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MULTIPLE SCLEROSIS BEST EVIDENCE-BASED STRATEGIES AND TREATMENT/THERAPIES FOR REHABILITATION

Cognitive Impairment: Pharmacological Interventions

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Disclosures

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Lay Summary of the Evidence

Interventions favouring a benefit for one or more cognitive outcomes

- Mixed amphetamine salts may be beneficial for visual processing speed, but not other forms of processing speed, in persons with MS.

- Lisdexamfetamine dimesylate may improve visual processing speed and verbal memory, but not other cognitive functions or the subjective impact of cognitive impairment on daily activities, in persons with MS.

- L-amphetamine may improve verbal and visuospatial memory, but not other cognitive functions or subjective measures of cognition, in persons with MS.

- Simvastatin may be beneficial for improving executive function, but not other cognitive functions, in persons with secondary progressive MS.

- A tryptophan-enriched whey-based diet may acutely improve memory, but not other cognitive functions, in persons with MS.

- *Achillea millefolium* may be beneficial for improving auditory processing speed and verbal learning and memory, but not other cognitive functions, at 12 months in persons with relapsing-remitting MS.

- Modafinil may improve working memory, but not other cognitive functions.

- Armodafinil may improve verbal memory, but not other cognitive functions.

- 4-Aminopyridine immediate release compared to placebo may be beneficial for improving the domains of memory, verbal fluency, executive function, and visuospatial skills, but not other cognitive functions, in persons with relapsing-remitting MS. Slow-release 4-aminopyridine formulations compared to placebo may not improve cognitive function in multiple cognitive domains tested in persons with MS.

- Preliminary evidence suggests methylphenidate may improve auditory processing speed in persons with relapsing-remitting MS.

- *Boswellia serrata* may improve verbal memory and learning and visuospatial memory, but not other cognitive functions, in persons with relapsing-remitting MS.

- *Boswellia papyrifera* may improve visuospatial memory, but not other cognitive functions, in persons with relapsing-remitting MS.

- Preliminary evidence suggests that vitamin D may improve mild cognitive impairment and visuospatial memory, but not other cognitive functions, in persons with MS.

- Melatonin may not be beneficial for improving auditory processing speed in persons with relapsing-remitting MS but may improve self-reported cognitive fatigue.

- Preliminary evidence supports that there is no difference in cognitive outcomes between treatment with interferon beta 1b or fingolimod over an 18-month period in relapsing-remitting MS.

- Preliminary evidence supports that fingolimod or natalizumab similarly improve global cognitive performance at two years in persons with relapsing-remitting MS.

- Fingolimod or injectable disease modifying therapies may maintain verbal processing speed at 48 weeks.

- Preliminary evidence suggests alemtuzumab may have stabilizing effects on overall cognitive function and may be beneficial for improving processing speed in persons with relapsing-remitting MS.

- Preliminary evidence suggests that rituximab may improve visual processing speed in persons with relapsing-remitting MS.

- Preliminary evidence suggests dimethyl fumarate may slow cognitive decline or improve cognitive impairment in persons with relapsing-remitting MS.

- Natalizumab as monotherapy or as combination therapy with interferon beta 1a may not be superior to interferon beta 1a alone for improving cognitive function but may be superior in terms of delaying cognitive decline in relapsing-remitting MS.

- Natalizumab may delay a decline in processing speed at two years in relapsing-remitting MS.

- Preliminary evidence supports that natalizumab may improve auditory processing speed more than other first line disease modifying therapies.

- Preliminary evidence suggests that improvement in processing speed after natalizumab treatment may be observed as early as four weeks post treatment.

- Interferon formulations may reduce the rate of cognitive decline in some cognitive domains for persons with relapsing MS. It is unclear if there is a dose-dependant protective effect against cognitive decline.

- High dose or low dose estroprogestins in combination with interferon beta may improve cognition similar to interferon beta alone in persons with relapsing-remitting MS.

- Ozanimod may protect against worsening cognitive function, based on 12-month data.

- Preliminary evidence suggests that teriflunomide may have stabilizing effects on clinical and subjective measures of cognitive function in persons with MS.

- Preliminary evidence supports that mitoxantrone may have stabilizing effects on cognitive functions in persons with MS.

- Preliminary evidence suggests cyclophosphamide combined with methylprednisolone may improve general cognitive impairment efficiency, verbal memory, inhibition, and phonemic fluency in persons with progressive MS.

- Daclizumab may be more effective than interferon beta 1a for preventing worsening of processing speed; however, daclizumab is no longer available.

Interventions with inconclusive or conflicting findings

- There is mixed evidence regarding the effect of different interferon beta preparations on cognitive impairment in relation to one another in persons with MS.

- Preliminary evidence supports that interferon beta 1a, 1b, and glatiramer acetate may have similar effects on cognitive impairment in persons with relapsing-remitting MS.

- Glatiramer acetate may not improve cognitive function more than placebo over two years in persons with relapsing-remitting MS.

- Preliminary evidence supports that fingolimod, natalizumab, or interferon are not more effective compared to one another for maintaining cognition over one year in persons with relapsing-remitting MS.

- The effects of natalizumab on maintaining or improving function in different cognitive domains are inconsistent.

- There are conflicting results for the effects of natalizumab on maintaining processing speed at three years.

Interventions with no observed benefit on cognitive outcomes

- Amantadine does not improve cognitive function in persons with MS.

- Donepezil does not improve memory, processing speed, verbal fluency, or executive function in persons with MS.

- Memantine does not improve cognitive impairment in persons with MS.

- Rivastigmine does not improve cognitive impairment in multiple cognitive domains tested in persons with MS; there is conflicting evidence for its effect on processing speed.

- Erythropoietin may not be beneficial for improving cognitive impairment in persons with primary or secondary progressive MS.

- Fluoxetine or prucalopride may not improve cognitive impairment in persons with relapsing-remitting MS.

- Naturopathic medicine may not improve cognitive impairment in persons with relapsing-remitting MS.

- *Ginkgo biloba* does not improve cognitive impairment in several cognitive domains in persons with MS; however, there is conflicting evidence for its effect on cognitive interference and mental flexibility.

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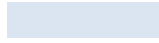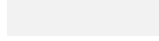
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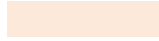
Abbreviations

ADHD	Attention-Deficit Hyperactivity Disorder
BiCAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BRB	Brief Repeatable Battery
BVMT-R	Brief Visuospatial Memory Test-Revised
CAM	Complementary and alternative medicine
CI	Cognitive impairment
CIS	Clinically isolated syndrome
CNS	Central nervous system
COGIMUS	Cognitive Impairment in Multiple Sclerosis study
CVLT-II	California Verbal Learning Test, 2nd edition
DMT	Disease modifying therapy
EDSS	Expanded Disability Status Scale
FSMC	Fatigue Scale for Motor and Cognitive Functions
GB	Ginkgo biloba
IFN-β	Interferon Beta
MACFIMS	Minimal Assessment of Cognitive Function in Multiple Sclerosis
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
NMDA	N-methyl-D-aspartate
PASAT	Paced Auditory Serial Addition Test
PCT	Prospective controlled trial
PEDro	Physiotherapy Evidence Database
PPMS	Primary progressive multiple sclerosis
PRMS	Progressive relapsing multiple sclerosis
PwMS	Persons with multiple sclerosis
RCT	Randomized Controlled Trial
RRMS	Relapsing-remitting multiple sclerosis
S1P	sphingosine 1-phosphate
SCWT	Stroop Color-Word Test
SDMT	Symbol Digit Modalities Test
SPMS	Secondary progressive multiple sclerosis
SRT	Selective Reminding Test

Cognitive Impairment:

Pharmacological Interventions

1.0 Introduction

Cognitive impairment (CI) is common among individuals with multiple sclerosis (MS), yet for many decades the presence and impact of CI in MS has remained under-recognized. As many as 40-65% of persons with MS (PwMS) experience CI (Rao, 1995). CI may occur as early as the first demyelinating episode, prior to a confirmed diagnosis of MS (Feuillet et al., 2007; Glanz, Healy, Hviid, Chitnis, & Weiner, 2012). CI does not correlate strongly with the level of physical impairment and may be dismissed or masked by co-morbid psychological disorders (Akbar, Honarmand, & Feinstein, 2011; Benedict et al., 2004).

In PwMS the cognitive domains most frequently affected include information processing speed, working memory, and episodic memory (Benedict et al., 2002; Rao, Leo, Bernardin, & Unverzagt, 1991). Less frequently affected are higher executive function, verbal fluency, and visual-spatial perception (Chiaravalloti & DeLuca, 2008). General intelligence and language abilities are relatively spared in PwMS, in contrast to the CI associated with Alzheimer's disease (Rao et al., 1991). PwMS often report forgetfulness, being slow to respond, difficulty with new learning and multi-tasking, and that simple tasks demand focus and attention (Benedict & Bobholz, 2007; Benedict et al., 2002; Bobholz & Rao, 2003). Some PwMS with CI may have little insight into their CI, or they do not identify MS as the cause of CI, supporting a role for objective routine cognitive screening (Freedman et al., 2013). CI in PwMS has a negative effect on personal relationships and self-esteem, and may lead to social isolation (Benedict, Priore, Miller, Munschauer, & Jacobs, 2001; Carone, Benedict, Munschauer, Fishman, & Weinstock-Guttman, 2005). CI is especially relevant to fitness for driving (Morrow et al., 2018; Schultheis et al., 2010) and correlates with employment status (Beatty, Blanco, Wilbanks, & Paul, 1995; Benedict et al., 2006; Benedict et al., 2005; Morrow et al., 2010; Parmenter et al., 2007).

Some of the challenges in comparing interventions for CI in PwMS include an incomplete understanding of the natural history and variability of CI in PwMS, the diversity of CI outcome measures utilized, and the need for validated and feasible outcome measures. Composite disability scores are frequently utilized in MS clinical trials and the cognitive sub-scores may not be reported separately. Longitudinal studies suggest that CI usually has a slow progressive course, which once present, is unlikely to remit (Amato, Ponziani, Siracusa, & Sorbi, 2001; Kujala, Portin, & Ruutiainen, 1997; Schwid, Goodman, Weinstein, McDermott, & Johnson, 2007). Improvements on cognitive tests may not translate to a change in cognitive function in real world settings, and practice effects on tests administered may occur.

Further research is needed to identify the most effective interventions delivered alone or in combination for delaying, treating, and preventing CI in PwMS. Pharmacological or non-pharmacological approaches for the prevention and treatment of CI in PwMS have largely been studied separately, and future research could explore combining approaches. To date, over two dozen different pharmacotherapy treatments have been studied with the aim of improving CI in PwMS, including the effects of stimulants (i.e., amphetamines, modafinil, amantadine), acetyl-cholinesterase inhibitors (i.e., donepezil), and numerous other agents (e.g., memantine, fampridine, *Ginkgo biloba*). A recent systematic review and meta-analsysis of randomized controlled trials (RCTs) targeting pharmacological interventions for CI in MS concluded that

there was a beneficial effect only for 4-Aminopyridine on the Symbol Digit Modalities Test (SDMT) and only on the subgroup analsysis (Motavalli et al., 2020). This review did not include MS disease modifying therapies (DMTs). A 2020 systematic review examined the effects of DMTs on processing speed, concluding a small beneficial effect (Marrie & Leavitt, 2020). The possible effects of DMTs on other cognitive domains were not explored.

This module provides an overview of pharmacological interventions trialed for cognitive impairment in PwMS, including both RCTs and lower quality studies, to provide insights on possible emerging evidence for pharmacological interventions. The levels of evidence for how interventions affect a specific cognitive domain (i.e., visual processing speed, memory etc.) are also included where available. This module is limited to studies published up until July 2020. In the future, living systematic reviews may update evidence as new research is published.

2.0 Cognitive Outcome Measures and Defining Cognitive Impairment

Recommended CI assessment tools for PwMS include the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS), the Brief International Cognitive Assessment for Multiple Sclerosis (BiCAMS), and Rao's oral version of the SDMT. The MACFIMS is a 90 to 120 minute assessment battery developed by a consensus committee (Benedict et al., 2002). The MACFIMS provides a comprehensive, valid, and reliable assessment of processing speed, memory, executive function, visuospatial processing, and word retrieval in PwMS (Benedict et al., 2006). The MACFIMS aimed to expand on the previously commonly used Rao's Brief Repeatable Battery (BRB) by testing more cognitive domains. The BRB remains widely utilized as it is available in multiple languages. A shorter 15-minute BiCAMS was also developed from the MACFIMS as a screening tool which includes processing speed and verbal and visuospatial immediate recall/learning assessments (Langdon et al., 2012). Within the BiCAMS battery, Rao's oral version of the SDMT assesses visual processing speed. The SDMT on its own has the advantage of being feasible and easy to use in routine clinical practice and clinical trials (Benedict et al., 2006; Freedman et al., 2013; Rao, 1991; Smith, 1982; Van Schependom et al., 2014). Clinically meaningful worsening on the SDMT occurs with some MS relapses (Benedict et al., 2014; Morrow, Jurgensen, Forrestal, Munchauer, & Benedict, 2011). A decline of three to four points on the SDMT indicates clinically meaningful worsening of CI (Benedict et al., 2014; Morrow et al., 2010; Morrow et al., 2011). The SDMT is recommended as the minimum bedside cognitive screening assessment tool in patients with MS (Freedman et al., 2020).

A list of the cognitive outcome measures utilized in MS pharmacological trials and the cognitive domain(s) each measure primarily assesses is displayed in Table 1. Brain atrophy occurs early in the MS disease course and is associated with CI. However, atrophy is not a sensitive surrogate measure of cognitive function at the individual level. In the future, advanced imaging techniques may be clinically applicable for improving the assessment and understanding of CI in MS (Bagnato et al., 2020). At this time, bedside assessment of cognitive function is recommended standard practice. Practice effects remain an issue with repeated cognitive testing. Therefore, in research settings, the inclusion of control groups is critical. Except for the SDMT, clinically meaningful change scores on cognitive outcome measures for PwMS are not well established. Generally, a test score 1.5 standard deviations below established values in control populations marks the threshold for defining CI. However, PwMS may describe cognitive symptoms they experience without meeting established thresholds for CI.

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Table 1. Cognitive Outcome Measures Utilized in the Reviewed Literature

Cognitive domain	Outcome measure
Attention	
	Brief Test of Attention (BTA)
	Stroop Test/Stroop Color-Word Test (SCWT)
Executive function	
	Delis-Kaplan Executive Function System (D-KEFS)[2]
	Stroop Test/Stroop Color-Word Test (SCWT)
	Tower of London (TOL/TOW)
Cognitive interference & mental flexibility	Stroop Test/Stroop Color-Word Test (SCWT)
Cognitive reasoning	Wisconsin Card Sorting Test (WCST)
Information processing speed	
	Modified Paced Visual Serial Addition Test (mPVSAT)
	Trail Making Test (TMT)
	Faces Symbol Test (FST)
Auditory processing speed	Paced Auditory Serial Addition Test (PASAT)[2,3]
Visual processing speed	Symbol Digit Modalities Test (SDMT)[1,2,3]
Visuospatial skills	
Spatial processing	Judgment of Line Orientation Test (JLO/JOLO)[2]
Visual perception	Motor-Free Visual Perception Test (MVPT)
Memory	
Spatial memory	10/36 Spatial Recall Test (10/36;10/36-SPART; SPART)[3]
Visuospatial memory	Brief Visuospatial Memory Test-Revised (BVMT-R)[1,2]
Visual memory	Benton Visual Retention Test
	Wechsler Memory Scale (WMS)
Verbal memory	Rey Auditory Verbal Learning Test (RAVLT)
	Wechsler Memory Scale (WMS)
Verbal learning & memory	California Verbal Learning Test II (CVLT-II)[1,2]
	Hopkins Verbal Learning Test (HVLT)
	Selective Reminding Test (SRT)[3]
	Word List Generation (WLG)[3]
	Word pair learning test
Working memory	Wechsler Adult Intelligence Scale-III (WAIS-III) letter-number sequencing
	Wechsler Adult Intelligence Scale-III (WAIS-III) digit span
	Wechsler Adult Intelligence Scale-Revised (WAIS-R) digit span
Verbal language skills	
Phonemic fluency	Phonemic Fluency Test
Verbal fluency	Controlled Oral Word Association Test (COWA/COWAT)
	Regensburger Verbal Fluency Test (RWT)
Word retrieval	Boston Naming Test (BNT)
General cognitive impairment	Montreal Cognitive Assessment (MoCA)
	Mini-Mental State Examination (MMSE)
	Global Intelligence Efficiency Test
	Brief International Cognitive Assessment for Multiple Sclerosis (BiCAMS)
	Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS)
	Rao's Brief Repeatable Battery (BRB)

[1]Components of the BiCAMS battery
[2]Components of the MACFIMS battery
[3]Components of Rao's BRB

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3.0 Pharmacological Interventions

3.1 Pharmacotherapy

Research on pharmacotherapy approaches for MS-related CI has focused on stimulants (i.e., amphetamine and related compounds such as methylphenidate and modafinil), cognitive-preserving agents (i.e., acetyl-cholinesterase inhibitors such as donepezil), and the effects of disease modifying MS drug therapies. Non-pharmacological adaptive approaches have an important role in the management of CI, but are not the topic of this module.

3.1.1 Amantadine

Amantadine is a synthetic antiviral agent and dopamine agonist used for the treatment of influenza A and dyskinesia associated with parkinsonism, although the mechanism of action is still unclear. Amantadine has also been used off-label, including for the treatment of MS-related fatigue ("Drug monograph: Amantadine," 2021).

Table 2. Study Examining Amantadine for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Cohen et al. 2019 *Safety and efficacy of ADS-5102 (amantadine) extended release capsules to improve walking in multiple sclerosis: a randomized, placebo-controlled, phase 2 trial* USA **RCT** PEDro=10 $N_{Initial}$=60, N_{Final}=53	**Population:** *Amantadine (n=27):* Mean age=53.3yr; Sex: males=8, females=19; Disease course: RRMS=23, SPMS=1, PPMS=1, PRMS=2; Mean EDSS=5.0; Mean disease duration=11.7yr. *Placebo (n=29):* Mean age=52.3yr; Sex: males=9, females=20; Disease course: RRMS=20, SPMS=3, PPMS=2, PRMS=4; Mean EDSS=5.2; Mean disease duration=13.8yr. **Intervention:** Participants were randomized to receive either amantadine extended release capsules (137mg 1x/d during wk 1, 274mg 1x/d during wks 2-4) or matching placebo for 4wks. Outcomes were assessed at baseline and at 2 and 4wks. **Cognitive Outcomes/Outcome Measures:** Brief International Cognitive Assessment for MS (BiCAMS).	1. There were no statistically significant between-group differences on the BiCAMS at 2 or 4wks.
Geisler et al. 1996 *The effects of amantadine and pemoline on cognitive functioning in multiple sclerosis* USA **RCT**	**Population:** *Placebo (n=16):* Mean age=40yr; Sex: males=2, females=14; Disease course: RRMS=13, chronic progressive=3; Mean EDSS=2.2; Disease duration: unspecified. *Pemoline (n=13):* Mean age=41yr; Sex: males=4, females=9; Disease course: RRMS=12, chronic progressive=1; Mean EDSS=2.6; Disease duration: unspecified. *Amantadine hydrochloride (n=16):* Mean age=40yr; Sex: males=4, females=12; Disease course: RRMS=13, chronic progressive=3;	1. There were no significant differences between the active treatment and placebo groups on any other neuropsychological outcomes. 2. The written SDMT showed a significant difference between treatment groups, with the amantadine group showing the greatest improvement.

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
PEDro=7 N$_{Initial}$=45, N$_{Final}$=45	Mean EDSS=3.1; Disease duration: unspecified. **Intervention:** Patients were randomized to receive treatment with amantadine, pemoline, or placebo for 6wks. Pemoline was taken at a dosage of 18.75mg daily and titrated upward to a maximum of 56.25mg/d by wk 3 and maintained for the next 3wks. Amantadine hydrochloride was taken at a dose of 100mg 2x/d for 6wks. Assessments were performed at baseline and after treatment. **Cognitive Outcomes/Outcome Measures:** Wechsler Adult Intelligence Scale-Revised (WAIS-R) digit span; Trail Making Test (TMT) A,B; Symbol Digit Modalities Test (SDMT); Benton Visual Retention Test; Selective Reminding Test (SRT): long-term retrieval, delayed recall, sum of recall.	

Discussion

Cohen et al. (2019) conducted a phase II RCT in which participants were randomized to receive either amantadine or placebo for four weeks. Cognitive function was included as a secondary endpoint and was assessed using the BiCAMS at baseline and at two and four weeks. This study did not identify any between-group differences in cognitive function at either follow-up time point.

One study examined the effects of amantadine or pemoline on CI in PwMS compared to placebo (Geisler et al. 1996). Pemoline is a central nervous system (CNS) stimulant which has subsequently been associated with hepatic failure. Participants were assessed at baseline and six weeks later. There was no significant difference in the change in cognition outcomes over six weeks between the amantadine, pemoline, and placebo groups, with the exception of change scores on the written version of SDMT, favouring the amantadine-treated group. The written version of the SDMT is not validated in persons with MS for the assessment of cognitive impairment because of a reliance on motor function.

Conclusion

There is level 1a evidence that amantadine compared to placebo may not improve cognitive function (two randomized controlled trials; Cohen et al. 2019, Geisler et al. 1996).

There is level 1b evidence that pemoline compared to amantadine or placebo may not improve cognitive function (one randomized controlled trial; Geisler et al. 1996).

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> Amantadine does not improve cognitive function in persons with MS.

3.1.2 Amphetamine/lisdexamfetamine

Amphetamine is a CNS stimulant. Amphetamines are used in other disorders to treat impaired processing speed and have been shown to improve symptoms in adults and children with attention-deficit hyperactivity disorder (ADHD) (Rhodes, Coghill, & Matthews, 2004). Amphetamines for ADHD may improve attention span, the ability to follow directions or complete tasks, decrease distractibility, and decrease impulsivity. Mixed amphetamine salts, extended release (MAS-XR; trade name Adderall XR), an extended release version of Adderall IR (immediate release), are composed of equal amounts of the sulfate salts of dextroamphetamine, amphetamine, d-amphetamine, and d-,l-amphetamine aspartate monohydrate, resulting in a 3:1 ratio of d to l-isomers of amphetamine (McGough et al., 2003). It is approved for the treatment of ADHD in children, adolescents, and adults. Similarly, lisdexamfetamine dimesylate is an inactive amphetamine prodrug that is converted to lysine and d-amphetamine. It is currently approved for the treatment of both children and adults diagnosed with ADHD and was developed to provide extended steady clinical effect.

Table 3. Studies Examining Amphetamine Drug Products for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Morrow & Rosehart 2015 *Effects of single dose mixed amphetamine salts - extended release on processing speed in multiple sclerosis: a double blind placebo controlled study* Canada **RCT** PEDro=8 $N_{Initial}$=62, N_{Final}=52	**Population:** *Treatment Group 1 (n=18)*: Mean age=49.4yr; Sex: males=4, females=14; Disease course: RRMS=16, SPMS=1, PPMS=1; Median EDSS=3.5; Mean disease duration=11.9yr. *Treatment Group 2 (n=20)*: Mean age=42.2yr; Sex: males=5, females=15; Disease course: RRMS=17, SPMS=3; Median EDSS=3.5; Mean disease duration=9.9yr. *Placebo (n=14)*: Mean age=46.5yr; Sex: males=6, females=8; Disease course: RRMS=10, SPMS=4; Median EDSS=3.5; Mean disease duration=10.8yr. **Intervention:** Patients were randomized to receive a single dose of one of three treatments: 5mg mixed amphetamine salts, extended release (MAS-XR, group 1), 10mg MAS-XR (group 2), or placebo. Participants were instructed to take treatment 7h prior to scheduled testing. Assessments were administered pre-dose and post-dose. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT).	1. There was a significant improvement on the SDMT in the 10mg MAS-XR group compared to placebo (mean SDMT increase: 5.2 10mg MAS-XR, 0.6 placebo; p=0.043), but a non-significant difference between the 5mg MAS-XR and placebo groups (mean SDMT increase: 3.3 5mg MAS-XR; p=0.150). 2. There was a non-significant difference in improvement between the treatment groups compared to placebo on PASAT (mean increase: 5.9 placebo, 5.2 5mg MAS-XR, p=0.804; 6.8 10mg MAS-XR, p=0.735), regardless of baseline impairment on the PASAT.

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Morrow et al. 2013 *Lisdexamfetamine dimesylate improves processing speed and memory in cognitively impaired MS patients: a phase II study* USA **RCT** PEDro=8 N_{Initial}=63, N_{Final}=48	**Population:** *Lisdexamfetamine dimesylate (LDX) Group (n=29)*: Mean age=48.7yr; Sex: males=6, females=23; Disease course: RRMS=22, SPMS=8; Mean EDSS=3.8; Mean disease duration=14.7yr. *Placebo (n=19)*: Mean age=46.7yr; Sex: males=7, females=12; Disease course: RRMS=16, SPMS=3; Mean EDSS=3.3; Mean disease duration=15.8yr. **Intervention:** Patients were randomized to receive a daily dose of either LDX or placebo for 8wks. The LDX treatment group received 30mg LDX daily, increased as tolerated by 20mg weekly during the first 4wks to 70mg daily. Neuropsychological testing was performed at baseline and on days 29 and 57. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT); California Verbal Learning Test 2 (CVLT2); Brief Visuospatial Memory Test Revised (BVMT-R); Behavioral Rating Inventory of Executive Function for Adults (BRIEF-A).	1. There was a significant difference between groups on SDMT after intervention (mean increase: 4.6 LDX, 1.3 placebo; p=0.05) but a nonsignificant difference on SDMT after the highest tolerated dose was achieved and maintained for 4wks in either group (group x time interaction day 29 vs. day 57; p=0.544). 2. There was a nonsignificant difference between groups on PASAT (p=0.105) and BVMT-R (p=0.261) after intervention. 3. CVLT2 scores increased significantly more with LDX compared to placebo (mean increase: 4.7 LDX, -0.9 placebo; p=0.017). 4. There were no significant differences in change over time between groups on the BRIEF-A.
Morrow et al. 2009 *The effects of l-amphetamine sulfate on cognition in MS patients: results of a randomized controlled trial* USA **RCT** PEDro=9 N_{Initial}=151, N_{Final}=136	**Population:** *L-amphetamine (n=108)*: Mean age=47.8yr; Sex: males=28, females=80; Disease course: RRMS=70, SPMS=38; Severity: unspecified; Mean disease duration: unspecified. *Placebo (n=43)*: Mean age=50.4yr; Sex: males=8, females=35; Disease course: RRMS=28, SPMS=15; Severity: unspecified; Mean disease duration: unspecified. **Intervention:** Participants were randomized to receive either L-amphetamine or placebo for a duration of 4wks. The initial dose of L-amphetamine was 5mg, which was increased to 15mg after 7d, and increased again to 30mg after another 7d. Neuropsychological testing was performed on days 0 and 29, and tests of processing speed were also performed on day 15. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT); California Verbal Learning Test, second edition (CVLT2); Brief Visual Memory Test-revised (BVMTR); Paced Auditory Serial Addition Test (PASAT); Subject Global Assessment of Change (SGAC).	1. There was no significant difference between groups (30mg L-amphetamine vs. placebo) on SDMT (p=0.506), SGAC (p=0.879), or PASAT (p=0.205). 2. A significant difference was found between groups (30mg L-amphetamine vs. placebo) for CVLT2-Delayed Recall (p=0.012), BVMTR-Total Learning (p=0.041) and BVMTR-Delayed Recall (p<0.01), but not for CVLT2-Total Learning (p=0.912). 3. No severe or serious adverse events were reported throughout the study duration.
Sumowski et al. 2011	**Population:** *L-amphetamine (n=108)*: Mean age=47.8yr; Sex: males=28, females=80; Disease course: RRMS=70, SPMS=38; Severity: unspecified; Mean disease duration:	1. There was a significantly greater improvement on CVLT2-Delayed Recall performance in the L-amphetamine group compared to placebo (p=0.02),

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
(Secondary analysis of Morrow et al. 2009) *L-amphetamine improves memory in MS patients with objective memory impairment* USA $N_{Initial}$=151, N_{Final}=136	unspecified. *Placebo (n=43)*: Mean age=50.4yr; Sex: males=8, females=35; Disease course: RRMS=28, SPMS=15; Severity: unspecified; Mean disease duration: unspecified. **Intervention:** Secondary analysis of existing data to evaluate effect of L-amphetamine on memory in MS patients. Briefly, participants were randomized to receive either L-amphetamine or placebo for a duration of 4wks. **Cognitive Outcomes/Outcome Measures:** California Verbal Learning Test, second edition (CVLT-II); Brief Visuospatial Memory Test-revised (BVMT-R).	with the effect specific to participants with impaired auditory/verbal memory at baseline (49% improvement with treatment, 7% improvement with placebo; p=0.002). 2. There was no effect of L-amphetamine on CVLT2-Total Learning regardless of baseline memory function. 3. There was a significantly greater improvement on BVMT-R-Delayed Recall performance in the L-amphetamine group compared to placebo (p=0.012), with the effect specific to participants with baseline memory impairment (48% improvement with treatment, no improvement with placebo; p=0.002). 4. L-amphetamine significantly improved BVMT-R-Total Learning more than placebo, and this effect was specific to patients with baseline memory impairment (p=0.016).
Benedict et al. 2008 *Effects of l-amphetamine sulfate on cognitive function in multiple sclerosis patients* USA **RCT Crossover** PEDro=6 $N_{Initial}$=19, N_{Final}=19	**Population:** Mean age=48.1yr; Sex: males=3, females=16; Disease course: RRMS=16, SPMS=3; Median EDSS=2.5; Mean disease duration: unspecified. **Intervention:** Patients received four single dose administrations of placebo, 15mg, 30mg, or 45mg of *l*-amphetamine sulfate in a random order. Sessions were separated by 1wk. Assessments were performed 2hr after administration. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Test (PASAT); Symbol Digit Modalities Test (SDMT); Trail Making Test A, B (TMT-A, TMT-B); Rey Auditory Verbal Learning Test (RAVLT); Brief Visuospatial Memory Test-Revised (BVMT-R).	1. Significant between-group differences were measured for PASAT (p=0.009), TMT-A (p=0.011), and SDMT (p=0.001) scores between the placebo and the 45mg dose groups. There were no significant differences between the placebo and lower dose groups. 2. There were no statistically significant between-group effects for the other outcome measures.

