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Treatment options of cognitive impairment in multiple sclerosis

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Abstract Multiple sclerosis (MS) is a progressive disease of the CNS, characterized by the production of widespread lesions in the brain and spinal cord. Inflammatory demyelination has traditionally been seen as the main disease process in MS; however, axonal damage or loss is increasingly being documented to occur early in the disease. Cognitive deficits can occur independently of physical disability, which complicates their identification and recognition. More recently, cortical demyelination has been identified among possible causes of cognitive impairment in MS. Neuropsychological studies have consistently demonstrated that 40–65% of patients with MS experience cognitive dysfunction, particularly in recent memory, information processing speed, and sustained attention. Early detection of cognitive impairment is essential to enable therapeutic intervention to alleviate symptoms or prevent further cognitive decline, although how best to manage MS-related cognitive impairment is currently unclear. Treatment strategies for cognitive impairment in MS are still in their infancy. This article will summarize several pharmacological attempts to enhance cognitive performances in people with MS.

Keywords Multiple sclerosis · Cognition · Treatment

Cognitive impairment in MS

Cognitive deficits occur in all multiple sclerosis (MS) subtypes and in clinically isolated syndrome and tend to worsen over time [1, 2]. Deficits correlate with lesion burden, brain atrophy and cortical demyelination. Localized lesions lead to specific deficits (e.g., frontal lesions associated with executive dysfunction) [3]. It is now well recognized that MS cognitive impairment results in considerable disruptions to the lives, lifestyles, employment status, and yearly earnings of affected individuals. It can further exert a detrimental effect on personal, occupational, and social functioning, affecting overall quality of life (QoL) [4].

The specific domains of cognition that are compromised are various, both between individuals at a given point in time and within a single individual over a period of time. There are areas of cognition that appear to be particularly vulnerable, with the most common impairments being in learning and memory [5]. Research is ongoing to define the minimum battery of NPS tests that will enable the routine assessment of cognitive function in MS. Such a test battery should be sensitive to changes in the cognitive domains most commonly affected by MS, but should be insensitive to motor dysfunction. Interestingly, the degree of cognitive impairment reported by patients has been shown to correlate less well with NPS test results than that reported by patient informants, such as a spouse or other family member [6, 7].

Treating cognitive impairment in MS

Available approaches include pharmacological and non-pharmacological treatments (behavioural and rehabilitative). Objective of this paper is to describe and shortly analyze the current available pharmacologic symptomatic treatment for cognitive impairment in MS.

Pharmacological interventions to enhance cognition are appealing in a variety of ways. A number of brain

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functions, many under the control of different neurotransmitter systems, are implicated in the cognitive impairments that are functionally relevant in people with multiple sclerosis. Several different pharmacological compounds have been shown to improve the cognitive performance in a variety of cognitively impaired populations, so there is proof of the concept that pharmacological agents can change cognition. Although the concept of pharmacological cognitive enhancement as a disability reduction strategy is appealing, the implementation of this strategy may be as complicated as the brain processes that underlie cognitive impairments themselves.

Pharmacological interventions for cognitive impairment in MS can be divided into two types: (1) disease-modifying therapies (DMTs) and (2) symptomatic medications that, more specifically, target cognitive symptoms.

Very few randomized studies and few other open label or small controlled studies have evaluated symptomatic treatments for cognitive deficits in MS. Initial studies of 4-aminopyridine, amantadine, and pemoline have been largely negative. AChEIs were tested in other cognitive disorders with variable success: traumatic brain injury, vascular dementia, autism, attention deficit disorder, supranuclear palsy, mild cognitive impairment, chronic fatigue, Parkinson disease, schizophrenia, and dementia with Lewy bodies. On these grounds, researchers tried to experiment the effects of these drugs on cognitive impairment in MS.

Disease-modifying treatment

It is suggested that the beneficial effects of disease-modifying drugs may occur in the short term due to the anti-inflammatory effects of the therapy, and in the long-term due to the protective effects on tissue damage in the brain. In particular, disease-modifying drugs, such as beta-interferons and glatiramer acetate, may prevent or reduce the progression of cognitive dysfunction by containing the development of new cerebral lesions or by reducing the progression of brain atrophy. Assessment of neuropsychological outcomes in trials of disease-modifying agents is a recent issue; however, there is evidence that DMDs could be effective in reducing worsening of cognitive impairment.

