrity of brain myelin and neurons, thereby preventing acetylcholine deficit, with procognitive effects [13].

The relationship between glatiramer acetate and cognitive disorders is still uncertain. Weinstein A. found higher cognitive performance relative to the original evaluation in the group who received glatiramer acetate and the placebo group, in his 1999 study. A follow-up study after 10 years of patients remaining from the original one, were achieved significant scores in the group who received glatiramer acetate [14].

Specific pharmaceutical products for dementia treatment
The following classes of pharmacological substances are used in the treatment of cognitive disorders and dementia [5]:
- acetylcholinesterase inhibitors: donepezil, galantamine - acetylcholinesterase and butyrylcholinesterase inhibitors: rivastigmine - NMDA receptor antagonists (N-methyl-D-aspartate): memantine

All listed and described pharmacological substances are approved, used and have demonstrated efficiency and procognitive effects in various pathologies such as Alzheimer’s disease, Parkinson’s disease, vascular dementia, dementia with Lewy bodies [5,15,16].

The most promising and most studied group of medicines for testing the effects on cognitive impairment in patients with multiple sclerosis are acetylcholinesterase inhibitors [2,17,18].

Donepezil
The procognitive mechanism of donepezil is the same in multiple sclerosis and in other types of dementia, namely inhibiting the action of acetylcholinesterase and increasing levels and action period of acetylcholine in the brain. Some studies provide data on donepezil role in hippocampus neuroprotection. [2,19-22].

Several studies with donepezil versus placebo were achieved. Most of these trials have included a small number of patients and the outcomes were favorable for the therapy with donepezil. According these results, this pharmacological product has proven utility in mild and moderate cognitive dysfunction in multiple sclerosis [22-25].

Krupp LB. stated that the procognitive effect of donepezil is revealed in clinical practice by improvement of memory and learning ability [26].

Rivastigmine
Rivastigmine is a pharmacological treatment for dementia with dual mechanism of action. It inhibits both enzymes that degrades acetylcholine, acetylcholinesterase and butyrylcholinesterase. Butyrylcholinesterase is synthesized at neuronal level and astrocytes. These cells are damaged in multiple sclerosis thus releasing a large amount from this enzyme. Therefore, the procognitive effect of rivastigmine is evidenced on non-neuronal level. The efficacy is been proven for treatment in Alzheimer disease and dementia in Parkinson’s disease. Procognitive benefits of rivastigmine have been emphasized for patients with cognitive impairment in multiple sclerosis [5,15, 16, 20, 27].

Parry AMM. show that rivastigmine manifest procognitive effect in multiple sclerosis by modulating brain plasticity and determine increased activity in the left medial prefrontal cortex. Increasing levels of acetylcholine after the administration of rivastigmine has a central role in this form of adaptive neuroplasticity to the reduced activity of the right prefrontal cortex as a result of neurological conditions. The strongest effect of rivastigmine was observed in patients with a greater degree of cerebral atrophy [2, 28].

Rivastigmine improves cognitive status mainly through increasing the speed of information processing [29,30].

Galantamine
Procognitive potential of galantamine in multiple sclerosis is less known and studied. Dr. Bartzokis G., neurologist at UCLA (University of California, Los Angeles) David Geffen School of Medicine, states that this pharmacological product can protect the integrity of myelin, so it improves neurons responsiveness to acetylcholine and availability of acetylcholine molecules. Galantamine has this effect by a dual mechanism of action of acetylcholinesterase inhibitor and allosteric modulator of nicotinic receptors. Galantamine is already being used to improve cognitive impairment in several types of dementia [31, 32] in schizophrenia [33] and may prove useful in cognitive impairment in multiple sclerosis. Nicotinic receptors activated by acetylcholine are also found in oligodendrocytes. This glial cells are the source of brain myelin. And, by the action of galantamine on these non-neuronal cells receptors, cognitive function in multiple sclerosis can be improved [34].