Discussion

Four studies were found which investigated the use of amphetamines for CI in PwMS. One study (Morrow & Rosehart, 2015) compared single doses of 5mg and 10mg of an extended-release form of a dextroamphetamine and amphetamine combination tablet (trade name: *Adderall XR*) with placebo. The 10mg treatment group significantly improved on the SDMT compared to placebo (5.2±4.5 vs. 0.6±4.4; *p*=0.043; effect size of 0.47 in favour of treatment). However, there was no significant improvement on the Paced Auditory Serial Addition Test (PASAT) in either treatment group when compared to placebo, regardless of baseline impairment on the PASAT.

A small pilot study examining l-amphetamine, the isomer of d-amphetamine, found a significant difference between the placebo group and the highest dose l-amphetamine (45mg) group on measures of processing speed, but not on measures of memory (Benedict et al., 2008). However, a larger, multi-center placebo-controlled study of l-amphetamine (30mg) did not find any significant between-group differences on these same measures of processing speed, but did find significant differences in favour of the treatment group on similar measures of memory (Morrow et al., 2009). A secondary analysis of the same dataset (Sumowski et al., 2011) suggested that baseline CI level may affect response to treatment. Among those with memory impairment at baseline, Sumowski et al. (2011) found significant interactions whereby l-amphetamine improved memory more than placebo in terms of performance on the California Verbal Learning Test (CVLT-II) delayed recall (p=0.02), and the Brief Visuospatial Memory Test-Revised (BVMT-R) delayed recall (p=0.012) and total recall.

A randomized placebo-controlled pilot study of lisdexamfetamine dimesylate, a prodrug that is metabolized to lysine and d-amphetamine, demonstrated improvements among participants on the SDMT by 4.6 points in the treatment group compared to 1.3 points in the placebo group after eight weeks (Morrow et al., 2013). There was also an increase in performance on the CVLT-II, a measure of verbal learning and memory, in the lisdexamfetamine group compared to the placebo group (4.7 vs. -0.9). As with Morrow & Rosehart (2015), the PASAT was not significantly different between the two groups following intervention (p=0.11). However, the PASAT is known to have a significant practice effect and a strong component of working memory in addition to processing speed which may have contributed to the lack of treatment effect on the PASAT (Brochet et al., 2008; Drake et al., 2010; Nagels, D'Hooghe M, Kos, Engelborghs, & De Deyn, 2008).

Amphetamines or products with similar mechanisms are of interest in the treatment of CI, but these products are not widely used in clinical practice. Clinical practice patterns of amphetamine use in PwMS may be explained by the lack of strong evidence to support their benefit, the paucity of data with respect to the long-term safety of amphetamine use, as well as little clinical experience with amphetamines to date.

Conclusion

There is level 1b evidence that mixed amphetamine salts, extended release compared to placebo may improve visual processing speed, but not auditory processing speed (one randomized controlled trial; Morrow & Rosehart 2015).

There is level 1b evidence that lisdexamfetamine dimesylate compared to placebo may improve visual processing speed, and verbal learning and memory, but not auditory processing speed, visuospatial memory, or subjective impact on daily activities (one randomized controlled trial; Morrow et al. 2013).

There is level 1b evidence that l-amphetamine compared to placebo may improve verbal and visuospatial memory (one randomized controlled trial; Morrow et al. 2009; Sumowski et al. 2011).

There is level 1b evidence that l-amphetamine compared to placebo may not improve auditory processing speed, visual processing speed, or subjective ratings of cognition (one randomized controlled trial; Morrow et al. 2009).

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Mixed amphetamine salts may be beneficial for visual processing speed, but not other forms of processing speed, in persons with MS.

Lisdexamfetamine dimesylate may improve visual processing speed and verbal memory, but not other cognitive functions or the subjective impact of cognitive impairment on daily activities, in persons with MS.

L-amphetamine may improve verbal and visuospatial memory, but not other cognitive functions or subjective measures of cognition, in persons with MS.

3.1.3 Methylphenidate

Methylphenidate is a CNS stimulant similar to amphetamines and indicated for use in ADHD. Stimulants may lead to improved attention span and ability to follow directions or complete tasks, decreased distractibility, and decreased impulsivity ("Drug monograph: Methylphenidate," 2020).

Table 4. Study Examining Methylphenidate for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Harel et al. 2009 *Single dose of methylphenidate improves cognitive performance in multiple sclerosis patients with impaired attention process* Israel **RCT** PEDro=8 $N_{Initial}$=26, N_{Final}=26	**Population:** *Treatment Group (n=14)*: Mean age=34.6yr; Sex: males=3, females=11; Disease course: RRMS; Mean EDSS=3.8; Mean disease duration=10.6yr. *Control Group (n=12)*: Mean age=40.1yr; Sex: males=3, females=9; Disease course: RRMS; Mean EDSS=3.1; Mean disease duration=11.5yr. **Intervention:** Patients received a one-time, single tablet dose of 10mg methylphenidate or placebo. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Test (PASAT).	1. Performance was significantly increased after treatment with methylphenidate on both PASAT 2" and 3" (mean increase 22.8% and 25.6% respectively, $p<0.001$). 2. No significant effect was observed in patients receiving placebo. 3. Results of between-group comparisons were not reported.

Discussion

One study has investigated methylphenidate for CI in MS. Harel et al. (2009) reported a significant within group improvement pre-post on the PASAT with a single 10mg dose of methylphenidate, while no significant change was reported pre-post for the placebo group. No between group comparisons were

provided for this RCT. Therefore, the trial provides lower-level evidence in favour of methylphenidate. Methylphenidate use in PwMS is limited due to the short duration of action and neuropsychiatric side effects.

Conclusion

There is level 4 evidence that methylphenidate compared to placebo may improve auditory processing speed in persons with relapsing-remitting MS (one randomized controlled trial; Harel et al. 2009).

> Preliminary evidence suggests methylphenidate may improve auditory processing speed in persons with relapsing-remitting MS.

3.1.4 Dalfampridine/Fampridine

Dalfampridine, also known as slow-release fampridine, is a slow-release formulation of 4-aminopyridine (Morrow et al., 2017). It is a neuronal potassium channel blocker that reduces potassium re-entry into axons during the action potential and increases conduction of the nerve impulse across demyelinated segments ("Drug monograph: Dalfampridine," 2018). Prior to the approval of slow-release fampridine, or in areas where it is not available, fampridine as an immediate-release formulation has been studied, although its use has been limited by adverse events, including seizures (Goodman et al., 2009). In this section, both formulations of fampridine (immediate and slow-release) are included.

Table 5. Studies Examining Fampridine or Dalfampridine for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Satchidanand et al. 2020 *Dalfampridine benefits ambulation but not cognition in multiple sclerosis* USA **RCT** PEDro=6 N$_{Initial}$=61, N$_{Final}$=57	**Population:** *Treatment group (n=45):* Mean age=47.6yr; Sex: males=7, females=38; Disease course: RRMS=37, SPMS=7, PPMS=1; Median EDSS=3.5; Mean disease duration=13.5yr. *Placebo group (n=16):* Mean age=53.0yr; Sex: males=6, females=10; Disease course: RRMS=12, SPMS=4; Median EDSS=3.5; Mean disease duration=13.8yr. **Intervention:** Participants were randomized to receive either dalfampridine (10mg 2x/d) or placebo for 12wks. Outcomes were assessed at baseline and at end of treatment. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT); California Verbal Learning Test 2 (CVLT); Brief	1. After treatment, there were no significant differences between groups on the SDMT (mean difference=6.42, p=0.395, d=0.59), PASAT (mean difference=4.74, p=0.441, d=0.32), CVLT (mean difference=7.25, p=0.578, d=0.71), BVMT (mean difference=5.35, p=0.722, d=0.90), or DKEFS (mean difference=0.49, p=0.394, d=0.17). 2. At baseline, there were no differences based on responder status with regard to any cognitive measures. 3. At end-point, there was no significant difference by responder status in change on the SDMT (mean difference=1.59, p=0.450), while performance on the

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	Visuospatial Memory Test Revised (BVMT); Delis Kaplan Executive Function System (DKEFS).	PASAT improved significantly among responders in the dalfampridine group compared to non-responders (3.68, p=0.034). 4. At end-point, there were no significant differences observed for CVLT (p=0.578), BVMT (p=0.722), or DKEFS (p=0.394) based on responder status.
Arreola-Mora et al. 2019 *Effects of 4-aminopyridine on attention and executive functions of patients with multiple sclerosis: randomized, double-blind, placebo-controlled clinical trial. Preliminary report* Mexico **RCT** PEDro=6 N_Initial=24, N_Final=21	**Population:** *4-aminopyridine (n=11):* Mean age=39.5yr; Sex: males=4, females=7; Disease course: RRMS; Mean EDSS=4.7; Mean disease duration=8.55yr. *Placebo (n=10):* Mean age=39.3yr; Sex: males=4, females=6; Disease course: RRMS; Mean EDSS=4.3; Mean disease duration=9.4yr. **Intervention:** Participants were randomized to receive 4-aminopyridine (10mg tabs not slow release), increased to a maximum dose of 0.7mg/kg of weight/d divided tid) or placebo over 20wks with 4-6 wks at the max dose. Outcomes were assessed at baseline and during wks 21-22 of the study. **Cognitive Outcomes/Outcome Measures:** Brief Repeatable Battery of Neuropsychological Tests for Multiple Sclerosis (BRBN-MS): Selective Reminding Test (SRT), 7/24 Spatial Recall Test (SRT-7/24), Paced Auditory Serial Addition Task 3, 2 seconds (PASAT-3, 2), Symbol Digit Modalities Test (SDMT), Word List Generation (WLG); Tower of London (TOL); Integrated Program of Neuropsychological Examination-Revised Barcelona test (IPNE): Digit Span Forward, Digit Span Backward, Memory of texts, Cubes; Color Trails Test; Wisconsin Card Sorting Test (WCST); Five Digit Test (FDT); Rey-Osterrieth Complex Figure test (ROCF).	1. Participants who received 4-aminopyridine showed significant improvement in Digit Span Forward-IPNE (p=0.001), WLG (p=0.028), TOL (total moves (p=0.017)), total correct (p=0.010), total execution time (p=0.001), total problem-solving time (p=0.001)), and ROCF (memory execution times (p=0.016), delayed memory execution times (p=0.032)) compared to the placebo group, with small to medium (0.20-0.70) effect sizes. 2. There were significant differences between groups favouring the placebo group for SDMT (p=0.001), SRT-7/24 (p=0.001), ROCF (p=0.002), and Cubes (p=0.027).
De Giglio et al. 2019 *Effect of dalfampridine on information processing speed impairment in multiple sclerosis* Italy **RCT** PEDro=9 N_Initial=120, N_Final=107	**Population:** *Dalfampridine (n=80):* Mean age=49.3yr; Sex: males=30, females=50; Disease course: RRMS=72, SPMS=7, PPMS=1; Median EDSS=4; Mean disease duration=14.7yr. *Placebo (n=40):* Mean age=46.7yr; Sex: males=16, females=24; Disease course: RRMS=31, SPMS=7, PPMS=2; Median EDSS=4.5; Mean disease duration=17.2yr. **Intervention:** Participants were randomized to receive either slow-release dalfampridine (10mg 2x/d) or placebo for 12wks. Outcomes were assessed at baseline, after treatment, and at 4wks follow-up.	1. At 12wks, there was a significant difference between groups in SDMT raw scores, with an average change from baseline of 9.9 [8.5, 11.4 95% CI] for the dalfampridine group and 5.2 [2.8, 7.6 95% CI] for the placebo group (p=0.0018, d=0.60). This difference was no longer significant at a further 4wks follow-up. 2. At 12 wks, there was a significant difference between groups in SDMT z scores, with an average change from baseline of 0.8 [0.6, 1.0 95% CI] for the dalfampridine group and 0.3 [-0.0, 0.5 95% CI] for the placebo group (p=0.0013,

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	Cognitive Outcomes/Outcome Measures: Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test 3, 2 seconds (PASAT-3, 2); Selective Reminding Test - Long-term storage (SRT-LTS), Consistent long-term retrieval (SRT-CLTR), Delayed recall (SRT-D); 10/36 Spatial Recall Test (10/36-SPART); 10/36 SPART-delayed recall (10/36-SPART-D)[2]; Word List Generation, Stroop Test; Tower of London (TOW).	d=0.61). This difference was no longer significant at a further 4wks follow-up. 3. The proportion of participants with a ≥4 point increase in SDMT raw score and a ≥20% increase in the SDMT was significantly higher in the dalfampridine group compared to the placebo group (86.1% vs. 60.3%, [p=0.0029] and 75.9% vs. 44.5% [p=0.0012], respectively). 4. The average improvement in PASAT-3 z scores was 0.6 [0.3, 0.9 95% CI] for the dalfampridine group and 0.1 [-0.2, 0.5 95% CI] for the placebo group (p=0.0327, d=0.39). 5. The average improvement in PASAT-2 z scores was 0.6 [0.4, 0.8 95% CI] for the dalfampridine group and 0.2 [-0.1, 0.5 95% CI] for the placebo group (p=0.0319, d=0.40). 6. There were no between-group differences for the remaining cognitive tests at either assessment time point.
Broicher et al. 2018 *Positive effects of fampridine on cognition, fatigue and depression in patients with multiple sclerosis over 2 years* Switzerland **RCT Crossover** PEDro=8 N_Initial=32, N_Final=20	**Population:** *Participants completing first yr (n=32):* Mean age=50.3yr; Sex: males=13, females=19; Disease course: RRMS=15, PPMS=3, SPMS=14; Mean EDSS=5.0; Mean disease duration=11.3yr. *Participants completing second yr (n=20):* Mean age=51.4yr; Sex: males=10, females=10; Disease course: RRMS=9, PPMS=2, SPMS=9; Mean EDSS=4.8; Mean disease duration=11.3yr. **Intervention:** Participants received 10mg of open-label treatment with prolonged release (PR)-fampridine 2x/d for 11.5mo, followed by a 2wk washout period. Continuous treatment with PR-fampridine was re-initiated for another 11.5mo. Participants were then randomized to receive PR-fampridine for 2wks followed by 2wks of placebo, or vice versa. Outcomes were assessed during open-label treatment, after the washout period, and at the end of the second yr. **Cognitive Outcomes/Outcome Measures:** Test of Attentional Performance (TAP): alertness test, selective attention task, working memory task; Symbol Digit Modalities Test (SDMT for psychomotor speed); Regensburger verbal fluency test; HAMASCH-5-point test.	1. At the end of the second year, PR-fampridine had beneficial effects on phasic alertness compared to placebo (p=0.0010), but there were no significant between-group differences for tonic alertness (TAP, p=0.3534), selective attention (TAP, p=0.9636), psychomotor speed (SDMT, p=0.9932), verbal fluency (Regensburger verbal fluency test, p=0.2263), figural fluency (HAMASCH-5-point test, p=0.0810), or working memory (TAP reaction time p=0.3163; total errors p=0.3786).

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Morrow et al. 2017 *The effect of Fampridine-SR on cognitive fatigue in a randomized double-blind crossover trial in patients with MS* Canada **RCT Crossover** PEDro=6 $N_{Initial}$=60, N_{Final}=48	**Population:** *Fampridine-slow release (SR) (n=29):* Mean age=46.2yr; Sex: males=6, females=23; Disease course: RRMS=17, SPMS=8, PPMS=4; Median EDSS=3.5; Mean disease duration=11.3yr. *Placebo (n=31):* Mean age=46.7yr; Sex: males=8, females=23; Disease course: RRMS=24, SPMS=6, PPMS=1; Median EDSS=3.0; Mean disease duration=10.0yr. **Intervention:** Patients were randomized to receive Fampridine-SR 10mg 2x/d or matching placebo for 4wks. After a 1wk washout period, subjects crossed over to the other treatment group for 4wks. Assessments were performed at baseline and at the end of each treatment block. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Test (PASAT); PASAT cognitive fatigue.	1. A significant treatment*time interaction was observed for the PASAT cognitive fatigue (p=0.006) and PASAT raw scores (0.047). 2. Evaluation of mean scores for both measures suggested that participants experienced a greater improvement while on placebo compared to the active medication.
Jensen et al. 2016 *Effect of slow release-Fampridine on muscle strength, rate of force development, functional capacity and cognitive function in an enriched population of MS patients. A randomized, double blind, placebo controlled study* Denmark **RCT** PEDro=9 $N_{Initial}$=37, N_{Final}=35	**Population:** *Fampridine (n=17):* Mean age=50.8yr; Sex: males=53%, females=47%; Disease course: unspecified; Mean EDSS=5.8; Mean disease duration=9.5yr. *Placebo (n=20):* Mean age=48.4yr; Sex: males=35%, females=65%; Disease course: unspecified; Mean EDSS=5.5; Mean disease duration=9.8yr. **Intervention:** Participants who previously responded to slow-release fampridine were randomized to slow-release fampridine 10mg 2x/d or placebo treatment for 4wks. Assessments were performed at baseline and on days 26-28. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT).	1. There were no significant between-group differences on change in SDMT following treatment (p=0.9).
Bakirtzis et al. 2018 *Long-term effects of prolonged-release fampridine in cognitive function, fatigue, mood and quality of life of MS patients: The IGNITE study* Greece	**Population:** Mean age=51yr; Sex: males=29, females=31; Disease course: RRMS=18, PPMS=17, SPMS=25; Median EDSS=5.5; Mean disease duration=13.7yr. **Intervention:** Participants were treated with prolonged-release fampridine for 12mo. Outcomes were assessed at baseline and at 6 and 12mo. **Cognitive Outcomes/Outcome Measures:** Brief International Cognitive Assessment in MS (BICAMS): Symbol Digit Modalities Test (SDMT), Greek Verbal Learning Test (GVLT),	1. For responders (i.e., improvement of ≥15-20% in timed 25ft walk performance after 2wks of treatment), significant improvement was observed on the SDMT at 6mo (35.6; p<0.001) and 12mo (34.7; p<0.001) compared to baseline (32.0). There were no significant changes from baseline for non-responders. 2. There were no significant changes on the remaining outcome measures for either group at either assessment time point.

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Pre-Post $N_{Initial}$=60, N_{Final}=52	Brief Visuospatial Memory Test Revised (BVMT-R).	3. For responders, 51.4% and 51.5% demonstrated a clinically meaningful change on the SDMT (4-point improvement) at 6 and 12mo, respectively, while the rest remained stable. 4. For non-responders, 5.2% and 10.5% demonstrated a clinically meaningful change on the SDMT at 6 and 12mo, respectively, while 5.5% demonstrated a 4-point decline at 12mo.
Korsen et al. 2017 *Dalfampridine effects on cognition, fatigue, and dexterity* Germany **Pre-Post** $N_{Initial}$=39, N_{Final}=34	**Population:** *Nonresponders (n=12):* Mean age=48.4yr; Sex: males=5, females=7; Disease course: RRMS=5, SPMS=4, PPMS=3; Median EDSS=4.5; Mean disease duration: unspecified. *Responders (n=22):* Mean age=48.0yr; Sex: males=7, females=15; Disease course: RRMS=13, SPMS=8, PPMS=1; Median EDSS=4.0; Mean disease duration: unspecified. **Intervention:** MS patients with impaired mobility received dalfampridine treatment 10mg 2x/d for 12-14d. Patients were categorized as responders or non-responders based on improved walking ability while taking dalfampridine. Assessments were performed at baseline and after treatment. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Test (PASAT).	1. Following dalfampridine treatment, a significantly improved overall mean PASAT score was observed (p=0.029).
Jensen et al. 2014 *Changes in cognition, arm function and lower body function after Slow-Release Fampridine treatment* Denmark **Pre-Post** $N_{Initial}$=108, N_{Final}=105	**Population:** Mean age=48.6yr; Sex: males=41.7%, females=58.3%; Disease course: unspecified; Mean EDSS=5.6; Mean disease duration=10.8yr. **Intervention:** Patients received slow-release fampridine 10mg 2x/d for 4wks. Assessments were performed before and after treatment. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT).	1. A significant increase of 4.6% was observed in the mean SDMT score after treatment (p=0.003).

Discussion

Nine studies have examined the effect of dalfampridine, slow-release fampridine, or 4-aminopyridine on cognitive impairment in PwMS.

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Five RCTs have examined the effect of slow-release fampridine or dalfampridine compared to placebo. A trial by Jensen et al. (2016) did not find any significant treatment effects between slow-release fampridine and placebo groups on the SDMT after four weeks of treatment. Morrow et al. (2017) performed a RCT crossover examining the effect of slow-release fampridine on cognitive fatigue and auditory processing speed in MS. After four weeks, results showed a significant treatment by time interaction for both outcomes, with further evaluation indicating a greater improvement in both cognitive fatigue and auditory processing speed in favour of the placebo compared to the active medication. De Giglio et al. (2019) found a positive effect of slow-release dalfampridine on visual and auditory processing speed after 12 weeks of treatment, as measured by the SDMT and PASAT, respectively, but not for other cognitive functions. However, Satchidanand et al. (2020) did not observe any differences on cognitive measures after 12 weeks of treatment with dalfampridine, including the SDMT and PASAT. Finally, Broicher et al. (2018) conducted an open-label and randomized placebo-controlled crossover study to assess the long-term effect of slow-release fampridine on cognitive performance over a period of two years. The authors classified the SDMT as a test to evaluate primarily the psychomotor speed domain rather than primarily visual processing speed. Presumably the written version of the SDMT was utilized and this version has not been validated in PwMS. Compared to placebo, significant fampridine-induced improvements were limited to phasic alertness, while other measures of attentional, processing speed, and executive function remained unchanged.

One small RCT by Arreola-Mora et al. (2019) examined the effect of immediate release 4-aminopyridine compared to placebo over a duration of 20 weeks in participants with relapsing-remitting MS (RRMS), using an extensive battery of neuropsychological tests to assess cognitive function. Results demonstrated that 4-aminopyridine significantly improved some cognitive processes, including attention span, executive function, graphical praxias, and visuospatial skills, but not others. Of note, significant improvements were observed in the placebo group compared to the 4-aminopyridine group on four tests, which may have been due to a placebo effect. Whether this positive result is due to the immediate release formulation use or weight-based dosing (dalfampridine has only one prescribed dose) is not known.

Finally, three studies examined dalfampridine or slow-release fampridine using an uncontrolled pre-post design. Bakirtzis et al. (2018) found that participants treated with slow-release fampridine demonstrated a significant and clinically meaningful improvement on the SDMT after six and 12 months, but did not demonstrate changes in terms of visual or verbal memory. Similarly, Jensen et al. (2014) found that participants demonstrated a statistically significant and potentially clinically meaningful improvement on the SDMT after four weeks of treatment with slow-release fampridine. Korsen et al. (2017) examined the effect of dalfampridine on cognitive function, using the PASAT as the cognitive outcome measure. Similar to the visual processing speed results of Bakirtzis et al. (2018) and Jensen et al. (2014), there was a significant improvement in performance on the PASAT following a treatment duration of approximately two weeks.

Conclusion

There is conflicting evidence regarding whether dalfampridine compared to placebo improves visual and auditory processing speed after 12 weeks of treatment (two randomized controlled trials; De Giglio et al. 2019; Satchidanand et al. 2020).

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There is level 1a evidence that dalfampridine compared to placebo may not improve verbal learning and memory, visuospatial memory, or executive function after 12 weeks of treatment (two randomized controlled trials; De Giglio et al. 2019; Satchidanand et al. 2020).

There is level 1b evidence that dalfampridine compared to placebo may not improve verbal fluency after 12 weeks of treatment (one randomized controlled trial; De Giglio et al. 2019).

There is level 1b evidence that slow-release fampridine compared to placebo may not acutely improve auditory processing speed (one randomized controlled trial; Morrow et al. 2017) or visual processing speed (one randomized controlled trial; Jensen et al. 2016) or attention, with the exception of improving phasic alertness (one randomized controlled trial; Broicher et al. 2018).

There is level 4 evidence that slow-release fampridine may not improve visuospatial or verbal memory long-term (one pre-post study; Bakirtzis et al. 2018).

There is level 1b evidence that immediate release 4-aminopyridine compared to placebo may improve working memory, verbal fluency, executive function and visuospatial skills, but not other cognitive functions, in persons with relapsing-remitting MS (one randomized controlled trial; Arreola-Mora et al. 2019).

Conclusion

4-aminopyridine immediate release compared to placebo may be beneficial for improving the domains of memory, verbal fluency, executive function, and visuospatial skills, but not other cognitive functions, in persons with relapsing-remitting MS. Slow-release 4-aminopyridine formulations compared to placebo may not improve cognitive function in multiple cognitive domains tested in persons with MS.

3.1.5 Donepezil

Donepezil is an acetylcholinesterase inhibitor, selectively inhibiting this enzyme to improve the availability of acetylcholine, and is approved for the treatment of Alzheimer's disease ("Drug monograph: Donepezil," 2020).