Fisher et al. evaluated the effects of interferon beta-1a (IFNbeta-1a, 30 mcg administered intramuscularly once weekly) on cognitive function. A comprehensive and a brief neuropsychological battery were administered to relapsing–remitting multiple sclerosis (RRMS). The results supported and extended previous observations of significant beneficial effects of IFNbeta-1a for relapsing MS [8].

In BENEFIT study, Kappos et al. examined interferon beta-1b treatment in patients with clinically isolated syndrome (CIS). It was found that subtests of multiple sclerosis functional composite (MSFC) score after 3 years were more pronounced in patients receiving early treatment [9].

Patti et al. assessed the effects of subcutaneous (sc) interferon beta-1a (IFNbeta-1a) on cognition in mildly disabled patients with RRMS. All patients underwent NPS evaluation at the baseline and every 12 months for 3 years. Data on cognitive function at 3 years were available for 318 patients (22 mcg, n¼153; 44 mcg, n¼165). Their analysis showed a 32% risk reduction for treatment with IFNbeta-1a 44 versus 22 mcg. Kaplan–Meier survival curves confirmed the benefits of receiving the higher dose treatment over time. The results of this study indicate that treatment with sc IFNbeta-1a may have dose-dependent cognitive benefits in mildly disabled patients with RRMS. Sc IFNbeta-1a was tolerated in this cohort of patients. These findings may support the early initiation of high-dose IFNbeta-1a treatment [10].

Acetylcholinesterase inhibitors

Donepezil

It is hypothesized that in MS, cholinergic deficits might derive from disruption of cholinergic pathways and impaired axonal transport of acetylcholine due to the demyelination and axonal transection. AChEIs currently used in Alzheimer disease (AD), such as donepezil, rivastigmine, and galantamine, have been recently tested also in other cognitive disorders including MS. Four small randomized clinical trials of donepezil have been conducted [11, 12], although only one has been published [11]. Three of these studies reported a cognitive benefit of donepezil on various areas of cognition, including word fluency, executive functions, new learning and memory, and patient and physician reports of cognitive improvement. The first study by Krupp et al. [11] is a randomized, double-blind, placebo-controlled, single-centre clinical trial of 69 patients with MS who were selected for initial memory difficulties. Subjects underwent neuropsychological assessment at weeks 0 and 24, consisting primarily of a modified version of the Brief Repeatable Battery. The selective reminding test (SRT) was chosen as the primary outcome measure from that battery because of positive results in all the previous MS AChEI clinical trials that included this test. Secondary outcome measures included: other neuropsychological tests from the brief repeatable battery, patient-reported change in memory, and physician-reported impression of cognitive change. Donepezil improved memory performance on the SRT when compared with placebo. This benefit remained significant even

after controlling for covariates such as the Expanded Disability Status Scale, MS subtype, interferon-β use, treatment group beliefs, gender, baseline SRT score, and reading ability. Patients in the donepezil group were significantly more likely to report memory improvement than those receiving placebo (65.7 vs. 32.4%). The drug was generally well tolerated, with the exception that unusual/abnormal dreams occurred more frequently in donepezil-treated (34.3%) than in placebo-treated patients (8.8%). A very recent double-blind randomized study of the same group investigated the effects of donepezil versus placebo in 120 cognitively impaired MS patients. After 24 weeks, donepezil was not capable to improve memory performance on SRT. The authors concluded that AChEI donepezil could not be considered as symptomatic drug to treat cognitive impairment in MS [13].

Rivastigmine

Parry et al. have suggested rivastigmine, a central cholinesterase inhibitor performs an acute modulation of potentially adaptive functional changes in cognitive processing. They studied ten patients with MS and eleven healthy controls using a functional MRI (fMRI) counting Stroop task. The two subject groups had comparable performances, but a predominantly left medial prefrontal region was more active during the task in patients than in controls (corrected $P < 0.001$), while a right frontal region was more active in controls than in patients (corrected $P = 0.004$). In 5 out of 10 MS patients, there was a relative normalization of the abnormal Stroop-associated brain activation, although no change in brain activation was found in any of four healthy controls taking the drug and tested in the same way. The authors suggested that the recruitment of medial prefrontal cortex was a form of adaptive brain plasticity that compensated, in part, for relative deficits in processing related to the reduced right prefrontal cortex activity in patients with MS. This functional plasticity could be modulated by cholinergic agonism [14].