Memantine
Memantine is an antagonist of N-methyl-D-aspartate receptors whose action is to modulate the glutamatergic activity to protect the brain from oxidative stress. Glutamate cerebral excess has negative effects on cognitive performances in multiple sclerosis. This pharmacological product has been effective in improving cognitive deficits in dementia from other etiologies [5, 35-37].

In order to research procognitive effects of memantine in multiple sclerosis, several studies have been conducted. Lovera J. indicated that the administration of memantine does not cause significant effects on cognitive functions in patients with this treatment [38].

In general, memantine showed reduced benefits in improving cognitive dysfunction in multiple sclerosis [39, 40].

The most recent study, in 2016, obtained limited results but only in relapsing-remitting form of the disease and mild cognitive deficit. Procognitive effect of memantine was minimal [41].
However, in 2014, Sühs KW determined that memantine protect retinal ganglion cells by reducing apoptosis, protect the axons and reduce optic nerve demyelination. The blockade of NMDA (N-methyl-D-aspartate)-like receptor cause side effects of administration of memantine. This receptor is AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid / kainate) receptor. Oligodendrocytes are using the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid / kainate) receptor. And for normal functioning of the brain cell is required signaling by both types of receptors. AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid / kainate) receptor blockade cause excessive calcium influx into the cells causing apoptosis. Procognitive effect of memantine has been highlighted by the mechanism of mild NMDA (N-methyl-D-aspartate) receptor blocker, achieving neuroprotection [42].

Discussions
Interferon beta has anti-inflammatory and neuroprotective activity. Galitramer acetate modulates the immune response by antigen-presenting cells and suppression of inflammatory cerebral process.

From the group of pharmacological products used in therapy of dementia, donepezil showed the best procognitive effect in multiple sclerosis.

Rivastigmine inhibits both enzymes that degrade acetylcholine, acetylcholinesterase and butyrylcholinesterase and has neuronal and non-neuronal procognitive effect in multiple sclerosis.

Galantamine and memantine have complex mechanisms of action and to demonstrate their procognitive effect in multiple sclerosis, more studies are required and from a different perspective.

Conclusions
The procognitive effect of interferon beta is probably that mediated by adenosine which delays neuronal damage and keep longer the optimal level of acetylcholine in the brain. Galitramer acetate has procognitive effect by preventing the occurrence of acetylcholine deficit because it stimulates the synthesis of neurotrophic factors and anti-inflammatory cytokines that preserves neuronal integrity. Donepezil inhibits the action of acetylcholinesterase and increases the level and action period of cerebral acetylcholine. Donepezil improves memory and learning ability.

Rivastigmine increases the speed of information processing. Galantamine has procognitive effect by increasing the availability of acetylcholine towards neuroreceptors.

Procognitive benefit of memantine is neuroprotection by modulating glutamate activity.

References
5. PPRELPECEANU D., Psihiatrie clinica, Editura Medicala, Bucuresti, 2011, p. 168-175
20. GAUTIER S., BALLARD C., Management of Dementia, 2, Informa HealthCare, New York, 2009, p.73-100
21. PATTI F., LEONE C., D’AMICO E., Neurol Sci., 2010; 31, 2, p. S265
22. HE D., ZHOU H., GUO D. et al, Cochrane Database Syst Rev. 2011, 10, CD008876
27. REDDY H., NARAYANAN S., ARNOTTE LIS, et al., Brain, 2000, 123, p. 2314
30. HOULMAN S., HÂMÂLÂÌNEÎN P., VOROBYEV V., Mult Scler., 2011, 17, p.1351
32. ARIASE E., ALES E., GABILAN N.H. et al., Neuropharmacology, 2004, 46, p. 103
34. BARTZOKIS G., Biol Psychiatry, 2007, 62, p. 294
41. SAINT PAUL S.P., CREVEUL C., HEINZLE O. et al., Journal of the Neurological Sciences, 2016, p. 69
42. SUHS K.W., FAIRLESS R., WILLIAMS S.K. et al., J Neuropathol Exp Neurol, 2014, 73, 6, p. 507

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