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Table 6. Studies Examining Donepezil for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Krupp et al. 2011 *Multicenter randomized clinical trial of donepezil for memory impairment in multiple sclerosis* USA **RCT** PEDro=9 N_{Initial}=120, N_{Final}=113	**Population:** *Placebo Group (n=59)*: Mean age=47.3yr; Sex: males=11, females=48; Disease course: RRMS=37, SPMS=19, PPMS=3; Mean EDSS=3.74; Mean disease duration=9.4yr. *Donepezil Group (n=61)*: Mean age=46.2yr; Sex: males=16, females=45; Disease course: RRMS=38, SPMS=18, PPMS=5; Mean EDSS=3.96; Mean disease duration=11.3yr. **Intervention:** Participants were randomized to receive either donepezil or placebo for a duration of 24wks. Donepezil was administered at a dose of 5mg/d, which was increased to 10mg/d at wk 4. Assessments were performed at baseline and at 24wks. **Cognitive Outcomes/Outcome Measures:** Selective Reminding Test (SRT); 10/36 Spatial Recall Test (10/36); Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT); Controlled Oral Word Association (COWA); Delis-Kaplan Executive Function System (D-KEFS); Judgment of Line Orientation (JOLO); Multiple Sclerosis Neuropsychological Questionnaire (MSNQ); Brief Assessment of Memory and Attention (BAMA).	1. No significant treatment effects were reported for any primary or secondary outcome measures. 2. A trend in favour of donepezil was reported for the evaluating clinician's impression of memory change (p=0.097).
Krupp et al. 2004/ Christodoulou et al. 2006 *Donepezil improved memory in multiple sclerosis in a randomized clinical trial/Effects of donepezil on memory and cognition in multiple sclerosis* USA **RCT** PEDro=10 N_{Initial}=69, N_{Final}=67	**Population:** *Donepezil (n=35)*: Mean age=42.49yr; Sex: males=15, females=20; Disease course: RRMS=24, SPMS=9, PPMS=2; Mean EDSS=3.14; Mean disease duration=7.09yr. *Placebo (n=34)*: Mean age=45.85yr; Sex: males=7, females=27; Disease course: RRMS=14, SPMS=19, PPMS=1; Mean EDSS=4.25; Mean disease duration=9.12yr. **Intervention:** Participants were randomized to receive either oral donepezil or placebo for 24wks. The initial dose of donepezil was 5mg/d, which was increased to 10mg/d at wk 4. Assessments were administered at baseline and at 24wks. **Cognitive Outcomes/Outcome Measures:** Selective Reminding Test (SRT); 10/36 Spatial Recall Test (10/36); Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT); modified Controlled Oral Word Association (COWA); Tower of Hanoi.	1. Memory performance improved more in participants receiving donepezil compared to those receiving placebo (4.57 vs. 068, respectively) on the SRT total recall change (p=0.043). 2. The mean percentage improvement on the SRT was also higher for donepezil compared to placebo participants (13.89% vs. 2.59%, respectively; p=0.028). 3. The benefit of donepezil over placebo remained significant after controlling for the following covariates: age, EDSS, baseline SRT score, and Wide Range Achievement Test 3 Reading score (p=0.029). 4. More participants who received donepezil (65.7%) compared to those who received placebo (32.4%) reported that their memory had improved (p=0.006). 5. There was a trend toward improved performance on the PASAT among those receiving donepezil compared to those

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
		receiving placebo (5.29 vs. 0.79, respectively; p=0.082). 6. There were no group differences on the other neuropsychological tasks.
Greene et al. 2000 *A 12-week, open trial of donepezil hydrochloride in patients with multiple sclerosis and associated cognitive impairments* USA **Pre-Post** N$_{Initial}$=17, N$_{Final}$=17	**Population:** Mean age=55yr; Sex: males=3, females=14; Disease course: unspecified; Mean EDSS=8; Mean disease duration=27.6yr. **Intervention:** Participants received 5mg donepezil HCl daily for 4wks, followed by 8wks of 10mg. Assessments were performed at baseline and after 4 and 12wks of treatment. **Cognitive Outcomes/Outcome Measures:** Hopkins Verbal Learning Test (HVLT); Mini-Mental State Examination (MMSE); Brief Test of Attention (BTA); Wechsler Adult Intelligence Scale-Revised (WAIS-R) digit span; Boston Naming Test (BNT); Controlled Oral Word Association Test (COWAT); Motor-Free Visual Perception Test (MVPT); Mattis Dementia Rating Scale; Trail Making Test (TMT); Clinical Global Impression of Change (CGIC).	1. Total MMSE scores significantly improved at 4 and 12wks compared to baseline and at 12wks with respect to 4wks (p=0.0003, p<0.0001, p=0.001 respectively). 2. The HVLT true positives score was significantly different at 4 and 12wks compared to baseline (p=0.02, p=0.003 respectively). There was no significant difference in the sum of the three free or delayed recall trials. 3. The CGIC severity of illness score was significantly improved at 12wks compared with baseline and 4wks (p=0.004, p=0.002, respectively). 4. The CGIC global improvement score was significantly improved at 4 and 12wks compared with baseline (p=0.004, p=0.001, respectively). 5. BTA scores were not significantly different after treatment compared to baseline. 6. The digit span test scores were significantly different at 12wks compared with baseline and 4wks (p=0.03, p=0.03, respectively). 7. BNT scores were significantly different at 4 and 12wks compared with baseline (p=0.03, p<0.0001 respectively) and at 12wks compared to 4wk assessment (p=0.002). 8. TMT data were excluded from analysis. 9. The COWAT category portion, MVPT recognition items, and Mattis Dementia conceptualization subtest scores were significantly different at 12wks compared with baseline (p=0.003, p=0.02 and p=0.04 respectively).

Discussion

Three studies were found which investigated the use of donepezil for CI in MS. A small uncontrolled 12-week study found that participants improved at four and/or 12 weeks on most cognitive measures apart from the Brief Test of Attention, as well as improving on the Clinical Global Impression of Change score (Greene et al., 2000). Krupp et al. (2004), in a small, randomized placebo 24-week pilot study, found a

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significant benefit of donepezil over placebo on a verbal learning and memory measure (Selective Reminding Test; SRT). However, in a larger multicenter placebo-controlled trial using many of the same outcome measures, there was no benefit noted on either subjective or objective cognitive measures, including the SRT (Krupp et al., 2011).

Conclusion

There is level 1a evidence that donepezil compared to placebo may not improve spatial memory, visual processing speed, auditory processing speed, or verbal fluency (two randomized controlled trials; Krupp et al. 2004; Krupp et al. 2011).

There is level 1b evidence that donepezil compared to placebo may not improve executive function or spatial processing (one randomized controlled trial; Krupp et al. 2011).

There is level 1b evidence that donepezil compared to placebo may not improve problem solving (one randomized controlled trial; Krupp et al. 2004).

Donepezil does not improve memory, processing speed, verbal fluency, or executive function in persons with MS.

3.1.6 Erythropoietin

Erythropoietin exerts a neuroprotective effect in the brain and might address pathophysiological mechanisms in progressive forms of MS (Brines & Cerami, 2005; Schreiber et al., 2017).

Table 7. Study Examining Erythropoietin for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Schreiber et al. 2017 *High-dose erythropoietin in patients with progressive multiple sclerosis: a randomized, placebo-controlled, phase 2 trial* Denmark **RCT** PEDro=9	**Population:** *Erythropoietin group (n=26)*: Mean age=52.7yr; Sex: males=13, females=13; Disease course: SPMS=16, PPMS=10; Mean EDSS=5.1; Mean disease duration=16.7yr. *Placebo group (n=26)*: Mean age=48.8yr; Sex: males=12, females=14; Disease course: SPMS=18, PPMS=8; Mean EDSS=5.5; Mean disease duration=14.9yr. **Intervention:** Patients were randomized to receive either recombinant erythropoietin-beta 48,000 IU or placebo, administered intravenously 17 times in 24wks; weekly during wks 1-12 and bi-weekly from wk 12 to wk 24. Assessments were performed at	1. No significant effects of treatment were observed between groups on cognitive outcome measures.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
N_Initial=56, N_Final=48	baseline and after 12, 24, and 48wks of treatment. **Cognitive Outcomes/Outcome Measures:** Trail Making Test B (TMT-B); Symbol Digit Modalities Test (SDMT); MS Functional Composite (MSFC).	

Discussion

In a phase II study evaluating the effects of high dose erythropoietin on progressive forms of MS (Schreiber et al., 2017), cognitive measures were included as primary and secondary outcomes. The study did not find any benefit of erythropoietin on any of the outcomes, including cognitive measures, compared to placebo.

Conclusion

There is level 1b evidence that erythropoietin compared to placebo may not improve cognitive impairment in persons with primary or secondary progressive MS (one randomized controlled trial; Schreiber et al. 2017).

Erythropoietin may not be beneficial for improving cognitive impairment in persons with primary or secondary progressive MS.

3.1.7 Fluoxetine

It has been hypothesized that fluoxetine and prucalopride may have a positive effect on phosphocreatine metabolism which is believed to be altered in progressive MS (Cambron et al., 2018).

Table 8. Study Comparing Fluoxetine vs. Prucalopride for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Cambron et al. 2018	**Population:** *Fluoxetine (n=15):* Mean age=45.4yr; Sex: males=6, females=10; Disease course: RRMS; Median EDSS=1.5. *Prucalopride (n=14):* Mean age=42.2yr; Sex: males=7, females=8; Disease course: RRMS;	1. There was no significant difference over time between any of the groups for the SDMT (p=0.899), CVLT-II (p=0.636), or COWAT semantic (p=0.126) and phonetic (p=0.258).

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Targeting phosphocreatine metabolism in relapsing-remitting multiple sclerosis: evaluation with brain MRI, 1H and 31P MRS, and clinical and cognitive testing Belgium **RCT** PEDro=6 N$_{Initial}$=42, N$_{Final}$=41	Median EDSS=1.5. *Placebo (n=13):* Mean age=42.8yr; Sex: males=4, females=10; Disease course: RRMS; Median EDSS=1.0. For total study sample: Mean disease duration=10.4yr. **Intervention:** Participants were randomized to receive either fluoxetine, prucalopride, or placebo for 6wks. Fluoxetine was administered at 20mg/d for 2wks and 40mg/d for 4wks. Prucalopride was administered at 1mg/d for 2wks and 2mg/d for 4wks. Outcomes were assessed at baseline and at 6wks. **Cognitive Outcomes/Outcome Measures:** California Verbal Learning Test II (CVLT-II); Symbol Digit Modalities Test (SDMT); Controlled Oral Word Association Test (COWAT).	

Discussion

Cambron et al. (2018) randomized participants with RRMS to receive either fluoxetine, prucalopride, or placebo for six weeks. Cognitive function was included as a secondary endpoint according to the CVLT-II, SDMT, and Controlled Oral Word Association Test assessed at baseline and six weeks. At the end of the trial, there were no differences in cognitive function on any outcome measures between treatment groups. However, the study was not powered to evaluate these clinical parameters.

Conclusion

There is level 1b evidence that fluoxetine compared to placebo may not improve cognitive impairment in persons with relapsing-remitting MS (one randomized controlled trial; Cambron et al. 2018).

There is level 1b evidence that prucalopride compared to placebo may not improve cognitive impairment in persons with relapsing-remitting MS (one randomized controlled trial; Cambron et al. 2018).

Fluoxetine or prucalopride may not improve cognitive impairment in persons with relapsing-remitting MS.

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3.1.8 Memantine

Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist and is approved for the treatment of Alzheimer's disease ("Drug monograph: Memantine," 2020). It blocks overstimulated NMDA receptors and is thought to prevent neurotoxicity normally caused by a massive glutamate release.

Table 9. Studies Examining Memantine for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Peyro Saint Paul et al. 2016 *Efficacy and safety profile of memantine in patients with cognitive impairment in multiple sclerosis: a randomized, placebo-controlled study* France **RCT** PEDro=8 $N_{Initial}$=93, N_{Final}=62	**Population:** *Memantine (n=48):* Mean age=39.6yr; Sex: males=14, females=34; Disease course: RRMS; Mean EDSS=3.1; Disease duration: <7yr=13, ≥7yr=35. *Placebo (n=38):* Mean age=43.9yr; Sex: males=15, females=23; Disease course: RRMS; Mean EDSS=3.4; Disease duration: <7yr=6, ≥7yr=31. **Intervention:** Patients were randomized to receive memantine (20mg/d) or placebo for 52wks (20mg/d was achieved through an upward adjustment of 5mg/wk over the first 3wks). Assessments were performed at baseline and after 1yr of treatment. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Test (PASAT); Set of Tests of Attention Performance (TAP); Digit span: forward, backward.	1. No significant difference was observed between the two groups on any cognitive outcome measures at 1yr.
Lovera et al. 2010 *Memantine for cognitive impairment in multiple sclerosis: a randomized placebo-controlled trial* USA **RCT** PEDro=9 $N_{Initial}$=126, N_{Final}=114	**Population:** *Placebo (n=65):* Mean age=50.4yr; Sex: males=15, females=50; Disease course: RRMS=47, PPMS=6, SPMS=12; Mean EDSS=4.4; Mean disease duration=13.3yr. *Memantine (n=54):* Mean age=50.5yr; Sex: males=9, females=45; Disease course: RRMS=28, PPMS=12, SPMS=14; Mean EDSS=4.5; Mean disease duration=14.0yr. **Intervention:** Patients were randomized to receive either memantine therapy or placebo for 16wks. Memantine was given at a dose of 10mg 2x/d titrated up for 4wks and followed by 12wks at the highest tolerated dose. Assessments were performed at baseline and after 12wks of therapy. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Test (PASAT); California Verbal Learning Test-II (CVLT-II): Long Delay Free Recall (LDFR); Symbol Digit Modalities Test (SDMT); Controlled Oral Word Association Test (COWAT); Delis Kaplan Executive Function System (D-KEFS); Stroop Test; Perceived Deficits Questionnaire (PDQ); MS Neuropsychological Screening Questionnaire (MSNSQ).	1. No significant differences in change in PASAT (p=0.9), CVLT-LDFR (p=0.4), or other cognitive measure scores were observed between groups. 2. The placebo group reported significantly greater improvement on the MSNSQ than the treatment group (p=0.02). 84 subjects' family members completed the MSNSQ. 3. There was a trend in favour of the placebo group improving more than the memantine group on the PDQ (p=0.07).

Discussion

Two studies have examined the effects of memantine on CI in PwMS. In the first study, participants were treated with memantine or placebo for 16 weeks. The were no significant differences between the two groups at the end of the study on objective cognitive measures; interestingly, the family members reported a significantly greater subjective improvement in the placebo group compared to the treatment group (Lovera et al., 2010). A second study in 2016 compared memantine to placebo over 52 weeks and also did not find any significant differences on cognitive measures between groups (Peyro Saint Paul et al., 2016).

Conclusion

There is level 1a evidence that memantine compared to placebo may not improve cognitive impairment (two randomized controlled trials; Peyro Saint Paul et al. 2016; Lovera et al. 2010).

Memantine does not improve cognitive impairment in persons with MS.

3.1.9 Modafinil/Armodafinil

Modafinil is a non-amphetamine CNS stimulant with wakefulness-promoting properties. Armodafinil is the R-enantiomer of modafinil. Both are used to promote wakefulness and decrease somnolence in numerous medical disorders ("Drug monograph: Modafinil," 2020).

Table 10. Studies Examining Modafinil or Armodafinil for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Ford-Johnson et al. 2016 *Cognitive effects of modafinil in patients with multiple sclerosis: a clinical trial* USA **RCT Crossover** PEDro=7 N$_{Initial}$=18, N$_{Final}$=16	**Population:** *Group 1 (n=9):* Mean age=41.67yr; Sex: males=2, females=7; Disease course: RRMS=6, PPMS=1, SPMS=1, unknown=1; Mean EDSS=3.11; Mean disease duration=10.33yr. *Group 2 (n=7):* Mean age=43.43yr; Sex: males=1, females=6; Disease course: RRMS=4, SPMS=2, unknown=1; Mean EDSS=4.79; Mean disease duration=9.5yr. **Intervention:** Participants were randomized to receive 200mg modafinil or placebo daily for 2wks, then switched to the alternate treatment after a 1wk washout period. Group 1 started with modafinil treatment and Group	1. No significant benefit of modafinil was observed compared with placebo in terms of CVLT-II total learning scores. 2. A significant improvement in WAIS-III letter-number sequencing raw scores was observed after modafinil compared to placebo (p=0.041). 3. No other significant differences in cognitive outcome measures were observed.

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	2 started with placebo. Assessments were performed at baseline and after each therapy segment. **Cognitive Outcomes/Outcome Measures:** Digit Vigilance Test (DVT); Wechsler Adult Intelligence Scale-III (WAIS-III) digit span: forward, backward, total; WAIS-III letter-number sequencing; Symbol Digit Modalities Test (SDMT); California Verbal Learning Test-second edition (CVLT-II); Modified Fatigue Impact Scale (MFIS): cognitive.	
Bruce et al. 2012 *Impact of armodafinil on cognition in multiple sclerosis: a randomized, double-blind crossover pilot study* USA **RCT Crossover** PEDro=8 N~Initial~=33, N~Final~=30	**Population:** *Placebo/Armodafinil (n=16):* Mean age=49.94yr; Sex: males=2, females=14; Disease course: RRMS=9, SPMS=7; Mean EDSS=4.28; Mean disease duration=12.69yr. *Armodafinil/Placebo (n=14):* Mean age=47.71yr; Sex: males=3, females=11; Disease course: RRMS=8, SPMS=6; Mean EDSS=5.14; Mean disease duration=11.21yr. **Intervention:** The first group of participants were randomized to receive a dose of lactose placebo followed by a single 250mg dose of armodafinil after a washout period of 1wk. The other participants received the drug and placebo in the reverse order. Assessments were performed at baseline and 2hr after receiving treatment. **Cognitive Outcomes/Outcome Measures:** Rey Auditory Verbal Learning Test (RAVLT); Brief Visuospatial Memory Test-Revised (BVMT-R); Stoop Test; Word Generation task; Paced Auditory Serial Addition Test (PASAT); Conners Continuous Performance Test II - reaction time.	1. A significant improvement was observed on the RAVLT-delayed recall when participants were taking armodafinil compared with placebo (p=0.0005). 2. No other significant differences in cognitive outcome measures were observed.

Discussion

Studies with either modafinil or armodafinil have been mixed in terms of improving cognitive function in PwMS. Bruce et al. (2012) performed a double-blind crossover study with armodafinil in which participants were tested after a single dose of the drug and placebo, separated by one week. This study found a significant difference on a delayed verbal recall measure with armodafinil compared to the placebo treatment, but no other between-group differences were found for any other cognitive measures. In 2016, Ford-Johnson et al. published a crossover study in which participants were randomly assigned to either modafinil or placebo for two weeks, followed by the alternative treatment after a one-week washout period. There was a significant difference on a measure of working memory favouring the modafinil group. In this study, no other between-group differences were found for any of the other cognitive tests, including no between group differences on the CVLT-ll evaluating verbal memory. Several

factors may explain why verbal memory improved after a dose of armodafinil in the armodafinil study, but did not improve in the modafinil study. These factors include different outcome measures utilized to assess verbal memory, different trial designs, and different drug products. Armodafinil contains the R-enantiomer of modafinil while modafinil contains a racemic mixture of R- and S-modafinil.

Conclusion

There is level 1b evidence that modafinil compared to placebo may improve working memory on the WAIS-III letter-number sequencing, but not visual processing speed or verbal memory and learning (one randomized controlled trial; Ford-Johnson et al. 2016).

There is level 1b evidence that armodafinil compared to placebo may improve verbal memory, but not visuospatial memory, cognitive interference and mental flexibility, verbal fluency, auditory processing speed, or sustained attention and impulsivity (one randomized controlled trial; Bruce et al. 2012).

> Modafinil may improve working memory, but not other cognitive functions.
>
> Armodafinil may improve verbal memory, but not other cognitive functions.

3.1.10 Pemoline

For studies on pemoline see section 3.1.1 of this module.

3.1.11 Prucalopride

For studies on prucalopride see section 3.1.7 of this module.

3.1.12 Rivastigmine

Rivastigmine is a cholinesterase inhibitor with both acetylcholinesterase and butylcholinesterase activity, and is approved for the treatment of dementia associated with Alzheimer's disease and Parkinson's disease ("Drug monograph: Rivastigmine," 2020).

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Table 11. Studies Examining Rivastigmine for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Mäurer et al. 2013 *Randomised multicentre trial on safety and efficacy of rivastigmine in cognitively impaired multiple sclerosis patients* Germany **RCT** PEDro=7 N_Initial=86, N_Final=68	**Population:** *Rivastigmine group (n=43):* Mean age=44.6yr; Sex: males=20, females=23; Disease course: RRMS, SPMS; Severity: unspecified; Disease duration: unspecified. *Placebo group (n=38):* Mean age=44.0yr; Sex: males=18, females=20; Disease course: RRMS, SPMS; Disease severity: unspecified; Disease duration: unspecified. **Intervention:** Participants were randomized to receive rivastigmine therapy or placebo for 16wks. Rivastigmine was given with a patch initially at a dose of 4.6mg/d. The dose was increased to 9.5mg/d over 4wks if well tolerated and this level was maintained for 12wks. If it was well tolerated the treatment could be continued as an open-labelled therapy (unblended) for up to 12mo. Assessments were performed at baseline, at the end of the treatment phase (wk 16), and during the open label treatment phase (32 and 68wks). **Cognitive Outcomes/Outcome Measures:** Selective reminding test (SRT): long-term storage, delayed recall (SRTDR); 10/36 Spatial Recall Test (SPART); SPART delayed recall (SPARTDR); Symbol Digit Modalities Test (SDMT); Faces Symbol Test (FST); Paced Auditory Serial Addition Test-3 seconds (PASAT-3).	1. Differences between the treatment and control groups were not statistically significant from baseline to 16wks.
Huolman et al. 2011 *The effects of rivastigmine on processing speed and brain activation in patients with multiple sclerosis and subjective cognitive fatigue* Finland **RCT** PEDro=7 N_Initial=42, N_Final=28	**Population:** *MS participants (n=15):* Mean age=42.3yr; Sex: females=15; Disease course: RRMS; Mean EDSS=1.5; Mean disease duration=4.2yr. *Healthy controls (n=13):* Mean age=42.1yr; Sex: females=13. **Intervention:** Participants were randomized to receive a single dose of rivastigmine or placebo. Assessments were performed at baseline and 2.5hr after treatment. **Cognitive Outcomes/Outcome Measures:** Modified Paced Visual Serial Addition Test (mPVSAT).	1. A significant improvement of 9.9% was observed on the mPVSAT compared to baseline in MS patients receiving rivastigmine (p=0.043). 2. In the MS group receiving placebo, and in the healthy control groups receiving either rivastigmine or placebo, there were no significant changes in performance from baseline on the mPVSAT. 3. Results of between-group comparisons were not reported.
Shaygannejad et al. 2008	**Population:** *Rivastigmine group (n=30):* Mean age=33.4yr; Sex: males=15, females=15; Disease course: RRMS=9, SPMS=15, PPMS=6; Mean EDSS=4.0; Mean disease duration=6.3yr. *Placebo group (n=30):* Mean	1. The average general memory score on the WMS did not change significantly between groups at the end of treatment. 2. The treatment group scored significantly lower on the following WMS subscales:

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Effects of rivastigmine on memory and cognition in multiple sclerosis Iran **RCT** PEDro=7 N$_{Initial}$=60, N$_{Final}$=60	age=31.6yr; Sex: males=12, females=18; Disease course: RRMS=11, SPMS=16, PPMS=3; Mean EDSS=3.9; Mean disease duration=4.5yr. **Intervention:** Participants were randomized to the rivastigmine group or to the placebo group for 12wks. Rivastigmine was administered at a dose of 1.5mg 1x/d titrated over 4wks to 3mg 2x/d. Assessments were performed at baseline and after 12wks of treatment. **Cognitive Outcomes/Outcome Measures:** Wechsler Memory Scale (WMS).	information (p<0.01), mental control (p<0.001), digit span (p<0.001), and visual reproduction (p<0.001) compared to placebo, but scored significantly higher on logical memory (p<0.05) and associative learning (p<0.001).

Discussion

Three studies have examined the effects of rivastigmine on cognition in PwMS. The first study examined memory measures after 12 weeks of rivastigmine treatment compared to placebo. There was no significant difference on the average Wechsler Memory Scale general memory score between the two groups at the end of the study (Shaygannejad et al., 2008). Another prospective randomized placebo-controlled study of rivastigmine for 16 weeks, followed by 12 months of open label treatment, also did not find any significant differences between the rivastigmine and placebo groups on measures of cognitive function (Maurer et al., 2013). A small pre-post randomized placebo-controlled study, included participants with MS as well as normal controls, found a significant 9.9% improvement in visual processing speed in PwMS treated with rivastigmine compared to baseline (p=0.043), while MS participants who received placebo did not demonstrate a significant change from baseline. However, direct between-group statistical comparisons were not reported. Although this study was initially designed as an RCT it only reports within group pre-post results, which provides lower quality evidence (Huolman et al., 2011).

Conclusion

There is level 1a evidence that rivastigmine compared to placebo may not improve memory or general cognitive impairment (two randomized controlled trials; Mäurer et al. 2013; Shaygannejad et al. 2008).

There is conflicting evidence regarding whether or not rivastigmine compared to placebo improves processing speed (two randomized controlled trials; Huolman et al. 2011; Mäurer et al. 2013).

Rivastigmine does not improve cognitive impairment in multiple cognitive domains tested in persons with MS; there is conflicting evidence for its effect on processing speed.

3.1.13 Simvastatin

Simvastatin is a prodrug requiring hydrolysis for activation. Once hydrolyzed, it generates mevinolinic acid and interferes with the activity of the enzyme HMG-CoA reductase to reduce the quantity of mevalonic acid, a precursor of cholesterol, thereby reducing total and low-density lipoprotein cholesterol ("Drug monograph: Simvastatin," 2021).

Table 12. Study Examining Simvastatin for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Chan et al. 2017 (Secondary analysis of Chataway et al. 2014) *Effect of high-dose simvastatin on cognitive, neuropsychiatric, and health-related quality-of-life measures in secondary progressive multiple sclerosis: secondary analyses from the MS-STAT randomised, placebo-controlled trial* UK **RCT** PEDro=10 N_Initial=140, N_Final=120	**Population:** *Simvastatin (n=70):* Mean age=51.5yr; Sex: unspecified; Disease course: SPMS; Mean EDSS=5.8; Mean disease duration=22.1yr. *Placebo (n=70):* Mean age=51.1yr; Sex: unspecified; Disease course: SPMS; Mean EDSS=5.9; Mean disease duration=20.3yr. **Intervention:** Participants were randomized to receive simvastatin (80mg daily) or placebo for 24mo. Outcomes were assessed at baseline, 12mo, and 24mo. **Cognitive Outcomes/Outcome Measures:** National Adult Reading Test (NART); Wechsler Abbreviated Scale of Intelligence (WASI); Graded Naming Test (GNT); Birt Memory and Information Processing Battery (BMIPB); Visual Object and Space Perception battery (VOSP) cube analysis task; Frontal Assessment Battery (FAB); Paced Auditory Serial Addition Test (PASAT-3).	1. At 24mo, the change in FAB scores from baseline was significantly better in the simvastatin group (0.3 [-0.4, 0.9 95% CI] compared to the placebo group (-0.9 [-1.9, -0.1 95% CI]; between-group difference=1.2 [0.2, 2.3 95% CI], p value not provided due to bootstrapping). 2. There were no other significant differences between groups for any other cognitive outcomes.

Discussion

One study has examined the effect of simvastatin on cognitive impairment in PwMS (Chataway et al. 2014), for which a secondary analysis of cognitive outcomes was undertaken and published (Chan et al. 2017). Participants with secondary progressive MS (SPMS) were randomized to receive either simvastatin or matching placebo for 24 months. A neuropsychological test battery covering a broad range of cognitive domains was administered at baseline and at 12 and 24 months. At the end of treatment, changes in the overall cognitive profile were similar between groups on most cognitive domains, with a significantly better treatment effect only on frontal lobe (executive) function in the simvastatin group compared to placebo.

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Conclusion

There is level 1b evidence that simvastatin compared to placebo may improve executive function, but not other cognitive functions, in persons with secondary progressive MS (one randomized controlled trial; Chan et al. 2017).

> Simvastatin may be beneficial for improving executive function, but not other cognitive functions, in persons with secondary progressive MS.

3.1.14 Disease Modifying Therapies

Most phase III trials on DMTs in PwMS evaluate MS relapses, magnetic resonance imaging (MRI) outcomes, and progression of physical disability as the outcomes of primary interest. Existing DMT practice recommendations generally focus on optimizing these outcomes (Freedman et al., 2020; Montalban et al., 2018; Rae-Grant et al., 2018). The Canadian MS Treatment Optimization Recommendations published in 2020 state that there is insufficient evidence to support switching DMTs to improve cognition. However, cognition is considered in the assessment of disability, with a recommendation to administer the SDMT every two to three years (Freedman et al., 2020). In older adults with non-active MS (Lublin et al., 2020) and/or advanced disability, DMT discontinuation is generally recommended (Knox, Saini, & Levin, 2020). DMTs are not indicated for the treatment of existing MS symptoms. Starting DMTs early in the disease course of MS is more likely to delay the progression of physical disability (Iaffaldano et al., 2021). Most studies to date evaluating cognitive disability and DMT treatment are observational in nature or involve the analysis of secondary cognitive outcomes from RCTs.

3.1.14.1 Alemtuzumab

Alemtuzumab is a monoclonal antibody directed against the CD52 surface antigen on T- and B-lymphocytes, natural killer cells, monocytes, and macrophages. Although the mechanism of action of alemtuzumab in MS is unknown, its therapeutic effect involves cell surface binding to T- and B-lymphocytes to mediate lysis and depletion of T- and B-cells ("Drug monograph: Alemtuzumab," 2021).