In a 3-month single-center double-blind placebo-controlled clinical trial, Shaygannejad et al. enrolled 60 definite MS patients with cognitive impairment. They were randomly allocated to receive a 12-week treatment course of either rivastigmine (1.5 mg once a day increment over 4 weeks to 3 mg twice daily) or placebo. Response to treatment was assessed by the Wechsler Memory Scale (WMS) at baseline and 12 weeks after start or therapy. A slight, but significant memory improvement occurred in both groups. The average WMS general memory score at the end of trial did not change between rivastigmine and placebo group (mean difference 0.4, 95% CI −2.0, 2.8). The authors found no significant differences between rivastigmine and placebo on the mean (SD) WMS general memory score. The improved performances in both groups could be probably due to learning effect which is a frequent confounder of the effects of any treatment on cognitive impairment [6].

Memantine

A 3-month multi-center double-blind placebo-controlled clinical trial in MS patients with cognitive impairment ($n = 126$: RR, PP, and SP) was conducted by Lovera et al. Fifty-eight patients treated with Memantine at 20 mg/die and 68 controls were tested at baseline and a 3 months. The first results showed that Memantine patients did not improve as measurement of PASAT and CVLT-II. Treatment with memantine was safe and well tolerated [15].

Other authors (Villoslada et al.) successively conducted a 1-year, randomized, double-blind, crossover trial to comparing memantine (30 mg/day) against a placebo in 60 patients with MS and cognitive impairment. Cognitive impairment was defined as the performance 1.5 standard deviations below the normative data in at least two tests of two cognitive domains in the brief repeatable battery–neuropsychology. The primary endpoint was improvement of verbal memory and the secondary endpoints were safety and improvements in the other cognitive domains, disability and quality of life. The study indicated that intermediate to high doses of memantine could have induced reversible neurologic impairment in patients with MS suffering moderate to severe physical disability. These effects did not appear at lower doses, below 20 mg/day, despite the mild escalation regimen (10 mg weekly escalation), and they disappeared shortly after reducing the dosage. The biologic bases of such symptoms are unknown. The similarity of these pseudo-exacerbations suggested that they could share a common mechanism, such as transient axonal blockage due to the energy depletion of demyelinated axons. The authors hypothesized that the partial inhibition of overactive glutamatergic pathways by memantine coupled with the presence of demyelinated axons could contribute to produce transient axonal blockage. Memantine is a non-competitive inhibitor of NMDA receptors, implying that the blocking effect is enhanced when glutamatergic pathways are more strongly activated, as associated with the brain plasticity. The block of conduction in demyelinated axons seems to be secondary to the energy failure associated with ion channel and mitochondrial dysfunction. These negative results regarding safety of memantine discourages its use to treat cognitive impairment in MS [16].

Amantadine/pemoline

Amantadine and Pemoline are generally used to treat the fatigue of multiple sclerosis (MS), but may also improve attention and other cognitive functions in MS. Geisler et al. studied the effects of 6-week treatment with amantadine, pemoline, or placebo on cognitive functioning in MS, evaluating 45 ambulatory patients with MS and severe fatigue. All patients underwent comprehensive neuropsychological testing to determine treatment effects on cognitive functioning. Primary outcome measures were tests of attention (Digit Span, Trail Making Test, and Symbol Digit Modalities Test), verbal memory (Selective Reminding Test), non-verbal memory (Benton Visual Retention Test), and motor speed (Finger Tapping Test). Fatigue did not significantly correlate with any of the neuropsychological outcome measures at baseline or after treatment. All three treatment groups improved on tests of attention, verbal memory, and motor speed. There were no significant differences between amantadine, pemoline, and placebo. Cognitive functioning in MS resulted independent of fatigue. Neither amantadine nor pemoline enhanced cognitive performance in MS compared with placebo. Also in this experiment, the practice effect was probably responsible for the observed improved effects [17].

Ginkgo biloba

It was hypothesized that ginkgo biloba (GB) could improve the cognitive performance among subjects with MS. The first, double-blind, placebo-controlled trial was published by Lovera J. et al. This study demonstrated a slight, but not significant, benefit on cognitive functioning of treatment with GB. The Stroop test was the only test in the battery that assessed susceptibility to interference and mental flexibility. Therefore, the lack of effect on the other five tests could reflect only poor effects of GB on cognitive performance in MS patients [18].