Table 13. Study Examining Alemtuzumab for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Riepl et al. 2018 *Alemtuzumab improves cognitive processing speed in active multiple sclerosis*	**Population:** Mean age=32.38yr; Sex: males=11, females=10; Disease course: RRMS; Mean EDSS=2.12; Mean disease duration=4.98yr. **Intervention:** Participants received treatment with alemtuzumab. Outcomes were assessed at baseline prior to the first infusion of alemtuzumab, and after the second course of	1. At baseline, 38% of participants were impaired in ≥2 tests, and 24% were impaired in ≥3 tests. At follow-up, 29% of participants were impaired in ≥2 tests, and 14% were impaired in ≥3 tests. These changes from baseline were not statistically significant (p>0.05 for all).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
– *a longitudinal observational study* Germany **Pre-Post** N_{Initial}=21, N_{Final}=21	alemtuzumab (mean time span: 15.05mo). **Cognitive Outcomes/Outcome Measures:** Rey Auditory Verbal Learning Test (RAVLT); Digit span forwards, backwards; Rey Complex Figure Test (RCFT); S-words and animals; Trail Making Test (TMT-A, B); Symbol Digit Modalities Test (SDMT); Standard Progressive Matrices (SPM).	2. Compared to baseline, a significantly lower proportion of participants was impaired in the domain of processing speed (as measured by SDMT, RCFT time, and TMT-A) at follow-up (p=0.031). No other domain demonstrated significant changes between baseline and follow-up. 3. There was a significant improvement in mean SDMT and RCFT time scores from baseline to follow-up (SDMT: 44.20 vs. 48.52, p<0.001; RCFT: 240.38 vs. 168.95, p=0.002). 4. No other test results reached statistical significance between baseline and follow-up.

Discussion

One pre-post study by Riepl et al. (2018) has examined the effect of alemtuzumab on cognitive function in PwMS. Twenty-one participants with RRMS received two treatments of alemtuzumab and were followed for an average duration of 15 months. Cognitive function was assessed using an extensive neuropsychological test battery (verbal learning and memory, visual memory, attentional span, processing speed, visuoconstruction, and executive function). There were non-significant decreases in the percentage of participants with CI at baseline compared to last follow up; however, the only statistically significant improvements pre and post were on two tests of processing speed (SDMT and Rey Complex Figure Test), and these gains were reported as clinically meaningful change for 57% of participants.

Conclusion

There is level 4 evidence that alemtuzumab may have stabilizing effects on overall cognition and may improve processing speed in persons with relapsing-remitting MS (one pre-post study; Riepl et al. 2018).

Preliminary evidence suggests alemtuzumab may have stabilizing effects on overall cognitive function and may be beneficial for improving processing speed in persons with relapsing-remitting MS.

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3.1.14.2 Cyclophosphamide (with Methylprednisolone)

Cyclophosphamide is an alkylating chemotherapy drug which targets rapidly dividing cells by binding to deoxyribonucleic acid and interfering with mitosis. Cyclophosphamide crosses the blood brain barrier and therefore has good CNS bioavailability. Its mechanism of action in MS is through generalized suppression of cell-mediated and humoral immunity. Small open-label trials and one small placebo-controlled Canadian study supported the use of cyclophosphamide in MS. However, it is rarely utilized in MS care due to the risk of serious adverse events and the availability of more targeted MS DMTs (Awad & Stuve, 2009; Portaccio et al., 2003; The Canadian Cooperative Multiple Sclerosis Study Group, 1991).

Table 14. Study Examining Cyclophosphamide and Methylprednisolone for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Zephir et al. 2005 *One-year cyclophosphamide treatment combined with methylprednisolone improves cognitive dysfunction in progressive forms of multiple sclerosis* France **Pre-Post** N$_{Initial}$=30, N$_{Final}$=24	**Population:** *MS participants (n=30):* Mean age=40yr; Sex: unspecified; Disease course: PPMS=11, SPMS=19; Median EDSS=6; Mean disease duration=8yr. *Healthy controls (n=15):* Mean age=37.9; Sex: males=7, females=8. **Intervention:** Participants received cyclophosphamide treatment in monthly intravenous doses of 700 mg/m² with methylprednisolone (1g/d) for 12mo. Assessments were performed at baseline (M0) and after 6 (M6) and 12mo (M12). **Cognitive Outcomes/Outcome Measures:** Wechsler Adult Intelligence Scale-Revised (WAIS-R); Verbal intelligence quotient (VIQ); Performance intelligence quotient (PIQ); Global intelligence quotient (GIQ); Forward span; Backward span; Spatial Span; Grober and Buschke test (GB): immediate recall, free recall; Wechsler memory scale logical memory subtest: retention; Rey retention; Phonemic fluency; Semantic fluency; Go/no-go; Crossed tapping; Stroop Test 2-1; T/V fluency; Trail making test A; Trail making test B-A; Stroop 1.	1. A significant improvement was observed from M0 to M6 in MS patients on global intelligence efficiency (VIQ (p=0.001), GIQ (p=0.006)), verbal memory (WMS retention (p=0.001)), and inhibition (Go/no-go (p=0.011)) scores. 2. A significant improvement was observed from M0 to M12 in MS patients on global intelligence efficiency (VIQ (p=0.001), PIQ (p=0.005), GIQ (p=0.0002)), verbal memory (WMS retention (p=0.001)), phonemic fluency (p=0.01), and inhibition (Go/no-go (p=0.009)) scores.

Discussion

One study, a prospective uncontrolled 12-month study, examined cognitive outcomes in PwMS treated with cyclophosphamide in combination with methylprednisolone in progressive MS participants. When compared to baseline, there was a significant improvement on several cognitive measures at six and 12 months (Zephir et al., 2005). However, the study did not include an untreated MS control group.

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Conclusion

There is level 4 evidence that cyclophosphamide combined with methylprednisolone may improve general cognitive impairment, verbal memory, inhibition, and verbal language skills in persons with progressive MS (one pre-post study; Zephir et al. 2005).

Preliminary evidence suggests cyclophosphamide combined with methylprednisolone may improve general cognitive impairment efficiency, verbal memory, inhibition, and phonemic fluency in persons with progressive MS.

3.1.14.3 Dimethyl Fumarate

Dimethyl fumarate is indicated for the treatment of relapsing forms of MS. Dimethyl fumarate has anti-inflammatory and neuroprotective properties, and thus can have beneficial effects on inflammation and oxidative stress which are central pathologic factors in MS. As such, dimethyl fumarate may help delay disability and disease progression in MS ("Drug monograph: Dimethyl Fumarate," 2021). For other studies on dimethyl fumarate see also section 3.1.14.7.2 of this module.

Table 15. Study Examining Dimethyl Fumarate for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Amato et al. 2020 *Effects of 2-year treatment with dimethyl fumarate on cognition and functional impairment in patients with relapsing remitting multiple sclerosis* Italy **Pre-Post** $N_{Initial}$=217, N_{Final}=156	**Population:** Mean age=37.17yr; Sex: males=56, females=161; Disease course: RRMS; Mean EDSS=1.98; Mean disease duration=78.93mo. **Intervention:** Participants received dimethyl fumarate (120mg 2x/d increased to 240mg 2x/d) for 24mo. Outcomes were assessed at baseline and every 3mo thereafter. **Cognitive Outcomes/Outcome Measures:** Cognitive impairment (i.e., impaired cognitive function on ≥2 cognitive tests from the Brief Repeatable Battery and the Stroop Test): Paced Auditory Serial Addition Test 20, 30 seconds (PASAT-2, -3); Symbol Digit Modalities Test (SDMT); Spatial Recall Test (SPART); SPART delayed recall (SPART-D); Selective reminding test (SRT): consistent long-term retrieval (SRT-CLTR), delayed (SRT-D), long-term storage (SRT-LTS); Word List Generation (WLG); Cognitive Impairment Index (CII).	1. Cognitive impairment at baseline was reported in 22.6% of participants, with 27.2% and 9.7% of participants having cognitive impairment at 1 and 2yr, respectively. 2. Of participants exhibiting cognitive impairment at baseline who had data at 2yr, 44.1% worsened and 55.9% did not. 3. The CII showed a significant difference between participants' distribution at 2yr compared to the first year (p<0.0001); 37.2% improved, 10.7% worsened, and 52.1% remained unchanged. 4. There were significant improvements in 8 of 10 tests included in the test battery over the study duration compared to baseline: SRT-LTS, SRT-CLTR, PASAT-3, PASAT-2 (all p<0.0001), SPART (p=0.0006), SDMT (p=0.0023), SRT-D (p=0.0014), and SPART-D (p=0.0037). There were no significant improvements on the WLG (p=0.9523) or Stroop Test (0.5815).

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Discussion

Amato et al. (2020) conducted a pre-post study to examine the effect of dimethyl fumarate on CI in 217 participants with RRMS over 24 months. At baseline, 22.6% of participants exhibited CI, as defined by a failure in ≥2 of 10 tests from the BRB and the Stroop Test. The proportion of participants with CI remained stable at one year (n=59, 27.2%) and declined at two years (n=21, 9.7%). Of participants exhibiting CI at baseline who had available data at two years (n=34), 44.1% worsened and 55.9% did not experience worsening of cognition following treatment. The CI index improved significantly in one third of participants at two years compared to the first year (p<0.0001). Furthermore, there were significant improvements in most neuropsychological tests included in the battery over the study duration compared to baseline. Larger trials with a randomized design are needed to confirm the benefit of dimethyl fumarate on cognition in PwMS.

Conclusion

There is level 4 evidence that dimethyl fumarate may slow cognitive decline or improve cognitive impairment in persons with relapsing-remitting MS (one pre-post study; Amato et al. 2020).

> Preliminary evidence suggests dimethyl fumarate may slow cognitive decline or improve cognitive impairment in persons with relapsing-remitting MS.

3.1.14.4 Glatiramer Acetate

Glatiramer acetate is an immunomodulating, subcutaneous injectable therapy for use in RRMS. It is a synthetic protein composed of four amino acids. A proposed mechanism of action is through cross-reactivity with myelin basic protein, inhibiting the cell-mediated immune response to this antigen. For other studies on glatiramer acetate see also sections 3.1.14.5.2, 3.1.14.5.8, and 3.1.14.7.2 of this module.

Table 16. Studies Examining Glatiramer Acetate for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Weinstein et. al 1999 (Secondary analysis of Johnson et al. 1995) *Neuropsychologic status in multiple sclerosis after treatment with glatiramer*	**Population:** *Glatiramer (n=125)*: Mean age=34.6yr; Sex: males=37, females=88; Disease course: RRMS; Mean EDSS=2.8; Mean disease duration=7.3yr. *Placebo (n=126)*: Mean age=34.3yr; Sex: males=30, females=96; Disease course: RRMS; Mean EDSS=2.4; Mean disease duration=6.6yr. **Intervention:** Patients were randomized to receive daily subcutaneous injections of 20mg	1. There were no significant differences between groups for any of the neuropsychological tests after treatment. 2. Significant improvements in both groups were observed over time compared to baseline for the 10/36 Spatial Recall Test, PASAT, and components of the Buschke Selective Reminding Test (p<0.002).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
USA **RCT** PEDro=9 N$_{Initial}$=251, N$_{Final}$=248	glatiramer acetate or matching placebo for 2yr. Outcomes were assessed at baseline and after 12 and 24mo of treatment. **Cognitive Outcomes/Outcome Measures:** Buschke Selective Reminding Test; 10/36 Spatial Recall Test; Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT); Word List Generation (WLG).	3. Trends towards improvement over time were observed in both groups for the SDMT and the WLG. 4. Exploratory analysis of baseline cognitive impairment or time found no associations with change in cognition over time.
Ziemssen et al. 2016 *QualiCOP: real-world effectiveness, tolerability, and quality of life in patients with relapsing-remitting multiple sclerosis treated with glatiramer acetate, treatment-naïve patients, and previously treated patients* Germany **Pre-Post** N$_{Initial}$=754, N$_{Final}$=754	**Population:** Mean age=38.6yr; Sex: males=204, females=550; Disease course: RRMS=709, SPMS=25, PPMS=8; Mean EDSS=unspecified; Mean disease duration=56.53mo. **Intervention:** Patients received glatiramer acetate in daily subcutaneous doses of 20mg/mL over 24mo. Assessments were performed at baseline and after every subsequent 3mo period. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Test (PASAT); Multiple Sclerosis Inventory Cognition (MUSIC) scale: cognition.	1. Among a subset of 370 patients for whom data were available, a significant improvement in PASAT scores was observed (p<0.001). 2. Overall, there was a significant improvement in MUSIC cognition scores from baseline to the final evaluation (p<0.001).
Ziemssen et al. 2014 *A 2-year observational study of patients with relapsing-remitting multiple sclerosis converting to glatiramer acetate from other disease-modifying therapies: the COPTIMIZE trial* Germany **Pre-Post** N$_{Initial}$=672, N$_{Final}$=423	**Population:** Mean age=39.9yr; Sex: males=196, females=476; Disease course: RRMS=647, clinically isolated syndrome=1, other=9; Mean EDSS=3.0; Mean disease duration=97.2mo. **Intervention:** Patients who did not benefit from previous disease modifying treatment lasting 3-6mo were converted to receive glatiramer acetate at 20mg daily for 24mo. Assessments were performed at baseline and at 6, 12, 18, and 24mo. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Test (PASAT).	1. Among a subset of 72 patients for whom data were available, a significant improvement in PASAT scores was observed (p<0.0001).

Discussion

Only one RCT (Weinstein et al., 1999) compared the effects of glatiramer acetate to placebo on cognitive outcomes. The study sample included those enrolled in a phase III RCT of glatiramer acetate where the

primary outcome pertained to MS relapse rates (Johnson et al., 1995). The neuropsychological results were published separately and included assessment of sustained attention, perceptual processing, verbal and visual special memory, and verbal fluency. There were no between group differences for any of the cognitive outcomes at 12 and 24 months. A statistically significant improvement in both groups was observed over time for components of the Buschke Selective Reminding Test, the 10/36 Spatial Recall Test, and the PASAT. At baseline, only the Word List Generation test (assessing verbal fluency) was impaired by greater than two standard deviations for both groups. In both groups, the Word List Generation test trended towards improvement over the study period.

Two pre-post studies reported on the effects of glatiramer acetate on cognition. Both studies provide limited information since cognitive outcomes were available for only a portion of the study cohorts at last follow up. In the first multicentre study (Ziemssen et al., 2014), 672 participants switched from another disease-modifying therapy to 20mg of glatiramer acetate once daily. After two years of glatiramer acetate treatment, data on the PASAT was available for only 72 participants (PASAT scores improved compared to baseline by 4.29 ± 9.28, p<0.0001).

The second pre-post study (Ziemssen et al., 2016) also included participants already on a treatment for MS (previously treated group [n=237], of which 38 had been on glatiramer acetate) and those who had never been on a treatment for MS (treatment naïve group, n=481). The treatment naïve group was subsequently started on 20mg daily of glatiramer acetate. The 24-month study was a multicentre, prospective observational real-world study (n=754 participants enrolled). There were no significant differences between the previously treated and treatment-naïve groups in the cognitive outcomes at two years. Cognitive data (PASAT and Multiple Sclerosis Inventory scale outcomes) were available for less than 50% of the cohort at last follow up. The Multiple Sclerosis Inventory scale assesses verbal short- and long-term memory, interference susceptibility, processing speed, and verbal fluency. The Multiple Sclerosis Inventory and PASAT scores both improved compared to baseline in both groups. For the PASAT, the treatment-naïve group improved +3.65 points (n=246) and the previously treated group improved +4.13 points (n=103). No studies extended beyond twenty-four months of follow up.

Conclusion

There is level 1b evidence that glatiramer acetate compared to placebo may not improve cognitive impairment in persons with relapsing-remitting MS (one randomized controlled trial; Weinstein et al. 1999).

Glatiramer acetate may not improve cognitive function more than placebo over two years in persons with relapsing-remitting MS.

3.1.14.5 Interferon Beta

Interferon beta (IFN-β) are injectable immunomodulatory medications with IFN-β-1b being the first DMT approved for the treatment of RRMS. The full mechanism of action is not known, although long-term safety of interferon use is well established. Phase III trials have demonstrated efficacy in reducing and preventing relapses in RRMS, but results are less consistent for trials in SPMS (Kappos et al., 2001; Panitch,

Miller, Paty, Weinshenker, & North American Study Group on Interferon beta-1b in Secondary Progressive MS, 2004). The interferon trials leading to their approval for the treatment of MS did not include cognitive outcomes a priori. The majority of the data on interferons with respect to cognition are from registry or post-marketing studies. For other studies on IFN see also sections 3.1.14.5.1 to 3.1.14.5.8 and 3.1.14.7.2 of this module.

Table 17. Studies Examining Interferon Beta for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Rieckmann et al. 2019 *Adherence to subcutaneous IFN β-1a in multiple sclerosis: final analysis of the non-interventional study READOUTsmart using the dosing log and readout function of Rebismart®* Germany **Cohort** N_{Initial}=392, N_{Final}=368	**Population:** Mean age=36.8yr; Sex: females=69.6%; Disease course: RRMS=83.7%; Severity: unspecified; Mean disease duration: 2.7yr. **Intervention:** 22ug or 44ug interferon beta-1a (single arm) 3x/wk for 24mo. **Cognitive Outcomes/Outcome measures:** Symbol Digit Modalities Test (SDMT); Fatigue scale for motor and cognitive functions (FSMC) cognitive subscale at 3, 6, 12, 18 and 24mo.	1. Mean SDMT scores improved at 24mo (54.5 ±18.2) compared to baseline (51.6 ±16.9), p=0.0173. 2. Mean FSMC cognitive subscale scores worsened from 24.1 ± 10.1 to 26.0 ± 10.5, p<0.0001.
Kleiter et al. 2017 *Adherence, satisfaction and functional health status among patients with multiple sclerosis using the BETACONNECT® autoinjector: a prospective observational cohort study* Germany **Cohort** N_{Initial}=116, N_{Final}=75	**Population:** Median age=40yr; Sex: females=69.2%; Disease course: RRMS=95.1%, CIS=4.9%; Median EDSS=2.0; Median disease duration=29.9mo (range 0–372.6). **Intervention:** Interferon beta-1b every other day for 24wks. **Cognitive Outcomes/Outcome measures:** Symbol Digit Modalities Test (SDMT); Fatigue Scale for Motor and Cognitive Functions (FSMC).	1. Mean SDMT scores improved between baseline 47.9 (12.6) and 24wks: 51.5 (14.4). Statistically significant or clinically meaningful change on the SDMT were not reported. 2. Cognitive subscale mean FSMC scores improved between baseline and week 24 (baseline 23.0 (11.0); 24wks 22.2 (10.8)). Statistically significant or clinically meaningful change on the SDMT were not reported.
Mokhber et al. 2014 *Cognitive dysfunction in patients with multiple sclerosis treated with different types of*	**Population:** *Avonex (n=20):* Mean age=31.11yr; Sex: males=8, females=12; Disease course: unspecified; Mean EDSS=1.52; Mean disease duration: unspecified. *Rebif (n=23):* Mean age=27.78yr; Sex: males=9, females=14; Disease course: unspecified; Mean EDSS=2.32; Mean disease duration: unspecified. *Betaferon (n=22):* Mean age=28.95yr; Sex: males=6,	1. Within the Avonex group, significant improvements were observed at 12mo follow-up vs. baseline on the SRT total (p=0.015), SRTD (p=0.029), 10/36 delay (p=0.005), PASAT Easy (p=0.013), SDMT (p=0.011), and WLG (p=0.015). 2. Within the Rebif group, significant improvements were observed at 12mo follow-up vs. baseline on the SRT total

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
interferon beta: a randomized clinical trial Iran **RCT** PEDro=6 N_{Initial}=69, N_{Final}=63	females=16; Disease course: unspecified; Mean EDSS=2.16; Mean disease duration: unspecified. **Intervention:** Patients were randomized to one of three forms of interferon beta for 12mo: Avonex (IFN-β-1a), Rebif (IFN-β-1a), or Betaferon (IFN-β-1b). Avonex was administered 30mcg 1x/wk via intramuscular injection; Rebif was administered 44mcg 3x/wk via subcutaneous injection; Betaferon was administered 0.25mg every other day via subcutaneous injection. Assessments were performed at baseline and after 12mo. **Cognitive Outcomes/Outcome Measures:** Selective Reminding Test (SRT): total, delayed recall (SRTD); Paced Auditory Serial Addition Test: 2,3 seconds (PASAT); Word List Generation (WLG); 10/36 Spatial Recall Test (SPART); Symbol Digit Modalities Test (SDMT).	(p=0.028), 10/36 delay (p=0.034), PASAT Easy (p=0.016), SDMT (p=0.001), and WLG (p=0.000). 3. Within the Betaferon group, significant improvements were observed at 12mo follow-up vs. baseline on the SDMT (p=0.029) only. 4. There was a significant difference between Avonex vs. Rebif and Rebif vs. Betaferon on the PASAT Easy at 12mo follow-up. Significant mean differences at baseline between Avonex vs. Rebif and Rebif vs. Betaferon and after treatment between Rebif vs. Betaferon were observed in PASAT Easy scores (likelihoods not reported). 5. For the SDMT, a significant mean difference was noted at baseline between Rebif vs. Betaferon and after treatment between Avonex vs. Betaferon and Rebif vs. Betaferon (likelihoods not reported). 6. The WLG test showed significant mean differences at baseline between Avonex vs. Betaferon and Avonex vs. Rebif, and after treatment between Avonex vs. Betaferon and Avonex vs. Rebif (likelihoods not reported).
Fischer et al. 2000 (Secondary analysis of Jacobs et al. 1996) *Neuropsychological effects of interferon beta-1a in relapsing multiple sclerosis* USA **RCT** PEDro=8 N_{Initial}=276, N_{Final}=166	**Population:** *Interferon beta 1a group (n=83)*: Mean age=36.1yr; Disease course: relapsing MS; Mean EDSS=2.3; Mean disease duration=6.7yr. *Placebo group (n=83)*: Mean age=36.2yr; Disease course: relapsing MS; Mean EDSS=2.4; Mean disease duration=6.4yr. For total study sample: Sex: males=38, females=128. **Intervention:** Participants were randomized to receive interferon beta 1a (IFNβ-1a) or placebo. IFNβ-1a 30μg or placebo were administered intramuscularly 1x/wk for 104wks (2yr). Assessments were performed at baseline and 2yr. **Cognitive Outcomes/Outcome Measures:** Comprehensive Neuropsychological (NP) Battery: Set A (information processing/memory), Set B (visuospatial abilities/executive functions), Set C (verbal abilities/attention span); Brief NP Battery; Paced Auditory Serial Addition Test (PASAT).	1. There was significantly improved performance after 2yr in the IFNβ-1a group on Set A compared to placebo (p=0.011; which was most pronounced on the California Verbal Learning Test (p=0.025)), and on Set B compared to placebo (p=0.085). 2. No treatment effects were observed for Set C. 3. The IFNβ-1a group had a significantly greater mean slope for Brief NP Battery performance after 2yr compared to placebo (p=0.020). 4. Sustained deterioration in Brief NP Battery composite performance was observed in fewer IFNβ-1a patients (17.7%) than placebo patients (29.7%), with a trend for IFNβ-1a to lengthen time to onset of sustained deterioration (p=0.094). 5. The IFNβ-1a group had a greater mean slope for PASAT performance after 2yr compared to placebo, although this did

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
		not reach statistical significance (p=0.090). 6. IFNβ-1a significantly lengthened time to onset of sustained deterioration in the PASAT processing rate (p=0.023), with fewer IFNβ-1a patients (19.5%) than placebo patients (36.6%) meeting criteria for sustained PASAT deterioration by the end of the treatment phase.
Benešová & Tvaroh 2017 *Cognition and fatigue in patients with relapsing multiple sclerosis treated by subcutaneous interferon β-1a: an observational study SKORE* Czech Republic **Pre-Post** N$_{Initial}$=300, N$_{Final}$=272	**Population:** Mean age=36.33yr; Sex: males=102, females=198; Disease course: RRMS; Mean EDSS=2.85; Mean disease duration=61.6mo. **Intervention:** Participants were treated with subcutaneous interferon β-1a over 2yr. Assessments were performed at baseline, and after 6, 12 and 24mo. Patients were subdivided into low-dose (22 mcg 3x/wk), high-dose (44 mcg 3x/wk), and dose escalation subgroups. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Task (PASAT).	1. The mean PASAT score improved throughout the follow-up period in the total study population (p=0.00026). 2. For the entire study population, the mean PASAT scores improved at each time point (6 mo p=0.006, 12 mp=0.001, 24m p=0.004) compared to baseline. 3. Subgroup analyses showed that the improvement in the mean PASAT scores throughout the follow-up period was significant in the low-dose group (p=0.004), but not in the high-dose or dose escalation groups. 4. Subgroup analyses at 24 mo showed a stable or improved PASAT score in 64.6%, 60.6% and 48.9% of patients in the low-dose, high-dose and dose-escalation subgroups, respectively.
Hamdy et al. 2013 *Does the disease course or treatment type have impact on executive functions and cognition in multiple sclerosis patients? A clinical and 3 tesla MRI study* Egypt **Cohort** N$_{Initial}$=30, N$_{Final}$=30	**Population:** Mean age=24yr; Sex: males=8, females=22; Disease course: RRMS=25, SPMS=5; Mean EDSS=2.22; Mean disease duration=3.54yr. **Intervention:** 16 MS patients who were treated with interferon-β therapy were compared to non-interferon treated patients. **Cognitive Outcomes/Outcome Measures:** California Verbal Learning Test-2nd edition (CVLT-II); Brief Visuospatial Memory Test-Revised (BVMT-R); Paced Auditory Serial Addition Task (PASAT); Symbol Digit Modalities Test (SDMT); Wisconsin Card Sorting Test (WCST); Controlled Oral Word Association Test (COWAT).	1. Patients on interferon therapy showed significantly better performance than non-interferon treated patients on the BVMT-R (recall after the delay interval), SDMT, percentage of conceptual responses, PASAT, and number of trials to complete the 1st set. 2. No statistically significant differences were found for other neuropsychological parameters.
Lacy et al. 2013 *The effects of long-term interferon-beta-1b*	**Population:** *Interferon beta (IFN-β-1b) group (n=9):* Mean age=37.11yr; Sex: unspecified; Disease course: RRMS; Mean EDSS=3.72; Disease duration: unspecified. *Placebo/IFN-β-1b group (n=7):* Mean age=33.14yr; Sex:	1. A significant decrease was observed in the whole cohort at 16yr compared with 2yr assessment in WMS Logical Memory immediate (p=0.042) and delayed (p=0.031).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
treatment on cognitive functioning in multiple sclerosis: a 16-year longitudinal study USA **PCT** N$_{Initial}$=16, N$_{Final}$=16	unspecified; Disease course: RRMS; Mean EDSS=2.29; Disease duration: unspecified. **Intervention:** Patients received IFN-β-1b treatment or placebo. After 5yr of treatment, all participants started IFN-β-1b for the remainder of the study. Assessments were performed after 2 and 4yr of treatment, and again at the 16yr mark. **Cognitive Outcomes/Outcome Measures:** Overall cognitive index score; Wechsler Memory Scale (WMS): Logical Memory subtest, Visual Reproduction subtest; Trail Making Test B (TMT-B); Stroop Color-Word Test (SCWT).	2. A significant increase was observed in the whole cohort at 16yr compared with 2yr assessment in WMS Visual Reproduction (immediate) (p=0.011). 3. A significant improvement was observed for the whole cohort at 16yr compared with 2yr assessment on the SCWT Color-Word (p=0.002) and interference (p=0.034) tasks. 4. A significant improvement was observed in the original IFN-β-1b group from the 2yr to 16yr assessments on TMT-B (p=0.039) and SCWT Color-Word (p=0.023) performance. 5. Patients in the original placebo group demonstrated a significant decline in performance from the 2yr to 16yr assessments on the WMS Logical Memory immediate (p=0.044) and delayed (p=0.049) tasks, and a significant increase in WMS Visual Reproduction immediate (p=0.012) and SCWT Color-Word tasks (p=0.053). 6. At the 16yr assessment there were significant differences between the original placebo group and IFN-β-1b group in performance on WMS Visual Reproduction immediate (p=0.021) and delayed (p=0.044), with members of the placebo group performing better than the IFN-β-1b group.
Patti et al. 2013 (Extension of Patti et al. 2009) *Subcutaneous interferon β-1a may protect against cognitive impairment in patients with relapsing-remitting multiple sclerosis: 5-year follow-up of the COGIMUS study* Italy **Cohort** N$_{Initial}$=265, N$_{Final}$=201	**Population:** *Total population (n=201):* Mean age=39yr; Sex: unspecified; Disease course: RRMS; Median EDSS=2.0; Mean disease duration=8yr. *Low dose group (n=93). High dose group (n=108).* **Intervention:** Patients received interferon beta-1a subcutaneously at a dose of 44 (high dose) or 22mcg (low dose) 3x/wk. This was a 5yr analysis; assessments were performed at baseline and every 12mo for 5yr. **Cognitive Outcomes/Outcome Measures:** Cognitive impairment (i.e., impaired cognitive function on ≥3 cognitive tests from Rao's Brief Repeatable Battery and the Stroop Test): Paced Auditory Serial Addition Test 20, 30 seconds (PASAT-20, -30); Symbol Digit Modalities Test (SDMT); Spatial Recall Test (SPART); Selective reminding test (SRT): consistent long-term retrieval (SRT-CLTR), delayed (SRT-D), long-term storage (SRT-LRS);	1. Overall, the proportion of patients with cognitive impairment did not increase significantly over the 5yr period (18% at baseline vs. 22.6% among patients with data available at all time points). 2. Over 5yr, there were small and non significant increases in the proportion of patients with cognitive impairment in each group (low dose: 20.5% vs. 21.7%; high dose: 15.6% vs. 16.7%). 3. The proportion of patients with cognitive impairment remained stable between 3 and 5yr follow-ups in both the low dose (21.8% vs. 21.8%) and high dose (18.1% vs. 16.0%) groups.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	Word List Generation (WLG); Cognitive impairment index.	
Mori et al. 2012 *Early treatment with high-dose interferon beta-1a reverses cognitive and cortical plasticity deficits in multiple sclerosis* Italy **Pre-Post** $N_{Initial}$=80, N_{Final}=76	**Population:** *Presence of gadolinium-enhancing lesions (Gd+) group (n=38):* Mean age=33yr; Sex: males=8, females=30; Disease course: RRMS; Mean EDSS=1.9; Mean disease duration=4.2yr. *Absence of gadolinium-enhancing lesions (Gd-) group (n=42):* Mean age=35yr; Sex: males=8, females=34; Disease course: RRMS; Mean EDSS=1.5; Mean disease duration=3.6yr. **Intervention:** Patients received high dose interferon beta-1a treatment, administered subcutaneously at a dose of 44mcg 3x/wk. Patients were grouped based on the presence of Gd-enhancing lesions on magnetic resonance imaging. Assessments were performed at baseline and after 6 and 24mo of treatment. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Test (PASAT).	1. At baseline, the Gd+ group showed significantly poorer performance on the PASAT than the Gd- group (p=0.037). 2. The per protocol analysis showed that the Gd+ group had significant improvement on the PASAT at 6mo (p=0.03) and at 24mo (p=0.027) compared to baseline. The ITT analysis showed that the Gd+ group had significant improvement on the PASAT at 6mo (p=0.023) and at 24mo (p=0.034) compared to baseline. 3. The Gd- group had stable PASAT scores over the course of treatment compared to baseline (p>0.05), as per the per protocol analysis and ITT analysis.
Melanson et al. 2010 *Fatigue and cognition in patients with relapsing multiple sclerosis treated with interferon beta* Canada **PCT** $N_{Initial}$=50, N_{Final}=40	**Population:** *Subcutaneous (SC) interferon beta (IFNβ)-1a group (n=18):* Mean age=38.33yr; Sex: unspecified; Disease course: RRMS; Mean EDSS=1.49; Mean disease duration=5.45yr. *Intramuscular (IM) IFNβ-1a group (n=8):* Mean age=36.50yr; Sex: unspecified; Disease course: RRMS; Mean EDSS=1.72; Mean disease duration=5.04yr. *SC IFNβ-1b group (n=14):* Mean age=39.14yr; Sex: unspecified; Disease course: RRMS; Mean EDSS=1.71; Mean disease duration=4.21yr. **Intervention:** Participants received IFNβ therapy in one of three conditions: SC IFNβ-1a, SC IFNβ-1b, or IM IFNβ-1a. Assessments were performed at baseline, and at 6 and 12mo. **Cognitive Outcomes/Outcome Measures:** Buschke Selective Reminding Test (BSRT); 10/36 spatial recall test (SPART); Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Task (PASAT); Word List Generation (WLG).	1. For the total study group, there were significant improvements from baseline to 6mo on the SPART total delay correct (p=0.05), PASAT total correct (p=0.02), WLG total (p=0.05), and WLG letter 2 (p=0.001). 2. For the total study group, there were significant improvements from baseline to 12mo on the BSRT long term storage (p=0.004), BSRT consistent long-term retrieval (CLTR) (p=0.005), BSRT total delay (p=0.015), SPART total confabulations (p=0.033), PASAT total correct (p=0.07), and WLG letter 1 (p=0.04). 3. The SC IFNβ-1b group scored significantly worse than the other groups at 6mo on the BSRT-CLTR (likelihood not reported). 4. There were no other significant between-group differences.
Patti et al. 2010 (Extension of Patti et al. 2009)	**Population:** *Total population (n=459):* Mean age=33.3yr; Sex: males=158, females=301; Disease course: RRMS; Mean EDSS: 1.8; Mean disease duration=3.8yr. *Low dose group (n=223):* Mean age=33.8yr; Sex: unspecified; Disease course: RRMS; Mean EDSS=1.8; Mean disease duration=4.0yr. *High dose group*	1. At 3yr, the proportion of patients who were cognitively impaired increased from baseline (23.5% to 24.8%) in the low dose group, and remained stable at 15.2% in the high dose group. 2. At 3yr, there was a significantly lower proportion of patients with cognitive

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Effects of immunomodulatory treatment with subcutaneous interferon beta-1a on cognitive decline in mildly disabled patients with relapsing-remitting multiple sclerosis Italy **Cohort** N$_{Initial}$=459, N$_{Final}$=331	*(n=236)*: Mean age=32.8yr; Sex: unspecified; Disease course: RRMS; Mean EDSS=1.8; Mean disease duration=3.6yr. **Intervention:** Patients received interferon beta-1a subcutaneously at a dose of 44 (high dose) or 22mcg (low dose) 3x/wk. This was a 3yr interim analysis; assessments were performed at baseline and every 12mo for 3yr. **Cognitive Outcomes/Outcome Measures:** Cognitive impairment (i.e., impaired cognitive function on ≥3 cognitive tests from Rao's Brief Repeatable Battery and the Stroop Test): Paced Auditory Serial Addition Test 20, 30 seconds (PASAT-20, -30); Symbol Digit Modalities Test (SDMT); Spatial Recall Test (SPART); Selective reminding test (SRT): consistent long-term retrieval (SRT-CLTR), delayed (SRT-D), long-term storage (SRT-LRS); Word List Generation (WLG); Cognitive impairment index (CII).	impairment in the high dose group (15.2%) compared with the low dose group (24.8%; p=0.030). 3. The CII was significantly lower within both groups at 3yr compared to baseline (p<0.001 for both), but there were no significant differences between groups.
Patti et al. 2009 *Subcutaneous interferon beta-1a has a positive effect on cognitive performance in mildly disabled patients with relapsing-remitting multiple sclerosis: 2-year results from the COGIMUS study* Italy **Cohort** N$_{Initial}$=459, N$_{Final}$=358	**Population:** *Total population (n=459):* Mean age=33yr; Sex: males=158, females=301; Disease course: RRMS; Severity: unspecified; Mean disease duration=4.0yr. *Low dose group (n=223):* Mean age=33.8yr; Sex: unspecified; Disease course: RRMS; Mean EDSS=1.8; Mean disease duration=4.0yr. *High dose group (n=236):* Mean age=32.8yr; Sex: unspecified; Disease course: RRMS; Mean EDSS=1.8; Mean disease duration=3.6yr. **Intervention:** Patients received interferon beta-1a subcutaneously at a dose of 44 (high dose) or 22 μg (low dose) 3x/wk. This was a 2yr interim analysis; assessments were performed at baseline, and every 12mo for 2yr. **Cognitive Outcomes/Outcome Measures:** Cognitive impairment (i.e., impaired cognitive function on ≥3 cognitive tests from Rao's Brief Repeatable Battery and the Stroop Test): Paced Auditory Serial Addition Test 20, 30 seconds (PASAT-20, -30); Symbol Digit Modalities Test (SDMT); Spatial Recall Test (SPART); Selective reminding test (SRT): consistent long-term retrieval (SRT-CLTR), delayed (SRT-D), long-term storage (SRT-LRS); Word List Generation (WLG); Cognitive impairment index (CII).	1. At 2yr, the proportion of patients with cognitive impairment was significantly lower in the high dose treatment group (17.0%) compared with the low dose group (26.5%; p=0.034). 2. The high dose group showed significantly higher scores than the low dose group on the SRT-CLTR test (p=0.039) at year 2. Other cognitive measures were not significantly different between groups at year 2. 3. The CII did not change significantly from baseline to year 2 in both treatment groups, and there were no significant differences between groups at either time point.

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Flechter et al. 2007 *Cognitive dysfunction evaluation in multiple sclerosis patients treated with interferon beta-1b: An open-label prospective 1 year study* Israel **Pre-Post** N$_{Initial}$=16, N$_{Final}$=16	**Population:** Mean age=37.6yr; Sex: males=5, females=11; Disease course: relapsing forms of MS; Mean EDSS=2.9; Mean disease duration=6.2yr. **Intervention:** Participants received interferon beta-1b on alternate days for 1yr. Assessments were performed at baseline and after 1yr. **Cognitive Outcomes/Outcome Measures:** Wisconsin Card Sorting Test (WCST).	1. The WCST Perseverative Response (raw score) and Perseverative Response (US Census age-matched standard score) showed significant improvements after 1yr of treatment (p=0.001 and p=0.0025, respectively).
Lanzillo et al. 2006 *Neuropsychological assessment, quantitative MRI and ApoE gene polymorphisms in a series of MS patients treated with IFN beta-1b* Italy **Pre-Post** N$_{Initial}$=52, N$_{Final}$=46	**Population:** Median age=30yr; Sex: males=19, females=33; Disease course: RRMS; Median EDSS=2.0; Median disease duration=3.4yr **Intervention:** Patients received interferon beta-1b treatment for 2yr. Assessments were performed at baseline and at 2yr follow-up. **Cognitive Outcomes/Outcome Measures:** Mini Mental State Examination (MMSE); Weigl Test; Raven Matrices Test; Verbal Fluency Test; Stroop Test; Paced Auditory Serial Addition Test 2, 3 seconds (PASAT-2, -3); Corsi spatial span; Verbal span; Rey short-term test; Rey long-term test; Story recall test; Token test; Constructive apraxia test; Rey's figure test.	1. At 2yr follow-up, global cognitive score was stable in 65.2%, improved in 32.7%, and worsened in 2.1% of patients. 2. There was a significant increase in raw scores at 2yr follow-up for Weigl (p<0.05), verbal fluency (p<0.01), and PASAT-2, -3 (p<0.0003).
Barak & Achiron 2002 *Effect of interferon-beta-1b on cognitive functions in multiple sclerosis* Israel **PCT** N$_{Initial}$=46, N$_{Final}$=41	**Population:** *Interferon-beta-1b (IFNβ-1b) group (n=23)*: Mean age=47.4yr; Sex: unspecified; Disease course: RRMS; Mean EDSS=3; Mean disease duration=14.5yr. *Control group (n=23)*: Mean age=40.1yr; Sex: unspecified; Disease course: RRMS; Mean EDSS=2.9; Mean disease duration=9.6yr. **Intervention:** The IFNβ-1b group received IFNβ-1b on alternate days for 1yr. The control group did not receive treatment. Assessments were performed at baseline and after 1yr. **Cognitive Outcomes/Outcome Measures:** Selective Reminding Test (SRT); 10/36 Spatial Recall Test (SPART); Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Task (PASAT); Word List Generation (WLG).	1. At baseline, all cognitive parameters were significantly better in the control group compared to the IFNβ-1b group. 2. In the IFNβ-1b group, SRT, SPART and PASAT scores were significantly improved at 1yr compared to baseline (p=0.006, p=0.005, p=0.024, respectively). Results on the WLG showed a tendency for improvement, although did not reach statistical significance. No deterioration occurred on the other cognitive measures. 3. In the control group, SPART, WLG, and PASAT scores significantly deteriorated at 1yr compared to baseline (p=0.01, p=0.004, p=0.023, respectively). 4. No between-group differences were reported at the end of the study, when accounting for the difference noted at baseline.

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Gerschlager et al. 2000 *Electrophysiological, neuropsychological and clinical findings in multiple sclerosis patients receiving interferon β-1b: A 1-year follow-up* Austria **Cohort** N$_{Initial}$=28, N$_{Final}$=28	**Population:** *MS participants (n=14):* Mean age=37.5yr; Sex: males=3, females=11; Disease course: RRMS; Mean EDSS=3.14; Mean disease duration=10yr. *Healthy controls (n=14).* **Intervention:** Participants were treated with interferon beta-1b for 1yr. Assessments were performed at baseline and 12mo later. **Cognitive Outcomes/Outcome Measures:** Selective Reminding Test (SRT); Concentration endurance test (d2); 7/24 Spatial Recall Test (SRT 7/24); Paced Auditory Serial Addition Test; Verbal fluency test.	1. A significant main effect was found for time and group for the SRT 7/24 ($p<0.021$), indicating an improvement in the healthy control group ($p<0.001$) but less improvement in the MS patient group ($p<0.055$). 2. The total participant cohort improved significantly compared to baseline on the SRT immediate recall, 7/24 SRT delayed recall, PASAT, verbal fluency, and d2. However, no significant between-group differences were found.
Pliskin et al. 1996 *Improved delayed visual reproduction test performance in multiple sclerosis patients receiving interferon beta-1b* USA **PCT** N$_{Initial}$=30, N$_{Final}$=30	**Population:** *Total population (n=30):* Mean age=37yr; Sex: males=11, females=19. *High-dose group (n=9):* Mean age=38.9yr; Disease course: RRMS. No further information provided. *Low-dose group (n=8):* Mean age=38.0yr; Disease course: RRMS. No further information provided. *Placebo group (n=13):* Mean age=36.2yr; Disease course: RRMS. No further information provided. **Intervention:** Patients received either high or low dose interferon beta (IFN-β) 1b or placebo for 4yr. IFN-β-1b was administered at a dose of 8 million units (8 MIU, high-dose), or 1.6 MIU (low-dose). Assessments were performed at baseline, and after 2 and 4yr. **Cognitive Outcomes/Outcome Measures:** Wechsler Memory Scale (WMS): Logical Memory subtest, Visual Reproduction subtest; Trail Making Test B (TMT-B); Stroop Color-Word Test (SCWT).	1. A significant main effect for time ($p<0.001$) and a significant treatment*time interaction effect ($p<0.03$) were found for WMS Visual Reproduction delayed recall. Follow-up analyses indicated a significant improvement in the high-dose group from the 2 to 4yr assessments on the WMS Visual Reproduction (delayed recall, $p<0.003$) test. No similar significant changes were observed for the placebo or low-dose groups. 2. For Visual Reproduction immediate recall, improvement was greatest in the high-dose group, but this did not reach statistical significance. 3. The total cohort improved significantly between the first and second assessment on the WMS Visual Reproduction immediate ($p<0.001$) and SCWT Word Reading ($p<0.03$) tests. 4. No significant changes were observed for the total cohort or for any group over time on the TMT-B. 5. No significant changes were observed between assessments for the total cohort on the SCWT (Color and Color-Word, Word Reading), or WMS Logical Memory (immediate and delayed). 6. There were no between-group differences on the SCWT or WMS Logical Memory at either assessment.

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Discussion

Two non-randomized studies investigated IFN-β for CI, compared to untreated controls. Barak and Achiron (2002) compared IFN-β-1b treated RRMS participants to an equal number of untreated participants on cognitive measures over a one-year period. The untreated cohort group had less CI at baseline compared to the treated cohort and they demonstrated significant worsening on the 10/36 Spatial Recall Test, Word List Generation, and PASAT over the year. The IFN-β treated cohort from this study significantly improved in two of these same measures (10/36 Spatial Recall Test, PASAT), in addition to improving on the SRT, and there was no significant deterioration on other cognitive measures. The second small study by Hamdy et al. (2013) compared IFN-treated patients to non-treated patients and found that the treated group demonstrated significantly improved visuospatial memory, visual processing speed, working memory and auditory processing speed, and cognitive reasoning, but not verbal learning and memory, or verbal fluency. This study did not specify the type of IFN used.

Three studies investigated IFN-β for CI, compared to placebo. Fischer et al. (2000) compared IFN-β-1a to placebo over a duration of two years. Comprehensive and brief neuropsychological batteries were used to evaluate cognitive function. At the end of the study, a significant beneficial effect of IFN-β-1a was demonstrated in terms of reduced cognitive deterioration compared to placebo. The two other studies used a subset of participants who were included in the pivotal randomized placebo-controlled trial for IFN-β-1b in RRMS (The IFNB Multiple Sclerosis Study Group, 1993; The IFNβ Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group, 1995). The study by Pliskin et al. (1996) compared participants receiving high-dose IFN-β-1b, low-dose IFN-β-1b, and placebo. Results demonstrated a significant improvement in delayed visual memory performance in participants treated with high-dose IFN-β-1b compared to low-dose IFN-β-1b and placebo between years two and four of the pivotal clinical trial but did not find other significant between-group differences for verbal memory, processing speed, or selective attention. The third study by Lacy et al. (2013) was a small longitudinal extension study using a subset of 16 participants from Pliskin et al. (1996). The findings from this small extension trial are subject to bias from attrition. At the 16-year assessment, the original placebo group (later treated with IFN-β-1b) performed significantly better than the original IFN-β group in the domain of visual memory performance. Contrary to this, on further within group analysis, only the originally treated IFN-β-1b group improved from year two to year 16 on measures of processing speed and selective attention. The original placebo group worsened on measures of verbal memory but exhibited increased visual memory and selective attention performance. For this extension study, cognitive measures were administered two years into the trial, and repeated at year four. At year five, subjects originally treated with placebo (n=7) were switched to receive IFN-β-1b, and cognitive assessments were performed again at year 16. This study found that the cohort as a whole did demonstrate worsening performance on verbal memory measures over time, but improved on measures of visual memory, processing speed, and selective attention. However, when the two groups were examined separately, it was found that those participants originally randomized to IFN-β-1b demonstrated an improvement from year two to year 16 on measures of processing speed and selective attention, while those participants who were originally randomized to placebo worsened on measures of verbal memory but exhibited increased visual memory and selective attention performance. At the 16-year assessment, there were significant differences between the original placebo group and IFN-β-1b group in visual memory performance, with members of the placebo group performing better than the IFN-β group.

Three studies investigated comparisons between IFN-β doses or formulations. The Cognitive Impairment in Multiple Sclerosis (COGIMUS) study was a prospective, non-randomized cohort study comparing low

dose IFN-β-1a (22 mcg) and high dose (44 mcg) at two, three, and five years (Patti et al. 2009, 2010, 2013). The COGIMUS study used a liberal definition of CI, defined as scoring one standard deviation below the mean on at least three cognitive tests from Rao's Battery. Other studies have applied a more stringent criterion of 1.5 or 2 standard deviations below the mean. After two years, the proportion of participants with CI was significantly lower in the high dose group (17%) compared to the low dose group (26.5%; p=0.034). The low dose group started with a higher proportion of people with CI at baseline compared to the high dose group (18.6% vs. 24.2%; p=0.145). After three years, the proportion of participants with CI remained significantly lower in the high dose group (15.2%) compared to the low dose group (24.8%; p=0.030). Finally, five-year results indicated that the proportion of patients with CI remained stable between three and five years of treatment. Another study by Mokhber et al. (2014) compared the effects of three different interferon treatments on cognitive outcomes over a 12-month period. Participants with relapsing MS were randomized to either IFN-β-1a (Avonex or Rebif) or IFN-β-1b (Betaferon). Cognitive assessments were performed at baseline and after 12 months. Within all three treatment groups, there was improvement on the cognitive test scores over time, although both IFN-β-1a groups improved on a greater number of cognitive outcome measures compared to the IFN-β-1b group. Differences in cognition at baseline between the groups and comparison between groups over time limit the interpretation of these results. Finally, Melanson et al. (2010) investigated three preparations of IFN-β; subcutaneous IFN-β-1a, subcutaneous IFN-β-1b, and intramuscular IFN-β-1a. For the total study group, there were significant improvements from baseline to six and 12 months in several cognitive domains; however, there were no differences in efficacy between groups in terms of improving cognitive function.

Six other studies with pre-post designs evaluated interferons and cognitive outcomes. Mori et al. (2012) and Benešová and Tvaroh (2017) both studied IFN-β-1a and demonstrated improvement on working memory and auditory processing speed. Lanzillo et al. (2006) and Flechter et al. (2007) investigated IFN-β-1b and found beneficial effects for cognitive stability and cognitive reasoning, respectively. Rieckmann et al. (2019) and Kleiter et al. (2017) both reported 24 week follow up data on the Fatigue Scale for Motor and Cognitive Functions (FSMC). In the Rieckmann study, mean total scores on this scale worsened from the "mild fatigue" range at baseline to the "moderate fatigue" range at 24 weeks. The Kleiter et al. study reported relatively stable FSMC scores over time. However incomplete follow up on cognitive outcomes was a limitation. Both of these studies also reported on the SDMT which, contrary to the FSMC, showed improvement over time.

Conclusion

Healthy control comparison:

There is level 2 evidence that interferon beta 1b treated healthy controls without MS and people with relapsing-remitting MS improve on cognitive testing, but healthy controls show greater improvement on verbal memory than those with relapsing-remitting MS (one cohort study; Gerschlager et al. 2000).

Comparing formulations:

There is conflicting evidence regarding whether or not different interferon beta (IFN-ß) preparations (subcutaneous IFN-ß-1a, subcutaneous IFN-ß-1b, intramuscular IFN-ß-1a) compared to one another improve verbal learning and memory, spatial memory, auditory

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processing speed, and verbal fluency (one randomized controlled trial and one prospective controlled trial; Mokhber et al. 2014; Melanson et al. 2010).

There is level 1b evidence that interferon beta 1a compared to interferon beta 1b may not be more effective for improving visual processing speed in persons with relapsing-remitting MS (one randomized controlled trial and one prospective controlled trial; Mokhber et al. 2014; Melanson et al. 2010).

There is level 2 evidence that different interferon beta (IFN-β) preparations (subcutaneous IFN-β-1a, subcutaneous IFN-β-1b, intramuscular IFN-β-1a) compared to one another may not be more effective for improving visual processing speed in persons with relapsing-remitting MS (one prospective controlled trial; Melanson et al. 2010).

<u>Specific interferon formulations:</u>

There is level 2 evidence that <u>interferon beta</u> compared to no treatment may improve visuospatial memory, visual processing speed and auditory processing speed, and cognitive reasoning, but not verbal learning and memory, or verbal fluency (one cohort study; Hamdy et al. 2013).

There is level 2 evidence that interferon <u>beta 1b</u> compared to no treatment may improve spatial memory, auditory processing speed, and may have stabilizing effects on verbal fluency in persons with relapsing-remitting MS (one prospective controlled trial; Barak & Achiron 2002).

There is level 4 evidence that interferon <u>beta 1b</u> may stabilize or improve cognitive function in persons with relapsing-remitting MS (one pre-post study; Lanzillo et al. 2006).

There is level 4 evidence that interferon <u>beta 1b</u> may improve cognitive reasoning in persons with relapsing MS (one pre-post study; Flechter et al. 2007).

There is level 2 evidence that interferon <u>beta 1b</u> may improve or stabilize visual processing speed in relapsing-remitting MS (one cohort study; Kleiter et al. 2017).

There is level 1b evidence that interferon <u>beta 1a</u> compared to placebo may be more effective for reducing cognitive deterioration in persons with relapsing MS (one randomized controlled trial; Fischer et al. 2000).

There is level 4 evidence that interferon <u>beta 1a</u> may improve auditory processing speed in persons with relapsing-remitting MS (two pre-post studies; Mori et al. 2012; Benešová & Tvaroh et al. 2017).

There is level 2 evidence that interferon <u>beta 1a</u> may improve or stabilize visual processing speed, but not cognitive fatigue symptoms, in relapsing-remitting MS (one cohort study; Rieckmann et al. 2019).

High dose versus low dose interferon:

There is level 2 evidence that high-dose interferon <u>beta 1b</u> compared to low dose interferon beta 1b or placebo may improve visual memory, but not verbal memory, processing speed, or selective attention in persons with relapsing-remitting MS (one prospective controlled trial; Pliskin et al. 1996).

There is level 2 evidence that high dose interferon <u>beta 1a</u> compared to low dose may be more effective for protecting against cognitive decline in persons with relapsing-remitting MS (one cohort study; Patti et al. 2009; 2010; 2013).

> Interferon formulations may reduce the rate of cognitive decline in some cognitive domains for persons with relapsing MS. It is unclear if there is a dose-dependant protective effect against cognitive decline.

> There is mixed evidence regarding the effect of different interferon beta preparations on cognitive impairment in relation to one another in persons with MS.

3.1.14.5.1 Interferon Beta vs. Interferon Beta plus Estroprogestins

Table 18. Study Comparing Interferon Beta vs. Estroprogestins for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
De Giglio et al. 2017 *Effect on cognition of estroprogestins combined with interferon beta in multiple sclerosis: Analysis of secondary outcomes from a randomised controlled trial*	**Population:** *Group 1 (n=46):* Mean age=30.4yr; Sex: males=0, females=46; Disease course: RRMS; Mean EDSS=1.7; Mean disease duration=4.2yr. *Group 2 (n=48):* Mean age=29.1yr; Sex: males=0, females=48; Disease course: RRMS; Mean EDSS=1.8; Mean disease duration=3.3yr. *Group 3 (n=48):* Mean age=30.6yr; Sex: males=0, females=48; Disease course: RRMS; Mean EDSS=1.6; Mean disease duration=3.5yr. **Intervention:** Patients were randomly assigned to receive subcutaneous IFN-β-1a	1. At 12mo there was no significant difference in the proportion of patients with cognitive impairment across groups (p=0.24). 2. At 24mo the proportion of cognitively impaired subjects in group 3 was significantly lower than in group 1 (p=0.03). 3. The SRT-LTS showed significant improvements from baseline to 24mo in all three groups (p<0.001 for all).

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Italy **RCT** PEDro=6 $N_{Initial}=150$, $N_{Final}=128$	44mcg 3x/wk (group 1), subcutaneous IFN-β-1a 44mcg 3x/wk plus ethinyl estradiol 20mcg and desogestrel 150mcg (group 2), or subcutaneous IFN-β-1a 44mcg 3x/wk plus ethinyl estradiol 40mcg and desogestrel 125mcg (group 3). Assessments were performed at baseline, and at 12 and 24mo. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Test: 2,3 seconds (PASAT-2, PASAT-3); Symbol Digit Modalities Test (SDMT); 10/36 Spatial Recall Test (10/36-SPART); 10/36-SPART-delayed recall (10/36-SPART-D); Selective Reminding Test (SRT)-Long Term Storage (SRT-LTS); SRT-Consistent Long-Term Recall (SRT-CLTR); SRT-delayed recall (SRT-D); Word List Generation (WLG).	4. The SRT-CLTR showed significant improvements from baseline to 24mo in all three groups ($p<0.01$, $p<0.05$, and $p<0.0001$, respectively). 5. The SRT-D showed significant improvements from baseline to 24mo in all three groups ($p<0.05$, $p<0.01$, and $p<0.05$, respectively). 6. The SPART-D showed significant improvements from baseline to 24mo in group 1 ($p<0.01$). 7. The PASAT-2 showed significant improvements from baseline to 24mo in all three groups ($p<0.0001$ for all). 8. The PASAT-3 showed significant improvements from baseline to 24mo in all three groups ($p<0.0001$, $p<0.001$, $p<0.0001$, respectively). 9. The SDMT showed significant improvements from baseline to 24mo in group 2 ($p<0.01$) and group 3 ($p<0.05$). 10. No significant between-group differences were found in WLG and SPART-D.

Discussion

One RCT by De Giglio et al. (2017) compared the addition of estroprogestins in different doses to IFN-β treatment on cognitive outcomes. All participants were treated with IFN-β-1a 44mcg three times per week and were randomized to either low or high doses of estroprogestins or no estroprogestin. At 12 months, the proportion of people with CI was similar in each group. While the high dose estroprogestin plus IFN-β group had a significantly smaller proportion of cognitively impaired participants when compared to the IFN-β only group at 24 months ($p=0.03$), after 24 months all groups demonstrated improvement on most of the cognitive measures.

Conclusion

There is level 1b evidence that high dose estroprogestins in combination with interferon beta may be more effective for <u>protecting against</u> cognitive decline compared to interferon beta alone in females with relapsing-remitting MS, but may not be more effective than low dose estroprogestins combined with interferon beta (one randomized controlled trial; De Giglio et al. 2017).

There is level 1b evidence that interferon beta in combination with either high dose or low dose estroprogestins may not be more effective than interferon-beta alone for <u>improving</u>

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cognitive function in females with relapsing-remitting MS (one randomized controlled trial; De Giglio et al. 2017).

> High dose or low dose estroprogestins in combination with interferon beta may improve cognition similar to interferon beta alone in persons with relapsing-remitting MS.