Fluoxetine

It was reported that the antidepressant fluoxetine, a known inhibitor of serotonin reuptake, can exert several effects such as neurons and astrocytes proliferation and astrocytic glycogenolysis stimulation with increase of energy source for axons. In multiple sclerosis patients fluoxetine administration may improve the energy supply in neuron cells and thus inhibit axonal degeneration. In a preliminary pilot study, 15 MS patients were examined by diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) in order to quantify the brain tissue diffusion properties (fractional anisotropy, apparent diffusion coefficient) and metabolite levels (choline, creatine and N-acetylaspartate) in cortical gray matter brain tissue, in normal appearing white matter and in white matter lesions. This provided preliminary evidence of a possible neuroprotective effect of fluoxetine in MS by the partial normalization of the structure-related MRS parameter N-acetylaspartate in white matter lesions. Mostert et al., in a double-blind, placebo-controlled exploratory study evaluated the effects of fluoxetine on new lesion formation in patients with relapsing MS. Forty non-depressed patients with relapsing-remitting or relapsing secondary progressive MS were randomized to oral fluoxetine 20 mg or placebo daily for 24 weeks.

Table 1 Symptomatic agents of cognitive impairment in MS: literature studies

Study	Drug	No. of patients	Study design	Outcome
Geisler et al. [17]	Amantadine/ pemoline	45, MS-severe fatigue	Placebo-controlled trial for 6 weeks	No effects
Krupp et al. [11]	Donezepil	69-Memory-impaired (RAVLT) (67 completed the trial)	Parallel groups, RCT, intention-to-treat analysis, 24 weeks of treatment	Improvement SRT, patient- and physician-reported cognition
Lovera et al. [18]	Ginkgo biloba	43, a score between 0.5 and 2.5 SD below PASAT/ CVLT-II	RCT, 120 mg twice a day or placebo for 12 weeks	No effects
Villoslada et al. [16]	Memantine	19, MS- cognitive impaired (1.5 SD below in at least two tests BRBN)	1-year crossover RCT, 30 mg daily	Trial halted after nine patients reported neurological worsening
Krupp et al. [13]	Donezepil	120-memory- and cognitive impaired ($\leq$0.5 SD below in RAVLT)	Multicenter RCT, 10 mg daily	No effects

RCT Randomized controlled trial, *PASAT* paced auditory serial addition test, *RAVLT* rey auditory verbal learning test, *SRT* selective reminding test, *CLVT II* California verbal learning test-II, *BRBN* brief repeatable battery-neuropsychology

New lesion formation was studied by assessing the cumulative number of gadolinium enhancing lesions on brain MRI performed on weeks 4, 8, 16, and 24. The analysis showed that the cumulative number of new enhancing lesions was 1.21 (2.6) in the fluoxetine group and 3.16 (5.3) in the placebo group ($p = 0.05$). The number of patients without enhancing lesions was 63% in the fluoxetine group versus 26% in the placebo group ($p = 0.02$). This study showed that the fluoxetine reduced the formation of new enhancing lesions in patients with MS [19]. If these effects are able to improve cognitive impairment in MS are questionable. However, a possible role of antidepressants use to treat cognitive impairment in MS should be taken into account (To summarize, see Table 1).

Conclusions

To date, at the best of our knowledge, no effective treatment has yet been established for this cognitive impairment in MS. The strongest evidence for symptomatic treatment of cognitive dysfunction in MS came from studies of AChEIs. Unfortunately, more recent studies did not confirm previous ones. Furthermore, there are still many unanswered questions regarding the use of AChEIs and other cognitive enhancer agents, including the effects of their long-term use in a chronic disease such as MS. A possible effect of agents used to enhance the cognition in MS could be due to their capability of counteracting the side effects of other drugs (such as benzodiazepines, baclophen, alpha lytic, etc.) which are currently used to treat other symptoms than cognitive impairment. On the whole, to date the research on this field in MS must be considered preliminary, and it is premature to recommend the clinical use of these classes of medications at present time. Their application in clinical practice is limited to their use as off-label prescriptions.

Conflict of interest The authors declare that there is no actual or potential conflict of interest in relation to this article.

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