3.1.14.5.2 Interferon Beta vs. Glatiramer Acetate

Table 19. Study Comparing Interferon Beta vs. Glatiramer Acetate for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Cinar et al. 2017 *Cognitive dysfunction in patients with multiple sclerosis treated with first-line disease-modifying therapy: a multi-center, controlled study using the BICAMS battery* Turkey **Cohort** N$_{Initial}$=163, N$_{Final}$=161	**Population:** *MS participants (n=161):* Mean age=30.4yr; Sex: males=51, females=110; Disease course: RRMS; Severity: unspecified; Mean disease duration=2.02yr. *Healthy controls (n=102):* Mean age=31.5yr; Sex: males=37, females=65. **Intervention:** Patients receiving disease-modifying drugs were monitored for 12mo. They were categorized into three groups: interferon beta 1a SC (IFNB1-a; n=53), interferon beta 1b (IFNB1-b; n=52), and glatiramer acetate (GA; n=56). Assessments were performed before treatment and 12mo after treatment. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT); California Verbal Learning Test, second edition (CVLT-II); Brief Visuospatial Memory Test Revised (BVMT-R).	1. SDMT scores improved in all MS subgroups at month 12 compared with baseline (IFNB1-a p=0.003, IFNB1-b p=0.004, GA p=0.003). 2. BVMT-R scores improved in all MS subgroups at month 12 compared with baseline (IFNB1-a p=0.003, IFNB1-b p=0.005, GA p=0.005). 3. CVLT-II scores improved in all MS subgroups at month 12 compared with baseline (IFNB1-a p=0.005, IFNB1-b p=0.006, GA p=0.006). 4. SDMT, BVMT-R, and CVLT-II scores were all significantly improved after therapy compared with baseline for the total MS patient group (p=0.003, p=0.004, and p=0.006, respectively). 5. No difference was found between patients using IFNB1-a, IFNB1-b, and GA. 6. Mean scores for all three cognitive tests were significantly higher in the healthy control group than in the MS patients (p<0.001 for all comparisons). 7. The number of cognitively impaired patients decreased from 46 (28.5%) at study entry to 33 (20.5%) at follow-up on the SDMT (p=0.009). 8. The number of cognitively impaired patients decreased from 51 (31.7%) to 35 (21.7%) on the CVLT (p=0.024). 9. The number of cognitively impaired patients decreased from 42 (26.1%) to 30 (18.6%) on the BVMT-R.

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Discussion

Cinar et al. (2017), in a non-randomized prospective study, evaluated cognitive function in newly diagnosed PwMS at baseline and 12 months after treatment with IFN-β-1a, IFN-β-1b, or glatiramer acetate. After 12 months, all MS participant subgroups demonstrated a significant increase in all three cognitive measure scores compared to baseline, with no differences based on the DMT used. The mean scores for all three cognitive tests were significantly higher in the healthy control group compared to the MS participants (p<0.001). For other studies on glatiramer acetate see also sections 3.1.14.4, 3.1.14.5.8, and 3.1.14.7.2 of this module.

Conclusion

There is level 2 evidence that interferon beta 1a, interferon beta 1b, and glatiramer acetate may not be more effective compared to one another for cognitive impairment in persons with relapsing-remitting MS (one cohort study; Cinar et al. 2017).

> Preliminary evidence supports that interferon beta 1a, 1b, and glatiramer acetate may have similar effects on cognitive impairment in persons with relapsing-remitting MS.

3.1.14.5.3 Interferon Beta vs. Daclizumab Beta

Daclizumab Beta is a humanized monoclonal antibody directed against the α subunit (CD25) of the interleukin-2 receptor. The mechanism of action is not fully delineated; however, it is believed to inhibit the activation of lymphocytes. Two phase III trials (SELECT (Gold et al., 2013) and DECIDE (Kappos et al., 2015)) led to the approval of daclizumab as a DMT for relapsing MS. Daclizumab was subsequently pulled from the market by the manufacturers following reports of inflammatory encephalitis and meningoencephalitis in patients in Europe.

Table 20. Study Comparing Interferon Beta vs. Daclizumab Beta for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Benedict et al. 2018 (Secondary analysis of Kappos et al. 2015) *Improved cognitive outcomes in patients with relapsing-remitting multiple sclerosis treated*	**Population:** *Daclizumab beta (n=919):* Mean age=36.4yr; Sex: males=294, females=625; Disease course: RRMS; Median EDSS=2.0; Mean disease duration=4.2yr. *Interferon beta-1a (n=922):* Mean age=36.2yr; Sex: males=295, females=627; Disease course: RRMS; Median EDSS=2.2; Mean disease duration=4.1yr. **Intervention:** Participants were randomized to receive daclizumab beta 150mg	1. There was a significantly greater mean improvement from baseline in SDMT scores in the daclizumab beta group compared with the interferon beta-1a group at wk 96 (mean change from baseline: 4.1 vs. 2.9, respectively; p=0.0274). This effect was sustained at wk 144 in a limited number of participants with SDMT scores who

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
with daclizumab beta: results from the DECIDE study USA **RCT** PEDro=10 N$_{Initial}$=1841, N$_{Final}$=1841	subcutaneously every 4wks and intramuscular placebo 1x/wk, or intramuscular interferon beta-1a 30μg 1x/wk and subcutaneous placebo every 4wks, for at least 96wks and no more than 144 wks. Outcomes were assessed at baseline and at 24wk intervals. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT).	completed 144wks of treatment (6.3 vs. 3.1, respectively; p=0.0024). 2. Significantly more participants treated with daclizumab beta showed clinically meaningful improvement on the SDMT (≥3-point increase) compared to interferon beta-1a at wk 96 (60.0% vs. 54.1%, respectively; 1.30 odds ratio [1.05, 1.62 95% CI]; p=0.0153), and at wk 144 (65.5% vs. 52.0%, respectively; 1.60 odds ratio [1.18, 2.19 95% CI]; p=0.0028). 3. Significantly more participants treated with daclizumab beta showed a ≥4-point improvement on the SDMT compared to interferon beta-1a at wk 96 (55.4% vs. 50.1%, respectively; 1.26 odds ratio [1.01, 1.56 95% CI]; p=0.0366), and at wk 144 (61.7% vs. 48.4%, respectively; 1.53 odds ratio [1.12, 2.07 95% CI]; p=0.0067). 4. Significantly fewer participants treated with daclizumab beta showed a clinically meaningful worsening on the SDMT (≥3-point decrease) compared to interferon beta-1a at wk 96 (19.4% vs. 24.8%, respectively; 0.72 odds ratio [0.56, 0.92 95% CI]; p=0.0103). There was no significant difference between groups in terms of clinically meaningful worsening at wk 144, although a trend for significance was observed. 5. There were no significant differences between groups in terms of clinically meaningful worsening, defined as a ≥4-point decrease, at either time point, although a trend for significance was observed at wk 96.

Discussion

A secondary analysis of the phase III DECIDE trial (Kappos et al. 2015) by Benedict et al. (2018) suggested that daclizumab may be more protective against CI and/or worsening of cognitive function over a 24-month period when compared to IFN-β. It is important to note that the SDMT was a tertiary outcome and the clinical significance of these findings is uncertain. Furthermore, daclizumab is no longer available.

Conclusion

There is level 1b evidence that daclizumab may be more effective at improving and preventing worsening of processing speed compared to interferon beta 1a after 92 weeks of treatment in relapsing-remitting MS (from one randomized controlled trial; Benedict et al. 2018).

> Daclizumab may be more effective than interferon beta 1a for preventing worsening of processing speed; however, daclizumab is no longer available.

3.1.14.5.4 Interferon Beta vs. Ozanimod

Ozanimod is a sphingosine 1-phosphate (S1P) receptor modulator that demonstrated superiority to IFN-β in two phase III pivotal trials (RADIANCE (Cohen, Comi, et al., 2019) and SUNBEAM (Comi et al., 2019)). The trials included relapsing-remitting MS participants where the primary outcomes were the annualized relapse rate. Secondary MRI outcomes also significantly favoured ozanimod. Ozanimod binds to S1P1 receptors on lymphocytes, preventing lymphocyte egress from lymph nodes and reducing the number of lymphocytes in circulation. Ozanimod is associated with reduced cardiac risk compared to non-specific SP1 receptor modulators by selectively blocking S1P receptors 1 and 5.

Table 21. Study Comparing Interferon Beta vs. Ozanimod for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Comi et al. 2019 *Safety and efficacy of ozanimod versus interferon beta-1a in relapsing multiple sclerosis (SUNBEAM): a multicentre, randomised, minimum 12-month, phase 3 trial* Italy **RCT** PEDro=10 $N_{Initial}$=1346, N_{Final}=1255	**Population:** *Ozanimod 1.0mg (n=447):* Mean age=34.8yr; Sex: males=164, females=283; Disease course: RRMS=438, PRMS=9; Mean EDSS=2.6; Mean disease duration=3.6yr. *Ozanimod 0.5mg (n=451):* Mean age=36.0yr; Sex: males=140, females=311; Disease course: RRMS=443, PRMS=5, SPMS=3; Mean EDSS=2.7; Mean disease duration=3.7yr. *Interferon beta-1a (n=448):* Mean age=35.9yr; Sex: males=148, females=300; Disease course: RRMS=441, PRMS=5, SPMS=2; Mean EDSS=2.6; Mean disease duration=3.7yr. **Intervention:** Participants were randomized to receive either ozanimod HCl 1.0mg 1x/d, ozanimod HCl 0.5mg 1x/d, or weekly interferon beta-1a 30μg for at least 12mo. **Cognitive Outcomes/Outcome Measures:** Multiple Sclerosis Functional Composite (MSFC) within which the Symbol Digit Modalities Test (SDMT) was substituted for	1. Mean change in SDMT z-scores from baseline to month 12 improved to a greater extent in both ozanimod groups compared to the interferon beta-1a group (p<0.05; raw or mean change scores not provided for the SDMT). 2. There was a significant difference on the MSFC z change scores in favour of both doses of ozanimod compared to interferon beta-1a (ozanimod 1.0mg vs. interferon beta: difference in mean change from baseline=0.111; p=0.0024; ozanimod 0.5mg vs interferon beta: difference in mean change from baseline=0.082; p=0.0246).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	the Paced Auditory Serial Addition Test (PASAT).	

Discussion

The results of this phase III trial support that ozanimod may provide greater protection against CI or worsening compared to IFN-β-1a over 12 months. Visual processing speed according to the SDMT trial results align with the relapse rate and MRI trial results in that they all significantly favoured ozanimod. However, not provided are the absolute change scores, and it is unclear whether the SDMT results were clinically meaningful. The Multiple Sclerosis Functional Composite (MSFC) z change scores (within which the SDMT was replaced for the PASAT in this trial) also favoured ozanimod. The SDMT may be a more sensitive outcome of processing speed than the PASAT. However, the MSFC also includes the Timed 25 Foot Walk Test and the upper limb Nine-Hole Peg Test and none of the sub-components of the MSFC were reported separately; therefore, it is unclear to what extent cognition contributed to the MSFC z change scores.

Conclusion

There is level 1b evidence that ozanimod may improve visual processing speed compared to interferon beta 1a over 12 months in relapsing-remitting MS (one randomized controlled trial; Comi et al. 2019).

Ozanimod may protect against worsening cognitive function, based on 12-month data.

3.1.14.5.5 Interferon Beta vs. Fingolimod

Fingolimod was the first oral Health Canada approved drug for the treatment of relapsing-remitting MS, based on the results of the FREEDOMS (Calabresi et al., 2014) and TRANSFORMS (Cohen et al., 2010) phase III trials. Fingolimod is a S1P receptor modulator which binds to S1P1 receptors 1,3,4, and 5 on lymphocytes, preventing lymphocyte egress from lymph nodes and reducing the number of lymphocytes in circulation. For other studies on fingolimod see also sections 3.1.14.5.7, 3.1.14.5.8, and 3.1.14.7.1 of this module.

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Table 22. Study Comparing Interferon Beta vs. Fingolimod for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Comi et al. 2017 *Efficacy of fingolimod and interferon beta-1b on cognitive, MRI, and clinical outcomes in relapsing-remitting multiple sclerosis: an 18-month, open-label, rater-blinded, randomised, multicentre study (the GOLDEN study)* Italy **RCT** PEDro=5 N$_{Initial}$=157, N$_{Final}$=127	**Population:** *Fingolimod (n=80):* Mean age=40.23yr; Sex: males=23, females=57; Disease course: RRMS; Mean EDSS=2.78; Mean disease duration=4.97yr. *Interferon beta-1b (n=28):* Mean age=37.64yr; Sex: males=9, females=19; Disease course: RRMS; Mean EDSS=2.09; Mean disease duration=4.71yr. **Intervention:** Participants were randomized to receive oral fingolimod (0.5mg/d) or subcutaneous interferon beta-1b (250µg every other day) for 18mo. Outcomes were assessed at screening and at 9 and 18mo. **Cognitive Outcomes/Outcome Measures:** Rao's Brief Repeatable Battery: Selective Reminding Test (SRT): long-term storage (SRT-LTS), consistent long-term retrieval (SRT-CLTR), delayed recall (SRT-d); 10/36 Spatial Recall Test (10/36 SPART): total correct responses (10/36 SPART-T), delayed recall (SPART-DR); Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT); Word List Generation; Delis-Kaplan Executive Function System (DKEFS) sorting test.	1. There were no significant between-group differences in the mean changes from screening to month 18 for any cognitive parameters. 2. Both treatment groups showed improvements in the mean changes from screening to month 18 for all cognitive parameters. 3. At baseline participants had to score <10th percentile compared to age matched controls on at least one cognitive test to be included. 4. Groups were not matched at baseline (i.e., SDMT mean score fingolimod 40.9 vs. interferon beta -1b 47.4; p=0.0183)

Discussion

A study by Comi et al. (2017) examined the changes on a battery of cognitive tests in a randomized, open label study comparing IFN-β-1b and fingolimod. Both groups demonstrated an increase in scores on all cognitive tests over time; there was no significant worsening noted. However, there was no difference in the change in scores based on the treatment group. There were a number of limitations with the study: the fingolimod group had significantly worse baseline disease activity and PASAT and SDMT scores, more participants in the interferon group were lost to follow up (40% compared to 8.5% in the fingolimod group, p≤0.0001), those lost to follow up in the interferon group had worse cognitive scores at baseline, and the study was not powered to evaluate between-group differences on the cognitive outcomes. These limitations significantly impact the ability to compare between-group results in terms of the cognitive outcomes.

Conclusion

There is level 2 evidence that fingolimod or interferon beta 1b may improve cognition on a comprehensive cognitive battery over 18 months in relapsing-remitting MS (one open label randomized controlled trial; Comi et. al. 2017).

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3.1.14.5.6 Interferon Beta and/vs. Natalizumab

Table 23. Studies Comparing or Combining Interferon Beta and Natalizumab for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Weinstock-Guttman et al. 2012 (Secondary analysis of AFFIRM RCT, Polman et al. 2006; and SENTINEL RCT Rudick et al. 2006) *Additional efficacy endpoints from pivotal natalizumab trials in relapsing-remitting MS* USA Not specified	**Population:** **SENTINEL:** *Natalizumab + interferon beta (IFNβ)-1a group:* Disease course: RRMS. *Placebo + IFNβ-1a group:* Disease course: RRMS. No further information provided. **Intervention:** In the SENTINEL trial participants were randomized to natalizumab 300mg or placebo once monthly plus IFNβ-1a. **Cognitive Outcomes/Outcome Measures:** Time to confirmed progression of cognitive deficit (0.5 SD worsening on PASAT-3 sustained for 12wks, and percentage of patients with cognitive progression at 2yr).	1. In the SENTINEL trial, there was no difference in the percentage of patients with cognitive decline at 2yr (13% for both groups).
Sundgren et al. 2016 *Cognitive function did not improve after initiation of natalizumab treatment in relapsing-remitting multiple sclerosis. A prospective one-year dual control group study* Sweden **PCT** N$_{Initial}$=42, N$_{Final}$=42	**Population:** *MS-Natalizumab (NZ) group (n=15):* Mean age=34.6yr; Sex: males=2, females=13; Disease course: RRMS; Mean EDSS=2.9; Mean disease duration=5.7yr. *MS-Control (MS-C) group (n=15):* Mean age=36.1yr; Sex: males=3, females=12; Disease course: RRMS; Mean EDSS=1.5; Mean disease duration=4.6yr. *Healthy control (HC) group (n=12):* Mean age=32.1yr; Sex: males=3, females=9. **Intervention:** Patients received either NZ or were in the control condition (MS-C) comprising interferon beta therapy, for 1yr. A HC group was also analyzed. **Cognitive Outcomes/Outcome Measures:** Benton Visual Retention Test; Rey Auditory Verbal Learning Test; Vocabulary Test; Controlled Oral Word Association Test; Digit Span forward, backward, total; Trail Making	1. The global cognitive z-score improved significantly in the MS-NZ (p=0.013) and MS-C groups (p<0.001). There was no significant difference between these groups. 2. The MS-NZ group improved significantly in memory (p=0.015), verbal ability (p=0.005), visual perception and organization (p=0.030), and processing speed (p=0.003). 3. The MS-C group improved significantly in memory (p=0.016), attention (p=0.030), executive function (p=0.016), visual perception and organization (p<0.001), and processing speed (p<0.001). 4. The HC group improved significantly in verbal ability (p=0.035), visual perception and organization (p=0.002), and processing speed (p=0.021).

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	Test 1-3 & 5; Color-Word Interference Test 1-4; Block Design Test; Symbol Search Test; Digit Symbol Coding Test; Global score (all tests and subtests).	
Portaccio et al. 2013 *Natalizumab may reduce cognitive changes and brain atrophy rate in relapsing-remitting multiple sclerosis: a prospective, non-randomized pilot study* Italy **PCT** N_{Initial}=26, N_{Final}=26	**Population:** *Natalizumab group (n=12):* Mean age=37.3yr; Sex: males=3, females=9; Disease course: RRMS; Mean EDSS=3.5; Mean disease duration=8.1yr. *IFNB group (n=14):* Mean age=39.0yr; Sex: males=3, females=11; Disease course: RRMS; Mean EDSS=1.3; Mean disease duration=8.6yr. **Intervention:** Patients received natalizumab or interferon beta (IFNB) therapy. Assessments were performed at baseline and after 18mo of treatment. **Cognitive Outcomes/Outcome Measures:** Selective Reminding Test (SRT) long-term storage (SRT-LTS), consistent long-term retrieval (SRT-CLTR), delayed (SRTD); Spatial Recall Test (SPART); SPART delayed (SPARTD); Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT); Word List Generation (WLG).	1. The mean number of neuropsychological tests that showed deterioration from baseline to follow-up (mean follow-up of 1.5yr) was significantly lower in patients treated with natalizumab (p=0.031).

Discussion

The multi-centre SENTINEL RCT compared natalizumab plus IFN-β-1a group versus IFN-β-1a group alone (Rudick et al. 2006). There were no between-group differences on the PASAT-3 outcome. Natalizumab is a higher efficacy MS disease drug for controlling MS disease activity (relapses and new MRI lesions) than IFN-β-1a. It is possible that early intervention in younger patients is important for detecting a response to higher efficacy treatment, or that natalizumab is not superior to IFN-β-1a on cognitive processing speed outcomes. The SENTINEL study participants were older with longer disease duration at the time they started the trial (mean age 38.9 years, SD ±7.7, disease duration median 7 years) compared to the participants in the AFFIRM trial (mean age 36 years, SD± 8.3, disease duration 5 years). The AFFIRM trial compared natalizumab to placebo and reported improvement on the PASAT-3.

Sundgren et al. (2016), in a small prospective non-randomized one-year study, compared three conditions: natalizumab treated; IFN-β treated; and healthy controls without an MS diagnosis. The global cognitive z score improved with no significant between-group differences. Importantly, the healthy controls and treated MS group z scores both improved. However, when examining specific cognitive domains (i.e., executive function, verbal ability, etc.) there were some differences between groups. This trial design with a healthy control group emphasizes the need to consider practice effects and the baseline CI level in the specific cognitive domains of interest when evaluating interventions for CI in MS.

Portaccio et al. (2013) compared participants with RRMS who were receiving either natalizumab or IFN-β in a small non-randomized study over a mean of 1.5 years (follow-up was not standardized). All

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participants in the natalizumab group had been treated with either IFN-β or glatiramer acetate prior to starting natalizumab. At baseline, the two groups were well-matched on the cognitive measures. Over time, the participants in the natalizumab group deteriorated on fewer tests compared to the IFN-β group (0.7 ± 0.7 vs. 1.7 ± 1.4, respectively; p=0.031). Although statistically significant, the clinical significance is not clear due to the non-continuous nature of the number of tests. For other studies on natalizumab see also sections 3.1.14.5.7, 3.1.14.7, 3.1.14.7.1, and 3.1.14.7.2 of this module.

Conclusion

There is level 1b evidence that natalizumab in combination with interferon beta 1a may not be superior to interferon beta 1a alone over 2 years for <u>delaying a decline</u> in auditory processing speed in persons with relapsing-remitting MS (one randomized controlled trial; Weinstock-Guttman et al. 2012; Rudick et al. 2006).

There is level 2 evidence that natalizumab may not be superior to interferon beta at 1 year for <u>improving </u>a global assessment summary score of cognitive tests in persons with relapsing-remitting MS (one prospective controlled trial; Sundgren et al. 2016).

There is level 2 evidence that natalizumab may be more effective for <u>reducing</u> cognitive deterioration compared to interferon beta after a mean of 1.5 years in persons with relapsing-remitting MS (one prospective controlled trial; Portaccio et al. 2013).

Natalizumab as monotherapy or as combination therapy with interferon beta 1a may not be superior to interferon beta 1a alone for improving cognitive function but may be superior in terms of delaying cognitive decline in relapsing-remitting MS.

3.1.14.5.7 Interferon vs. Fingolimod or Natalizumab

Table 24. Study Comparing Interferon vs. Fingolimod or Natalizumab for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Utz et al. 2016 *Cognitive functions over the course of 1 year in multiple sclerosis patients treated with disease modifying therapies*	**Population:** *Fingolimod (n=22):* Median age=35yr; Sex: males=8, females=14; Disease course: RRMS; Median EDSS=2.5; Median disease duration=68mo. *Natalizumab (n=11):* Median age=35yr; Sex: males=4, females=7; Disease course: RRMS; Mean EDSS=2.5; Median disease duration=28mo. *Interferon (n=7):* Median age=29yr; Sex: males=3,	1. 26.8% of RRMS patients declined overall on cognitive assessments while 73.2% remained stable or improved at 6mo assessment. 2. 24.4% of RRMS patients showed significant cognitive decline while 75.6% remained stable or improved in cognitive performance at 12mo assessment.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Germany **PCT** $N_{Initial}$=73, N_{Final}=41	females=4; Disease course: RRMS; Median EDSS=1.0; Median disease duration=24mo. **Intervention:** Patients received disease-modifying therapies (fingolimod, natalizumab, or interferon) over a 1yr period. Assessments were performed at baseline, and at 6 and 12mo follow-ups. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Test-3 (PASAT-3); 10/36 Spatial Recall Test (SPART); SPART delayed recall (SPARTDR); Digit span forward, backward; Spatial span forward, backward; Logical memory I; Go/Nogo; Divided attention; Visual search: reaction time (RT), movement time (MT).	3. No significant association was found between the type of medication received and likelihood of cognitive stability or decline after 6 or 12mo.

Discussion

Utz et al. (2016), in a non-randomized study, examined cognitive function at baseline, and six and 12 months after treatment in participants who were being treated with either interferon, fingolimod, or natalizumab. Overall, approximately 75% remained relatively stable over time, with improvements noted due to practice effects in 12-30%, depending on the measure used. There were no associations between treatments and declining or stable cognitive function at six or 12 months. The study did not include an untreated control group. For other studies on fingolimod and natalizumab see also sections 3.1.14.5.5, 3.1.14.5.6, 3.1.14.5.8, 3.1.14.7, 3.1.14.7.1, and 3.1.14.7.2 of this module.

Conclusion

There is level 2 evidence that fingolimod, natalizumab, and interferon may not be more effective compared to one another for cognitive stability in persons with relapsing-remitting MS (one prospective controlled trial; Utz et al. 2016).

Preliminary evidence supports that fingolimod, natalizumab, or interferon are not more effective compared to one another for maintaining cognition over one year in persons with relapsing-remitting MS.

3.1.14.5.8 Interferon vs. Fingolimod or Glatiramer Acetate

Table 25. Study Comparing Interferon vs. Fingolimod or Glatiramer Acetate for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Cree et al. 2018 *Phase IV study of retention on fingolimod versus injectable multiple sclerosis therapies: a randomized clinical trial* USA **RCT** PEDro=6 N$_{Initial}$=875, N$_{Final}$=713	**Population:** *Fingolimod (n=436):* Mean age=41.5yr; Sex: males=125, females=311; Disease course: RRMS; Median EDSS=2.0; Mean disease duration=4.42yr. *Injectable disease modifying therapies (iDMT; n=439):* Mean age=41.9yr; Sex: males=110, females=329; Disease course: RRMS; Median EDSS=2.0; Mean disease duration=4.21yr. **Intervention:** Participants were randomized to fingolimod 0.5mg/d or to an iDMT (interferon beta-1a, interferon beta-1b, glatiramer acetate) for 48wks. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT).	1. There were no significant between-group differences in SDMT change scores. 2. There were non-significant within group pre-post small improvements on the oral and written SDMT scores. On the oral SDMT, a subgroup of participants improved (least squares mean difference=3.1, p=0.033). This improvement was not significant after accounting for upper limb impairment and visual acuity (p=0.051). 3. Retention rates were significantly higher in the fingolimod compared to the iDMT group (81.3% vs. 29.2%).

Discussion

An RCT by Cree et al. (2018) included both the oral and written version of the SDMT in relapsing MS participants randomized to fingolimod or an injectable DMT (either glatiramer acetate or IFN-β). It is important to note that only the oral version is validated in the MS population and only the oral version has normative data for MS. It is also difficult to come to any conclusions for between-group differences on the oral SDMT in this study since there were low retention rates in the injectable DMT group. For other studies on fingolimod and glatiramer acetate see also sections 3.1.14.4, 3.1.14.5.2, 3.1.14.5.5, 3.1.14.5.7, 3.1.14.7.1, and 3.1.14.7.2 of this module.

Conclusion

There is level 1b evidence that fingolimod or injectable disease modifying therapies may maintain verbal processing speed at 48 weeks (one open label randomized controlled trial; Cree et al. 2018).

Fingolimod or injectable disease modifying therapies may maintain verbal processing speed at 48 weeks.

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3.1.14.6 Mitoxantrone

Mitoxantrone is a synthetic antineoplastic anthracenedione that was approved by the Food and Drug Administration for the treatment of worsening relapsing MS and progressive MS (Hartung et al., 2002). It is a small molecule that can cross the blood brain barrier, but also accumulates in several other organ tissues. It has rarely been used within the last two decades due to the high risk of cardiac toxicity (systolic dysfunction and heart failure) (Marriott et al., 2010).

Table 26. Study Examining Mitoxantrone for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Schröder et al. 2011 *Stability of cognitive functions under mitoxantrone therapy in patients with progressive multiple sclerosis: a pilot analysis* Germany **Cohort** N$_{Initial}$=26, N$_{Final}$=26	**Population:** *Treatment group (n=20):* Mean age=44.7yr; Sex: males=9, females=11; Disease course: SPMS=17, PPMS=1, PRMS=2; Mean EDSS=5.3; Mean disease duration: unspecified. *Control group (n=6).* No further information provided. **Intervention:** Participants received mitoxantrone (MX) therapy 10-12mg/m^2 in 3-4 monthly intervals for a total mean dose of 42mg/m^2. Assessments were performed at baseline and after 24mo. A small subset of 6 patients who did not receive MX therapy was used as a control group. **Cognitive Outcomes/Outcome Measures:** Leistungspruefsystem subtest 7; Regensburger Word Fluency Test; California Verbal Learning Test (CVLT); Wechsler Memory Scale (WMS-R): visual reproduction, digit span forward, digit span backward.	1. No significant changes in cognitive outcome measures were observed at 24mo assessment compared to baseline in the treatment group. 2. Performance worsened over the same time period in the control group (data available only for digit span backwards and Regensburger Word Fluency Test).

Discussion

Only one study was found which examined the effect of mitoxantrone on CI in PwMS (Schröder et al., 2011). It was a small pilot study that included PPMS, SPMS, and progressive relapsing MS participants, as well as participants with MS not receiving mitoxantrone. After 24 months, there was stability, but no significant change or improvement, in cognitive measures from baseline to 24 months in the mitoxantrone group. In contrast, the group of six untreated participants declined in their performance over the same time period, although data was only available for verbal short-term memory and cognitive flexibility outcomes in this group.

Conclusion

There is level 2 evidence that mitoxantrone compared to no treatment may be more effective for cognitive stability (one cohort study; Schröder et al. 2011).

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> Preliminary evidence supports that mitoxantrone may have stabilizing effects on cognitive functions in persons with MS.

3.1.14.7 Natalizumab

Natalizumab is a DMT for MS administered as an infusion medication. It is a monoclonal antibody, selective adhesion molecule inhibitor blocking α4 integrin and preventing T cell entry into the CNS. For other studies on natalizumab see also sections 3.1.14.5.6, 3.1.14.5.7, 3.1.14.7.1, and 3.1.14.7.2 of this module.

Table 27. Studies Examining Natalizumab for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Perumal et al. 2019 *Outcomes of natalizumab treatment within 3 years of relapsing-remitting multiple sclerosis diagnosis: a prespecified 2-year interim analysis of STRIVE* USA **Pre-Post** N$_{Initial}$=231, N$_{Final}$=177	**Population:** Mean age=34.0yr; Sex: males=61, females=161; Disease course: RRMS; Median EDSS=2.0; Mean disease duration=1.6yr. **Intervention:** Participants received natalizumab 300mg intravenously every 4wks for 2yr. Outcomes were assessed at baseline and after 1 and 2yr of treatment. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT).	1. SDMT scores improved significantly from baseline after 1yr (mean change from baseline=2.29, p=0.002) and 2yr (mean change from baseline=4.30, p<0.001) of treatment. 2. There was a clinically significant improvement for SDMT scores (increase of ≥ 4 points) in 41.9% and 49.4% of participants at 1 and 2yr, respectively.
Gudesblatt et al. 2018 *Improvement in cognitive function as measured by NeuroTrax in patients with relapsing multiple sclerosis treated with natalizumab: a 2-year retrospective analysis* USA **Case Series** N$_{Initial}$=52, N$_{Final}$=52	**Population:** Mean age=45.9yr; Sex: males=13, females=39; Disease course: RRMS; Median EDSS=2; Mean disease duration: 0-5yr=22, 6-10yr=14, 11-15yr=13, ≥16yr=3. **Intervention:** Participants received natalizumab 300mg intravenously every 4wks for ≥2yr. Outcomes were assessed at baseline and after 1 and 2yr of treatment. **Cognitive Outcomes/Outcome Measures:** Mindstreams Global Assessment Battery (NeuroTrax™): global cognitive score (GCS), memory, executive function, visual-spatial processing, verbal function, attention, information processing speed, motor function.	1. From baseline to 1yr the GCS did not significantly improve (mean change score=2.06, p=0.064 [-0.12, 4.24 95% CI]) and of the seven domains, only verbal function improved significantly (mean change score=6.36, p=0.007 [1.75, 10.97 95% CI]). 2. From baseline to 1yr, the percentage of participants achieving a clinically significant improvement in cognition increased in all domains (even though mean scores for the total sample did not change). 3. From baseline to 2yr the GCS significantly improved (mean change score=3.43, p=0.003 [1.18, 5.69 95% CI]), and there were significant improvements in mean change scores for four of the

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
		seven domains: memory (3.44, p=0.006 [0.97, 5.92 95% CI]), visual-spatial processing (4.31, p=0.025 [0.54, 8.08 95% CI]), attention (4.27, p=0.017 [0.76, 7.79 95% CI]), and information processing speed (5.15, p=0.002 [1.96, 8.34 95% CI]). 4. The percentage of participants achieving a clinically significant improvement in cognition (an increase in score >1 SD from baseline) for GCS increased from 21.6% at 1yr to 32.7% at 2yr. 5. Fewer participants scored in the cognitively impaired range (score <85) on the GCS or on any of the seven domains at 1 and 2yr compared to baseline.
Planche et al. 2017 *Improvement of quality of life and its relationship with neuropsychiatric outcomes in patients with multiple sclerosis starting treatment with natalizumab: a 3-year follow-up multicentric study* France **Pre-Post** N_{Initial}=48, N_{Final}=36	**Population:** Mean age=41.1yr; Sex: males=11, females=37; Disease course: RRMS; Median EDSS=3.0; Mean disease duration=8.0yr. **Intervention:** Participants received natalizumab 300mg intravenously every 4wks for 3yr. Outcomes were assessed at baseline, 18mo, and 36mo. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT); Paced Auditory Serial Addition Test (PASAT); forward and backward digit span subtest of Wechsler Adult Intelligence Scale-III; Selective Reminding Test (SRT); Stroop Test; Multiple Errands Test.	1. Cognitive scores remained unchanged at 18mo and 36mo compared to baseline for SDMT, PASAT, forward and backward digit span, SRT delayed recall, and Stroop Test. 2. There was a significant improvement in performance on the SRT learning scale at 18mo (69.9, p<0.01) and 36mo (70.0, p<0.05) compared to baseline (60.4). 3. There was a significant transient worsening in performance on the Multiple Errands Test at 18mo (64.3, p<0.05) compared to baseline (73.1), which was no longer significant at 36mo.
Talmage et al. 2017 *Natalizumab stabilizes physical, cognitive, MRI, and OCT markers of disease activity: a prospective, non-randomized pilot study* USA **Pre-Post** N_{Initial}=20, N_{Final}=15	**Population:** Mean age=39yr; Sex: males=2, females=13; Disease course: RRMS; Median EDSS=3; Median disease duration=3yr. **Intervention:** Participants received natalizumab 300mg intravenously every 4wks for 96wks. Outcomes were assessed at baseline, 48wks, and 96wks. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT).	1. Cognitive function remained stable over time during natalizumab treatment, as measured by SDMT z-scores (baseline: -1.5, 48wks: -1.2, 96wks: -1.2; p=0.17). 2. Parameter effect sizes demonstrated that SDMT z-scores were lower at baseline (B=-0.95, p=0.039) and at 48wks (B=-1.09, p=0.02) compared to 96wks.

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Weinstock-Guttman et al. 2012 (Secondary analysis of AFFIRM RCT, Polman et al. 2006; and SENTINEL RCT Rudick et al. 2006) *Additional efficacy endpoints from pivotal natalizumab trials in relapsing-remitting MS* USA Not specified	**Population:** **AFFIRM:** *Natalizumab group:* Disease course: RRMS. *Placebo group:* Disease course: RRMS. No further information provided. **Intervention:** In the AFFIRM trial participants were randomized to natalizumab treatment at 300mg or placebo once monthly. **Cognitive Outcomes/Outcome Measures:** Time to confirmed progression of cognitive deficit (0.5 SD worsening on PASAT-3 sustained for 12wks, and percentage of patients with cognitive progression at 2yr).	1. In the AFFIRM trial, the time to cognitive decline was delayed following natalizumab treatment compared with placebo (HR 0.57, 95% CI 0.37, 0.89, $p=0.013$). The percentage of patients with cognitive decline was 7% in the natalizumab group and 12% in the placebo group at 2yr (Kaplan-Meier estimate).
Jacques et al. 2016 *Cognitive evolution in natalizumab-treated multiple sclerosis patients* Canada **Pre-Post** $N_{Initial}$=63, N_{Final}=62	**Population:** *≤2yr treatment group (n=34):* Mean age=43.56yr; Sex: unspecified; Disease course: unspecified; Mean EDSS=3.09; Mean disease duration=11.65yr. *>2yr treatment group (n=28):* Mean age=46.14yr; Sex: unspecified; Disease course: unspecified; Mean EDSS=2.88; Mean disease duration=14.46yr. **Intervention:** All patients received further natalizumab treatment and were divided into 2 groups based on natalizumab treatment duration at baseline: ≤2yr or >2yr (mean treatment duration of 0.35yr and 3.6yr, respectively). Assessments were performed prospectively every 4wks for 2yr. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test; Cogstate battery test: International Shopping List Test, Groton Maze Learning Test, One Back, Detection, Identification.	1. Significant improvements were observed in both groups at 2yr follow-up with respect to scores on executive function ($p<0.0001$), verbal memory ($p<0.0001$), and working memory ($p=0.0012$). 2. No significant improvement or decline was observed on tests of processing speed or attention. 3. Baseline characteristics were not predictive of the trajectory of cognitive change over the 2yr follow-up.
Sundgren et al. 2016 *Cognitive function did not improve after initiation of natalizumab treatment in relapsing-remitting multiple sclerosis. A prospective one-year dual control group study* Sweden **PCT**	**Population:** *MS-Natalizumab (NZ) group (n=15):* Mean age=34.6yr; Sex: males=2, females=13; Disease course: RRMS; Mean EDSS=2.9; Mean disease duration=5.7yr. *MS-Control (MS-C) group (n=15):* Mean age=36.1yr; Sex: males=3, females=12; Disease course: RRMS; Mean EDSS=1.5; Mean disease duration=4.6yr. *Healthy control (HC) group (n=12):* Mean age=32.1yr; Sex: males=3, females=9. **Intervention:** Patients received either NZ or were in the control condition (MS-C) comprising interferon beta therapy, for 1yr. A HC group was also analyzed.	1. The global cognitive z-score improved significantly in the MS-NZ ($p=0.013$) and MS-C groups ($p<0.001$). There was no significant difference between these groups. 2. The MS-NZ group improved significantly in memory ($p=0.015$), verbal ability ($p=0.005$), visual perception and organization ($p=0.030$), and processing speed ($p=0.003$). 3. The MS-C group improved significantly in memory ($p=0.016$), attention ($p=0.030$), executive function ($p=0.016$), visual

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
N_{Initial}=42, N_{Final}=42	**Cognitive Outcomes/Outcome Measures:** Benton Visual Retention Test; Rey Auditory Verbal Learning Test; Vocabulary Test; Controlled Oral Word Association Test; Digit Span forward, backward, total; Trail Making Test 1-3 & 5; Color-Word Interference Test 1-4; Block Design Test; Symbol Search Test; Digit Symbol Coding Test; Global score (all tests and subtests).	perception and organization ($p<0.001$), and processing speed ($p<0.001$). 4. The HC group improved significantly in verbal ability ($p=0.035$), visual perception and organization ($p=0.002$), and processing speed ($p=0.021$).
Kunkel et al. 2015 *Impact of natalizumab treatment on fatigue, mood, and aspects of cognition in relapsing-remitting multiple sclerosis* Germany **Pre-Post** N_{Initial}=51, N_{Final}=31	**Population:** *Year 1 completers (n=51):* Mean age=33.9yr; Sex: males=11, females=40; Disease course: RRMS; Mean EDSS=4.0; Mean disease duration=5.3yr. *Year 2 completers (n=31):* Mean age: unspecified; Sex: males=7, females=24; Disease course: RRMS; Mean EDSS=3.9; Disease duration: unspecified. **Intervention:** Patients were treated with natalizumab for up to 2yr. Patients were analyzed depending on length of treatment (1 or 2yr). Assessments were performed at baseline and after 1 and 2yr of treatment. **Cognitive Outcomes/Outcome Measures:** Attention Test Battery (TAP): alertness (reaction time, reaction time cued), divided attention (reaction time visual, reaction time auditory, errors, omissions), flexibility (reaction time, errors, performance index), Symbol Digit Modalities Test (SDMT).	1. After 1yr of treatment, significant improvements were observed in scores on the alertness reaction time cued ($p=0.02$), divided attention reaction time visual ($p=0.02$) subtests of the TAP battery and on the SDMT ($p=0.02$). 2. After 2yr of treatment, significant changes were observed in scores on the divided attention reaction time visual ($p<0.001$), divided attention errors ($p=0.01$), divided attention omissions ($p=0.05$), flexibility reaction time subtests of the TAP battery ($p=0.05$), and the SDMT ($p=0.01$).
Mattioli et al. 2015 *Natalizumab significantly improves cognitive impairment over three years in MS: pattern of disability progression and preliminary MRI findings* Italy **Pre-Post** N_{Initial}=24, N_{Final}=24	**Population:** Mean age=36.8yr; Sex: males=11, females=13; Disease course: RRMS; Mean EDSS=4.52; Mean disease duration=12.15yr. **Intervention:** Patients received natalizumab for 3yr. Assessments were performed at baseline and yearly for 3yr. **Cognitive Outcomes/Outcome Measures:** Number of failed cognitive tests (i.e., a score of < -2.0 z-score below corresponding control mean): Raven's Colored Progressive Matrices (CPM Raven); Digit Span forward; Short Tale; Corsi block tapping test; Rey-Osterrieth Complex Figure Test (ROCFT); Paced Auditory Serial Addition Test 2,3 (PASAT 2, 3); Wisconsin Card Sorting Test (WCST): total errors (TE), perseverative responses (PR), perseverative errors (PE); Controlled Word Association Test (COWA).	1. The number of failed tests was significantly lower at 1yr ($p=0.005$), 2yr ($p=0.0002$), and 3yr ($p=0.0001$) follow-up compared to at baseline. Change in number of failed tests between follow-ups (i.e., yr 1-2 and 2-3) were not significant. 2. There were significant improvements over time for the PASAT 2, PASAT 3, WCST TE, WCST PE, WCST PR, Short tale, and Rey Figure cognitive tests (all $p<0.05$). 3. At 1yr follow-up compared to baseline, there were significant improvements on the PASAT 2 ($p=0.02$), WCST TE ($p=0.03$), WCST PR ($p=0.000$), WCST PE ($p=0.006$) and Rey figure recall ($p=0.002$) tests. 4. At 2yr follow-up compared to baseline, there were significant improvements on the PASAT 2 ($p=0.000$), PASAT 3 ($p=0.01$), WCST TE ($p=0.01$), WCST PR ($p=0.000$), WCST PE ($p=0.001$), Short tale ($p=0.001$), and Rey figure recall ($p=0.002$) tests.

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
		5. At yr 3 follow-up compared to baseline, there were significant improvements on the PASAT 2 (p=0.000), WCST TE (p=0.002), WCST PR (p=0.000), WCST PE (p=0.000), and Rey figure (p=0.007) tests.
Iaffaldano et al. 2014 *The improvement of cognitive functions is associated with a decrease of plasma Osteopontin levels in Natalizumab treated relapsing multiple sclerosis* Italy **Pre-Post** N$_{Initial}$=49, N$_{Final}$=49	**Population:** *MS Treatment group (n=49):* Mean age=34.23yr; Sex: males=12, females=37; Disease course: RRMS; Mean EDSS=3.5; Mean disease duration=10.54yr. *MS Treatment Naïve group (n=24):* Mean age=35.8yr; Sex: males=7, females=17; Disease course: RRMS; Mean EDSS=2.0; Mean disease duration=5.58yr. *Healthy controls (n=22):* Mean age=39.18yr; Sex: males=10, females=12. **Intervention:** Patients received natalizumab treatment for at least 1yr. Assessments were performed at baseline and every 12mo. **Cognitive Outcomes/Outcome Measures:** Cognitive impairment (i.e., impaired cognitive function on ≥3 cognitive tests from Rao's Brief Repeatable Battery and the Stroop Test): Paced Auditory Serial Addition Test 2, 3 seconds (PASAT-2, -3); Symbol Digit Modalities Test (SDMT); 10/36 Spatial Recall Test (SPART); Selective Reminding Test (SRT); Word List Generation (WLG)); Cognitive Impairment Index (CII); plasma osteopontin levels.	1. The mean CII value was significantly improved at 1yr of treatment compared with baseline (p=0.004). 2. The mean CII value was significantly improved in patients after 2yr of treatment compared with baseline (p<0.0001). 3. There was a significant improvement in CII seen in patients who received 2yr of treatment at 1 and 2yr with respect to baseline and 1yr assessments (p=0.003, p=0.007 respectively). 4. No other significant differences were observed. 5. After 1 and 2yr, improvement in the CII in the natalizumab group was correlated with a reduction in osteopontin levels (r=0.305, p=0.05; r=0.667, p=0.001; respectively).
Wilken et al. 2013 *Changes in fatigue and cognition in patients with relapsing forms of multiple sclerosis treated with Natalizumab: The ENER-G study* USA **Pre-Post** N$_{Initial}$=89, N$_{Final}$=89	**Population:** Mean age=41.3yr; Sex: males=10, females=81; Disease course: unspecified; Median EDSS=3.0; Median disease duration=8yr. **Intervention:** Patients received natalizumab treatment over 12mo. Natalizumab was given intravenously at a dose of 300mg every 4wks. Assessments were performed at baseline and 4, 8, 12, 24 and 48wks after treatment initiation. **Cognitive Outcomes/Outcome Measures:** Index of Cognitive Efficiency (ICE); Procedural Reaction Time (PRO); Code Substitution Delayed Memory (CDD).	1. Significant improvement was observed across 48wks of treatment in ICE (p=0.001) and PRO scores (p=0.034). ICE scores showed improvements starting at wk 8 and PRO scores showed improvements starting at wk 4; both ICE and PRO scores stabilized by wk 12. 2. No significant changes were observed in CDD scores.
Edwards et al. 2012 *Improvement of neuropsychological*	**Population:** Mean age=48.5yr; Sex: males=9, females=31; Disease course: RRMS; Mean EDSS=4.59; Mean disease duration: unspecified. **Intervention:** Patients received natalizumab 300mg every 4wks. Assessments were	1. The mean Neuropsychological Impairment Index score improved significantly following treatment (p=0.0002). 2. 52.5% of patients improved on the Neuropsychological Impairment Index,

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
function in cognitively impaired multiple sclerosis patients treated with natalizumab: a preliminary study USA **Case Series** N_{Initial}=40, N_{Final}=40	performed at baseline and after 6mo of treatment. **Cognitive Outcomes/Outcome Measures:** Neuropsychological Impairment Index calculated based on the results of nine cognitive tests: Digit Span subtest of the Wechsler Adult Intelligence Scale-IV; Stroop Color-Word Test; Letter Number Sequencing Test of the Wechsler Adult Intelligence Scale-IV; Paced Auditory Serial Addition Test-Revised; California Verbal Learning Test-II; Logical Memory subtest of the Wechsler Memory Scale-IV; Controlled Oral Word Association Test; North American Adult Reading Test-Revised; Symbol Digit Modalities Test.	30.0% had no change, and 17.5% worsened.
Iaffaldano et al. 2012 *Impact of natalizumab on cognitive performances and fatigue in relapsing multiple sclerosis: a prospective, open-label, two years observational study* Italy **Pre-Post** N_{Initial}=100, N_{Final}=53	**Population:** *1yr treatment (n=100):* Mean age=34.55yr; Sex: males=28, females=72; Disease course: RRMS; Mean EDSS=3.66; Mean disease duration=11.09yr. *2yr treatment (n=53):* Mean age=33.41yr; Sex: males=16, females=37; Disease course: RRMS; Mean EDSS=3.58; Mean disease duration=9.67yr. **Intervention:** Patients received natalizumab treatment for 2yr. Assessments were performed at baseline and every 12mo. **Cognitive Outcomes/Outcome Measures:** Cognitive impairment (i.e., impaired cognitive function on ≥3 cognitive tests from Rao's Brief Repeatable Battery and the Stroop Test): Paced Auditory Serial Addition Test 2, 3 seconds (PASAT-2, -3); Symbol Digit Modalities Test (SDMT); 10/36 Spatial Recall Test (SPART); Selective Reminding Test (SRT); Word List Generation (WLG)); Cognitive Impairment Index (CII).	1. At baseline 29/100 met criteria for cognitive impairment and at 1 yr 19/100 met criteria for cognitive impairment (p=0.031). 2. At 1yr (n=100) and at 2yr (n=53) mean CII values were both improved compared to baseline (p<0.0001). 3. For the subgroup with 2yr data (n=53), CII mean values improved at 2yr compared to their mean 1yr values (p=0.008). 4. Among the individual cognitive test outcomes, significant differences were observed after 1yr of treatment with respect to baseline in scores on the SDMT (p<0.0001), SPART (p<0.037), and PASAT-2 (p<0.026). 5. Significant differences were also observed in the 2yr treatment sub-group after 2yr of treatment compared with baseline on the SDMT (p=0.001), PASAT-2 (p=0.006), and PASAT-3 (p<0.0001).
Lang et al. 2012 *Natalizumab may improve cognition and mood in multiple sclerosis* Germany **Pre-Post** N_{Initial}=29, N_{Final}=29	**Population:** Mean age=33.7yr; Sex: males=5, females=24; Disease course: unspecified; Mean EDSS=3.5; Mean disease duration=10.5yr. **Intervention:** Patients underwent natalizumab therapy for 6mo. Assessments were performed at baseline and after 3 and 6mo of treatment. **Cognitive Outcomes/Outcome Measures:** Non-Verbal Learning Test (NVLT): correct, false, difference; Attention Test Battery (TAP); Auditory Verbal Learning Test (AVLT) trials 1-3, recognition; Paced Auditory Serial Addition	1. Significant differences were found for at least one time point compared with baseline for NVLT correct (p=0.016), NVLT difference (p=0.047), Alertness without warning stimulus (p<0.0001), Alertness with warning stimulus (p<0.0001), Mental fatigue (p<0.0001), AVLT1 (p=0.004), AVLT2 (p=0.017), AVLT3 (p=0.001), and PASAT (p=0.013).

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	Test (PASAT); Verbal Learning Test (VLT): false, difference.	
Stephenson et al. 2012 *Impact of natalizumab on patient-reported outcomes in multiple sclerosis: a longitudinal study* USA **Pre-Post** N$_{Initial}$=1275, N$_{Final}$=333	**Population:** Mean age=46.8yr; Sex: males=73, females=260; Disease course: unspecified; Disease severity: unspecified; Mean disease duration=10.6yr. **Intervention:** Patients received natalizumab therapy for 12mo in monthly intravenous infusions of 300mg. Assessments were performed at baseline and after 3, 6, 9, and 12mo. **Cognitive Outcomes/Outcome Measures:** Medical Outcomes Scale-Cognitive Functioning (MOS-Cog).	1. Patients reported a significant reduction in the impact of MS on cognitive functioning at the 3, 6, 9, and 12mo assessments (p<0.001 for all). 2. Compared to baseline, 65 to 69% of patients experienced either an improvement or no change in the impact of MS on cognition after 12 infusions.
Mattioli et al. 2011 *Natalizumab efficacy on cognitive impairment in MS* Italy **Pre-Post** N$_{Initial}$=39, N$_{Final}$=11	**Population:** Mean age=36.6yr; Sex: males=19, females=20; Disease course: RRMS; Mean EDSS=4.1; Mean disease duration=11.3yr. **Intervention:** Patients received natalizumab therapy at a dose of 300mg monthly for 1yr. A subset of 11 patients continued the treatment for an additional year. Assessments were performed at baseline, and after 1 and 2yr of treatment. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Test (PASAT); Wisconsin Card Sorting Test (WCST): total errors (TE), perseverative responses (PR), perseverative errors (PE); Controlled Oral Word Association Test (COWA); Short Tale Test; Selective Reminding Test (SRT); Rey Figure Test; 10/36 Spatial Recall Test (SPART); Raven's Colored Progressive Matrices (CPM Raven).	1. Significant improvements were observed in WCST TE (p=0.009), WCST PR (p<0.001), WCST PE (p=0.002), COWA with semantic cues (p=0.031), and CPM Raven (p<0.048) at 1yr follow-up compared with baseline. 2. Significant improvements were observed in PASAT (p<0.022), WCST PR (p=0.013), WCST PE (p=0.013), and Short Tale Test (p=0.013) at 2yr follow-up compared with baseline. 3. Statistically significant improvements were seen from 1yr to 2yr follow-ups in PASAT 2 (p=0.019), PASAT 3 (p=0.032), and COWA with semantic cues (p=0.041) scores.

Discussion

The effect of natalizumab as monotherapy compared to placebo on cognitive function in MS is reported in the AFFIRM multi-centre randomized trial (Polman et al. 2006). The PASAT-3 AFFIRM study results are detailed in a separate report by Weinstock-Guttman et al. (2012). The remaining natalizumab studies are pre-post or case series designs.

In the AFFIRM trial, time to clinically meaningful worsening on the PASAT-3 of 0.5SD was delayed significantly for the natalizumab treatment group compared to the placebo group (HR 0.57, 95% CI 0.37, 0.89, p=0.013). In addition, the percentage of patients with worsening on the PASAT-3 over the two years was higher in the placebo group (12%) compared to the natalizumab treatment group (7%). The AFFIRM

trial results support a protective effect on auditory processing speed with natalizumab compared to placebo.

In the pre-post and case series studies, cognition also improved compared to baseline in one or more cognitive domain. The most consistent improvements were in the domains of attention and processing speed. Improved cognition occurred among those with and without CI at baseline and as early as four weeks after treatment start. One study reported that just over half of the study sample improved on the cognitive testing, 30% were stable and 17.5% worsened over six months on natalizumab treatment (Edwards et al. 2012). These results support individual differences in the treatment response and the course of cognitive decline. Factors associated with cognitive decline and response to treatment, such as age and disease duration, warrant further research.

Other potential confounders on cognitive testing include fatigue and mood symptoms. These symptoms may negatively affect the treatment response (Planche et al. 2017; Kunkel et al. 2015; Wilken et al. 2013; Iaffaldano et al. 2012; Lang et al. 2012; Stephenson et al. 2012). Only one study reported on the patient's experience of cognitive symptoms in real world settings (Stephenson et al. 2012). Up to 69% of patients reported stabilization or improvement in their cognitive functioning.

Two small studies followed participants treated with natalizumab for three years (Planche et al. (2017) (n=48) and Mattioli et al. (2015) (n=24)). In the Mattioli et al. study, CI in the domains of memory, attention, and executive function improved within the first year. After the first year, cognitive outcomes stabilized, with the exception of verbal memory. Verbal memory continued to improve at two years and three years (p=0.07). After three years, preliminary MRI data supported an increase in the mean cortical volume of the dorsolateral prefrontal cortex and the parahippocampus regions. Planche et al. (2017) also found that verbal learning and memory continued to improve at three years, supporting a possible specific longer-term treatment effect in this cognitive domain. These results also suggest that when the rate of new MRI lesion formation decreases with treatment, it is possible for cognitive gains to occur over the longer term. Future imaging and functional imaging research may improve our understanding of the mechanism of treatment on cognitive function.

The studies of natalizumab treatment discussed in this section include people with relapsing-remitting MS with mean disease durations ranging from 1.6 years (Perumal et al. 2019) to 14.5 years (Jacques et al. 2016). The potential positive effects of natalizumab on cognitive function are promising; however, patient selection may be important.

Conclusion

There is level 1b evidence that natalizumab treatment over 2 years compared to placebo may <u>delay a decline</u> in auditory processing speed in persons with relapsing-remitting MS (one randomized controlled trial; Weinstock-Guttman et al. 2012; Polman et al. 2006).

There is level 4 evidence that natalizumab may <u>stabilize or improve</u> attention and processing speed after 2 years of treatment in persons with relapsing-remitting MS (seven pre-post studies; Perumal et al. 2019; Talmage et al. 2017; Jacques et. al 2016; Kunkel et al. 2015; Mattioli et al. 2015; Iaffaldano et al. 2012; Mattioli et. al. 2011).

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There is conflicting evidence that <u>improvements</u> in attention and processing speed after starting natalizumab treatment may be sustained at 3 years in persons with relapsing-remitting MS (two pre-post studies; Planche et al. 2017; Mattioli et al. 2013).

There is level 4 evidence that natalizumab treatment <u>may improve</u> attention and processing speed within 4 weeks to six months of starting treatment in persons with relapsing-remitting MS (three pre-post studies; Wilken et al. 2013; Edwards et al. 2012; Lang et al. 2012).

There is conflicting evidence regarding whether natalizumab <u>improves or maintains</u> cognition consistently across multiple cognitive domains in persons with relapsing-remitting MS (one prospective controlled study; Sundgren et al. 2016; ten pre-post studies; Planche et al. 2017; Jacques et. al 2016; Kunkel et al. 2015; Mattioli et al. 2015; Iaffaldano et. al. 2014; Wilken et al. 2013; Iaffaldano et al. 2012; Edwards et al. 2012; Lang et al. 2012; Mattioli et. al. 2011; one case series; Gudesblatt et al. 2018).

There is level 4 evidence that natalizumab treatment <u>improves or maintains</u> patient reported cognitive function on the Medical Outcomes Scale - Cognitive functioning in persons with relapsing-remitting MS (one pre-post study; Stephenson et al. 2012).

There is level 4 evidence that a decrease in serum osteopontin levels correlates with a globally improved cognitive index score in patients treated with natalizumab for at least one year in persons with relapsing-remitting MS (one pre-post study; Iaffaldano et al. 2014).

Natalizumab may delay a decline in processing speed at two years in relapsing-remitting MS.

Preliminary evidence suggests that improvement in processing speed after natalizumab treatment may be observed as early as four weeks post treatment.

There are conflicting results for the effects of natalizumab on maintaining processing speed at three years.

The effects of natalizumab on maintaining or improving function in different cognitive domains are inconsistent.

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3.1.14.7.1 Natalizumab vs. Fingolimod

Table 28. Study Comparing Natalizumab vs. Fingolimod for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Preziosa et al. 2020 *Effects of natalizumab and fingolimod on clinical, cognitive, and magnetic resonance imaging measures in multiple sclerosis* Italy **Cohort** N$_{Initial}$=63, N$_{Final}$=55	**Population:** *Fingolimod (n=25):* Mean age=37.5yr; Sex: males=10, females=15; Disease course: RRMS; Mean EDSS=2.63; Mean disease duration=11.1yr. *Natalizumab (n=30):* Mean age=36.8yr; Sex: males=12, females=18; Disease course: RRMS; Mean EDSS=2.36; Mean disease duration=9.5yr. *Healthy control (n=15).* **Intervention:** Participants with MS who started natalizumab or fingolimod were followed for 2yr. Outcomes were assessed at baseline, 12mo, and 24mo. **Cognitive Outcomes/Outcome Measures:** Cognitive performance (i.e., ≥2 abnormal test scores from the Brief Repeatable Battery of Neuropsychological Tests indicated cognitive impairment).	1. Compared to baseline, both treatments significantly improved global cognitive performance at 24mo (fingolimod: p=0.03; natalizumab: p=0.01), with no between-group differences. 2. Data was not reported for the healthy control group.

Discussion

One cohort study reported that cognitive performance significantly improved at two years in both the natalizumab and fingolimod groups, with no between-group differences. A small healthy control group was also included in the study with MRI brain atrophy outcomes. The rate of brain atrophy progression was similar between the MS treated groups, but higher than that observed in the healthy control group. Cognitive improvement in both MS treated groups trended towards improvement at one year but did not reach statistical significance. A limitation of this study is that the authors do not report the magnitude of the cognitive performance improvement, the specific cognitive domains affected, or the healthy control group cognitive performance scores. However, the authors do suggest that the improved cognitive performance had a positive impact on MS fatigue and depression outcomes. For other studies on fingolimod see also sections 3.1.14.5.5, 3.1.14.5.7, and 3.1.14.5.8 of this module.

Conclusion

There is level 2 evidence that global cognitive performance on the Brief Repeatable Battery improves similarly with natalizumab or fingolimod treatment at two years in persons with relapsing-remitting MS (one cohort study; Preziosa et al. 2020).

Preliminary evidence supports that fingolimod or natalizumab similarly improve global cognitive performance at two years in persons with relapsing-remitting MS.

3.1.14.7.2 Natalizumab vs. Interferon Beta, Glatiramer Acetate, or Dimethyl Fumarate

Table 29. Study Comparing Natalizumab vs. Interferon Beta, Glatiramer Acetate, or Dimethyl Fumarate for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Rorsman et al. 2018 *Cognitive functioning following one-year natalizumab treatment: a non-randomized clinical trial* Sweden **PCT** N$_{Initial}$=34, N$_{Final}$=30	**Population:** *Natalizumab (n=21):* Median age=41yr; Sex: males=7, females=14; Disease course: RRMS; Median EDSS=2; Median disease duration=4yr. *Control (n=13):* Median age=46yr; Sex: males=1, females=12; Disease course: RRMS; Median EDSS=2; Median disease duration=18yr. **Intervention:** Participants initiating natalizumab were recruited and compared to a quasi-control group treated with first-line disease modifying therapies (e.g., interferon beta, glatiramer acetate, dimethyl fumarate). Outcomes were assessed at baseline and at 12mo follow-up. **Cognitive Outcomes/Outcome Measures:** Claeson-Dahl Verbal Learning Test (C-D); Brief Visuospatial Memory Test (BVMT-R); Judgement of Line Orientation (JLO); Symbol Digit Modalities Test (SDMT); Delis-Kaplan Executive Function System Sorting Test (D-KEFS); Controlled Oral Word Association Test (COWAT); Paced Auditory Serial Addition Test (PASAT-3, -2).	1. Significant between-group differences were observed for the PASAT-2 at 12mo follow-up (Z=2,61, p=0.008 [-0.30, 1.28 95% CI]), with the natalizumab group showing a larger improvement from baseline compared to the control group. 2. 28.5% of participants in the natalizumab group demonstrated ≥1 SD improvement on the PASAT-2 (indicative of clinically significant change), compared with none in the control group. 3. No other significant between-group differences were observed at 12mo follow-up. 4. There were significant within-group improvements from baseline to 12mo follow-up in the natalizumab group on the BVMT-R recall (p=0.009) and learning (p=0.008), SDMT (p=0.001), PASAT-3 (p=0.002), and PASAT-2 (p=0.001). 5. Both groups demonstrated significant improvement on the COWAT from baseline to 12mo follow-up (natalizumab: p=0.003; control: p=0.01).

Discussion

One prospective controlled study by Rorsman et al. 2018 compared natalizumab with a second group which included participants on either interferon, glatiramer acetate, or dimethyl fumarate. The percentage of participants on each of the other first line DMTs in this second group, and the SDMT between group change scores were not reported. There were greater improvements in the natalizumab group at 12 months on the PASAT compared to the control group. However, more participants in the natalizumab group had experienced a relapse in the last 6 months. At baseline, the natalizumab group also had significantly worse scores on the SDMT compared to the control group. For other studies on

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natalizumab, glatiramer acetate, and dimethyl fumarate see also sections 3.1.14.3, 3.1.14.4, 3.1.14.5.2, 3.1.14.5.6, 3.1.14.5.7, 3.1.14.5.8, 3.1.14.7, and 3.1.14.7.1 of this module.

Conclusion

There is level 2 evidence that natalizumab is associated with greater improvements in auditory processing speed compared to interferon beta, glatiramer acetate, or dimethyl fumarate in relapsing-remitting MS (one prospective controlled trial; Rorsman et al. 2018).

> Preliminary evidence supports that natalizumab may improve auditory processing speed more than other first line disease modifying therapies.

3.1.14.8 Rituximab

Rituximab is a monoclonal antibody targeting the CD20 surface antigen and mediating B-cell and B-lymphocyte lysis and depletion. B-cells are believed to play an important role in the pathogenesis of MS ("Drug monograph: Rituximab," 2021).

Table 30. Study Examining Rituximab for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
de Flon et al. 2017 (Secondary analysis of De Flon et al. 2016) *Improved treatment satisfaction after switching therapy to rituximab in relapsing-remitting MS* Sweden **Pre-Post** N$_{Initial}$=75, N$_{Final}$=72	**Population:** Mean age=41.1yr; Sex: males=25, females=52; Disease course: RRMS; Median EDSS=1.5; Mean disease duration=9.5yr. **Intervention:** Participants switched from injection therapy to rituximab (2 doses of 1000mg administered intravenously 2wks apart). Outcomes were assessed at baseline and at 12 and 24mo thereafter. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT).	1. There was a significant improvement on mean SDMT scores from baseline (53.6) to 12mo (57.0; p<0.001) and from baseline to 24mo (56.8; p<0.001).

Discussion

One study by de Flon et al. (2017) involved a secondary analysis of data from a previous trial (de Flon et al. 2016). The effect of switching from first-line injectable treatment to rituximab was evaluated in a cohort of clinically stable participants with RRMS. There was a significant improvement in visual

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processing speed mean SDMT scores at 12 months compared to baseline (p<0.001), which remained unchanged or stable at 24 months. The lack of a control group is a limitation for interpreting the effect of rituximab on cognitive function in this study.

Conclusion

There is level 4 evidence that rituximab may improve visual processing speed in persons with relapsing-remitting MS (one pre-post study; de Flon et al. 2017).

> Preliminary evidence suggests that rituximab may improve visual processing speed in persons with relapsing-remitting MS.

3.1.14.9 Teriflunomide

Teriflunomide is an oral immunomodulator which inhibits dihydroorotate dehydrogenase, leading to a reduced concentration of activated T- and B-lymphocytes in the CNS. This may in turn reduce the inflammatory demyelination that occurs in MS.

Table 31. Study Examining Teriflunomide for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Coyle et al. 2018 (Secondary analysis of Coyle et al. 2017) *Patient-reported outcomes in patients with relapsing forms of MS switching to teriflunomide from other disease-modifying therapies: results from the global phase 4 Teri-PRO study in routine clinical practice* USA **Pre-Post** N_{Initial}=594, N_{Final}=594	**Population:** Mean age=47.5yr; Sex: males=23.6%, females=76.4%; Disease course: relapsing forms of MS; Mean EDSS=3.1; Mean disease duration=13.8yr. **Intervention:** Participants who were receiving another disease modifying therapy within the 6mo prior to study start were prescribed teriflunomide (14mg or 7mg 1x/d) for 48wks. Outcomes were assessed at baseline and at wk 48. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT); Multiple Sclerosis Performance Scale (MSPS) cognitive subscale.	1. Mean SDMT scores were stable over the course of the study from baseline (0.975 [0.971, 0.979 95% CI]) to wk 48 (0.978 [0.974, 0.982 95% CI]; p=0.8074). 2. Cognitive impairment as recorded by participants on the cognitive domain of the MSPS also remained stable over the course of the study.

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Discussion

One study by Coyle et al. (2018) conducted a secondary analysis of a previous phase IV trial (Coyle et al. 2017) to examine the effect of switching to teriflunomide from other DMTs on cognitive function in PwMS. Participants with relapsing forms of MS received teriflunomide for 48 weeks. Cognitive function was included as a secondary endpoint with the SDMT as well as the cognitive subscale of the patient-reported Multiple Sclerosis Performance Scale. Mean scores on the SDMT remained stable at 48 weeks compared to baseline (p=0.8074). The cognitive subscale of the Multiple Sclerosis Performance Scale also remained stable.

Conclusion

There is level 4 evidence that teriflunomide may have stabilizing effects on cognition (one pre-post study; Coyle et al. 2018).

Preliminary evidence suggests that teriflunomide may have stabilizing effects on clinical and subjective measures of cognitive function in persons with MS.

3.2 Complementary and Alternative Treatment

Complementary and alternative medicine (CAM) approaches have been used as an adjunct to traditional therapies in Western medicine for many years. CAM interventions include a heterogeneous mix of practices such as massage therapy, nutritional supplements, dietary modification, and the use of herbal medicines; however, there is limited data regarding the safety or effectiveness of these modalities. Few studies have evaluated CAM approaches for the treatment of CI in PwMS.

3.2.1 Achillea millefolium

Achillea millefolium, commonly known as yarrow, is a widely used medicinal plant. *Achillea millefolium* contains flavonoids including apigenin and luteolin, which are believed to be the pharmacologically active compounds (Applequist & Moerman, 2011). Based on animal studies, these compounds may have neuroprotective effects against cognitive decline (Liu et al., 2014; Patil et al., 2014).

Table 32. Study Examining Achillea millefolium for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Ayoobi et al. 2019	**Population:** *250mg A. millefolium (n=25):* Mean age=31.36yr; Sex: males=3, females=22; Disease course: RRMS=24, SPMS=1; Mean EDSS=1.18; Mean disease duration=2.82yr. *500mg A. millefolium*	1. Both treatment groups had significantly improved word-pair learning scores compared to the placebo group at 9mo (3.91 for placebo; 2.23,for the 250mg group ,p=0.039; 2.29, for the 500mg

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Achillea millefolium is beneficial as an add-on therapy in patients with multiple sclerosis: a randomized placebo-controlled clinical trial Iran **RCT** PEDro=9 N_Initial=75, N_Final=65	*(n=25):* Mean age=34.00yr; Sex: males=2, females=23; Disease course: RRMS=24, SPMS=1; Mean EDSS=1.95; Mean disease duration=3.52yr. *Placebo (n=25):* Mean age=34.68yr; Sex: males=3, females=22; Disease course: RRMS=24, SPMS=1; Mean EDSS=1.38; Mean disease duration=3.14yr. **Intervention:** Participants were randomized to receive either *A. millefolium* (250mg/d or 500mg/d) or placebo for 12mo. Outcomes were assessed at baseline and 3, 6, 9, and 12mo. All participants in all 3 groups also were taking either interferon or glatiramer acetate. **Cognitive Outcomes/Outcome Measures:** Mini-Mental Status Examination (MMSE); Wisconsin Card Sorting Test (WCST); Tower of London Test (TOL); word-pair learning; Paced Auditory Serial Addition Task (PASAT).	group, p=0.049) and at 12mo only the 500mg group remained significant compared to placebo (3.77 for placebo; 2.05 for 500mg, p=0.037). 2. Both treatment groups had significantly improved mean scores on the PASAT compared to the placebo group at 12 mo (mean placebo group PASAT 27.32 vs. 36.67 for the 250mg group, p=0.025 and 38.24 for the 500mg group, p=0.009). Other time point results were not reported. 3. There were significant improvements in both treatment groups compared to the placebo group on some indices of the WCST at various time points including the number of non perseverative errors, conceptual level response, and number of failures. 4. There were no significant differences between groups on the TOL or MMSE at any time point.

Discussion

One study has examined the effect of *Achillea millefolium* as an add-on therapy for CI in PwMS. Ayoobi et al. (2019) randomized participants with RRMS to either one of two doses of *Achillea millefolium* (250mg or 500mg per day) or placebo for a duration of 12 months. For the study, dried extract was processed from the flowering branches of the plant. *Achillea millefolium* had been used in complementary medicine for abortion. Therefore, study exclusion criteria included pregnant women or those contemplating pregnancy. Cognitive function was included as a secondary endpoint and was assessed using the word-pair learning test, PASAT, Wisconsin Card Sorting Test, Mini-Mental Status Examination, and Tower of London Test. The *Achillea millefolium* groups demonstrated significantly improved performance in the word-pair learning test, PASAT, and Wisconsin Card Sorting Test compared to placebo following nine to 12 months of treatment. However, the study was not powered to evaluate these clinical parameters and further research using a larger sample size may be warranted.

Conclusion

There is level 1b evidence that Achillea millefolium as an add-on therapy compared to placebo may improve auditory processing speed and verbal learning and memory in persons with relapsing-remitting MS, but not general cognition or executive functioning at 12 months (one randomized controlled trial; Ayoobi et al. 2019).

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> *Achillea millefolium* may be beneficial for improving auditory processing speed and verbal learning and memory, but not other cognitive functions, at 12 months in persons with relapsing-remitting MS.

3.2.2 Boswellia Serrata/Papyrifera

Boswellia serrata and *Boswellia papyrifera* are types of frankincense, a resinous extract secreted from *Boswellia* tree species (Archier & Vieillescazes, 2000). Boswellia acts as an anti-inflammatory by inhibiting 5-lipoxygenase (Zengion & Yarnell, 2011).

Table 33. Studies Examining Boswellia Serrata or Papyrifera for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Majdinasab et al. 2016 *Effect of Boswellia serrata on cognitive impairment in multiple sclerosis patients* Iran **RCT** PEDro=8 N$_{Initial}$=60, N$_{Final}$=60	**Population:** *Treatment group (n=30):* Mean age=30.17yr; Sex: males=8, females=22; Disease course: RRMS; Severity: unspecified; Mean disease duration=4.23yr. *Placebo group (n=30):* Mean age=31.5yr; Sex: males=9, females=21; Disease course: RRMS; Severity: unspecified; Mean disease duration=4.43yr. **Intervention:** Patients were randomized to receive *Boswellia serrata* (BS) in a 450mg capsule or placebo 2x/d for 2mo. Assessments were performed before and after treatment. **Cognitive Outcomes/Outcome Measures:** Brief Visuospatial Memory Test-Revised (BVMT-R); California Verbal Learning Test 2nd edition (CVLT-II); Symbol Digit Modalities Test (SDMT); Controlled Oral Word Association Test (COWAT); Judgment of Line Orientation test (JLO); Delis-Kaplan Executive Function System (D-KEFS); Paced Auditory Serial Addition Test (PASAT).	1. The BS treatment group scored significantly higher than the placebo group after treatment compared with baseline on the CVLTII-TL (p<0.01) and BVMTR-TL (p<0.01). 2. No other significant between-group effects of treatment were observed.
Sedighi et al. 2014 *Effect of Boswellia papyrifera on cognitive impairment in multiple sclerosis* Iran **RCT** PEDro=6	**Population:** *Treatment Group (n=38)*: Mean age=36.21yr; Disease course: RRMS; Disease severity: unspecified; Mean disease duration=6.87yr. *Placebo Group (n=38)*: Mean age=36.95yr; Disease course: RRMS; Disease severity: unspecified; Mean disease duration=7.95yr. *For total study sample*: Sex: males=12, females=64. **Intervention:** Patients were randomized into treatment and placebo groups. The treatment group received *Boswellia papyrifera* (BP)	1. No significant differences between groups were observed on SDMT (p=0.2) and CVLT (p=0.17) scores. 2. BVMT-R was improved significantly in 13 patients who received BP compared to the placebo group (p<0.001).

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
$N_{Initial}$=80, N_{Final}=76	300mg capsules 2x/d for 2mo while the control group received matched placebo. Assessments were performed before and after treatment. **Cognitive Outcomes/Outcome Measures:** Symbol Digit Modalities Test (SDMT); California Verbal Learning Test-II (CVLT-II); Brief Visual-spatial Memory Test-Revised (BVMT-R).	

Discussion

Sedighi et al. (2014) examined the effects of *Boswellia papyrifera* on cognitive function in participants with RRMS, compared to placebo for two months. At the end of the study, there was a significant improvement in the treatment group compared to the placebo group for visuospatial memory (BVMT-R). Another group examined the effects of *Boswellia serrata* for two months compared to placebo. There was a significant difference in change over time between the treatment and the placebo group for verbal memory and learning (CVLT-II) and visuospatial memory (BVMT-R), but not for other measures of cognitive function (Majdinasab et al., 2016).

Conclusion

There is level 1b evidence that Boswellia serrata compared to placebo may improve verbal memory and learning, and visuospatial memory, but not visual processing speed, executive function, verbal fluency, auditory processing speed, or spatial processing, in persons with relapsing-remitting MS (one randomized controlled trial; Majdinasab et al. 2016).

There is level 1b evidence that Boswellia papyrifera compared to placebo may improve visuospatial memory, but not verbal memory and learning or visual processing speed, in persons with relapsing-remitting MS (one randomized controlled trial; Sedighi et al. 2014).

Boswellia serrata may improve verbal memory and learning and visuospatial memory, but not other cognitive functions, in persons with relapsing-remitting MS.

Boswellia papyrifera may improve visuospatial memory, but not other cognitive functions, in persons with relapsing-remitting MS.

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3.2.3 Ginkgo Biloba

Ginkgo biloba (GB) is a supplement derived from the leaves of the *Ginkgo biloba* Linne tree ("Ginkgo Biloba Leaf Extract," 1998). GB contains ginkgolides that inhibit platelet-activating factor, which modulates presynaptic glutamate release. Thus, GB could antagonistically modulate glutamate excitotoxicity and improve cognition (Lovera et al., 2012). Although GB is frequently used among PwMS, there is limited information on the benefits of GB in this clinical population (Yadav et al., 2006).

Table 34. Studies Examining Ginkgo Biloba for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Lovera et al. 2012 *Ginkgo biloba does not improve cognitive function in MS: a randomized placebo-controlled trial* USA **RCT** PEDro=9 N$_{Initial}$=121, N$_{Final}$=116	**Population:** *Ginkgo group (n=61):* Mean age=51.3yr; Sex: males=32, females=29; Disease course: RRMS=42, PPMS=5, SPMS=14; Mean EDSS=4; Mean disease duration=20.9yr. *Placebo group (n=59):* Mean age=53yr; Sex: males=22, females=37; Disease course: RRMS=35, PPMS=4, SPMS=19, PRMS=1; Mean EDSS=4; Mean disease duration=19.3yr. **Intervention:** Patients were randomized to receive *Ginkgo biloba* in a 120mg tablet daily or placebo 2x/d for 12wks. Assessments were performed before and after treatment. **Cognitive Outcomes/Outcome Measures:** Stroop Colour-Word Test: interference; California Verbal Learning Test-II (CVLT-II); Controlled Oral Word Association Test (COWAT); Paced Auditory Serial Addition Test (PASAT).	1. After treatment the placebo group performed non-significantly better than the ginkgo group on the Stroop Test. 2. There were no significant between-group differences observed post treatment.
Lovera et al. 2007 *Ginkgo biloba for the improvement of cognitive performance in multiple sclerosis: a randomized, placebo-controlled trial* USA **RCT** PEDro=9 N$_{Initial}$=43, N$_{Final}$=39	**Population:** *Ginkgo group (n=20):* Mean age=47.8yr; Sex: males=6, females=14; Disease course: RRMS=11, SPMS=9; Mean EDSS=3.8; Mean disease duration=15.1yr. *Placebo group (n=19):* Mean age=50.2yr; Sex: males=6, females=13; Disease course: RRMS=11, PPMS=2, SPMS=6; Mean EDSS=3.5; Mean disease duration=15.6yr. **Intervention:** Patients were randomized to either the treatment group or the placebo group. The treatment group received *Ginkgo biloba* (GB) 120mg 2x/d for 12wks. Assessments were performed before and after intervention. **Cognitive Outcomes/Outcome Measures:** California Verbal Learning Test-II (CVLT-II): long delayed recall; Paced Auditory Serial Addition Test (PASAT); Controlled Oral Word Association Test (COWAT); Symbol Digit Modalities Test (SDMT); Stroop Test: color-word interference.	1. The color-word interference condition of the Stroop Test showed a statistical trend favouring GB compared to placebo (p=0.015), which did not reach statistical significance after adjusting for multiple comparisons. 2. There was a statistically significant interaction between the baseline performance on the Stroop Test: color-word interference condition and treatment group (p=0.008). 3. No other significant differences were observed for other cognitive outcomes between groups or over time.

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Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Noroozian et al. 2011 *Ginkgo biloba for improvement of memory and quality of life in multiple sclerosis: an open trial* Iran **Pre-Post** N_Initial=40, N_Final=30	**Population:** Mean age=33.7yr; Sex: males=10, females=20; Disease course: RRMS=26, SPMS=4; Severity: unspecified; Mean disease duration=6.23yr. **Intervention:** Patients received *Ginkgo biloba* 240mg/d (one patient received 120mg/d) for 8wks. Assessments were performed at baseline and after treatment. **Cognitive Outcomes/Outcome Measures:** Wechsler Memory Scale (WMS).	1. Subjects significantly improved on the WMS (p<0.001) after treatment.

Discussion

Three studies have examined the effect of GB on cognitive function in MS. In 2007, Lovera et al. compared cognitive function in participants with MS treated with GB or a placebo for 12 weeks. At the end of the 12 weeks, there was no significant difference in the change over time between the two groups, with the exception of the Stroop Color-Word Test (interference susceptibility and mental flexibility). However, after applying the Bonferroni correction for multiple comparisons, there was no significant difference between GB and placebo on cognitive function. Lovera et al. then conducted a larger follow up study (2012) with a similar design to the previous study. In this larger study, there was no significant difference noted on any of the cognitive outcomes over the 12-week study period. One other small, uncontrolled open label trial found an improvement on a memory measure in participants with MS after eight weeks of GB (Noroozian et al., 2011).

Conclusion

There is level 1a evidence that Ginkgo biloba compared to placebo may not improve auditory processing speed, verbal memory and learning, or verbal fluency (two randomized controlled trials; Lovera et al. 2012; Lovera et al. 2007).

There is conflicting evidence regarding whether or not Ginkgo biloba compared to placebo improves cognitive interference and mental flexibility (two randomized controlled trials; Lovera et al. 2012; Lovera et al. 2007).

There is level 1b evidence that Ginkgo biloba compared to placebo may not improve visual processing speed (one randomized controlled trial; Lovera et al. 2007).

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> *Ginkgo biloba* does not improve cognitive impairment in several cognitive domains in persons with MS; however, there is conflicting evidence for its effect on cognitive interference and mental flexibility.

3.2.4 Melatonin

Melatonin is a hormone that plays an important role in modulating several physiological functions. It has been suggested that melatonin may also have an immunomodulatory effect and may therefore modulate the immune response in MS (Roostaei et al., 2015).

Table 35. Study Examining Melatonin for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Roostaei et al. 2015 *Impact of melatonin on motor, cognitive and neuroimaging indices in patients with multiple sclerosis* Iran **RCT** PEDro=7 N$_{Initial}$=26, N$_{Final}$=25	**Population:** *Melatonin group (n=13):* Mean age=33.3yr; Sex: males=4, females=9; Disease course: RRMS; Mean EDSS=1.8; Mean disease duration=6yr. *Control group (n=12):* Mean age=34.5yr; Sex: males=0, females=12; Disease course: RRMS; Mean EDSS=0.77; Mean disease duration=2.8yr. **Intervention:** Patients were randomized to receive either 3mg/d (hora somni) of melatonin or placebo for 12mo. Assessments were performed before and after treatment. **Cognitive Outcomes/Outcome Measures:** Paced Auditory Serial Addition Test-3, 2 seconds (PASAT-3, -2).	1. No significant between-group differences were observed for the PASAT-3,-2 at 12mo.

Discussion

Only one study was found which examined the potential effects of melatonin on CI in PwMS. Participants were randomized to either placebo or melatonin for 12 months. There was no significant difference in mean change on the PASAT between groups. The authors also included the Modified Fatigue Impact Scale and reported that the cognitive fatigue subscale significantly improved in the melatonin group compared to the placebo group (p=0.006) (Roostaei et al. 2015). The measurement and evaluation of interventions addressing cognitive fatigue is beyond the scope of this module. However, cognitive fatigue does affect cognitive functioning in people with MS and warrants further systematic evaluation.

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Conclusion

There is level 1b evidence that melatonin compared to placebo may not improve auditory processing speed in persons with relapsing-remitting MS but may improve self-reported cognitive fatigue (one randomized controlled trial; Roostaei et al. 2015).

> Melatonin may not be beneficial for improving auditory processing speed in persons with relapsing-remitting MS but may improve self-reported cognitive fatigue.

3.2.5 Naturopathy

Naturopathic medicine aims to stimulate an individual's self-healing capacities using various therapeutic modalities and can be practiced as either a complement or an alternative to conventional medicine. Often, a combination of treatments is applied and adjusted as necessary for a patient's condition (Shinto & Calabrese, 2003).

Table 36. Study Examining Naturopathy for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Shinto et al. 2008 *A randomized pilot study of naturopathic medicine in multiple sclerosis* USA **RCT** PEDro=6 $N_{Initial}$=45, N_{Final}=45	**Population:** *Total Population (n=45):* Mean age=43.5yr; Sex: males=6, females=39; Disease course: RRMS; Mean EDSS=2.5; Mean disease duration=10.0yr. *Usual care group (n=15).* *Usual care plus naturopathic group (n=15).* *Usual care plus education group (n=15).* **Intervention:** Patients were randomized to one of three intervention arms: usual care, naturopathic medicine plus usual care, and MS education plus usual care. Treatment took place over 6mo. Patients randomized to the naturopathic intervention received usual MS care plus 8 visits with the naturopath following baseline assessments. Naturopathic intervention included daily supplementation of multivitamin/mineral without iron, vitamin C, vitamin E, fish oil, α-lipolic acid, and intramuscular vitamin B_{12} 1x/wk. It also included 4 levels of diet intervention (simple, moderately simple, moderate, and advanced). In the usual care plus MS education group the education sessions were matched to the frequency and duration of the naturopathic visits. Patients in this group received conventional care plus 8 visits with a nurse	1. There was no significant difference between groups on any cognitive outcome measures.

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
	that specialized in MS care who presented educational pamphlets the patients. Assessments were performed at baseline and after 6mo. **Cognitive Outcomes/Outcome Measures:** Stroop Test; Paced Auditory Serial Addition Test (PASAT-3).	

Discussion

Only one study was found which examined the potential effect of naturopathic medicine as an intervention for CI in PwMS. Shinto et al. (2008) performed a well designed randomized but unblinded study in which participants were randomized to usual care, usual care plus naturopathic treatment specifically tailored for PwMS, or usual care plus MS educational visits with a nurse. Treatment with all three arms of the study took place over six months. At the end of the study, there was a trend towards benefit with the naturopathic intervention on the non-cognitive outcomes, but no effect was noted on the cognitive outcomes.

Conclusion

There is level 1b evidence that naturopathic medicine combined with usual care compared to MS education plus usual care or usual care alone is not more effective for improving cognitive impairment in persons with relapsing-remitting MS (one randomized controlled trial; Shinto et al. 2008).

Naturopathic medicine may not improve cognitive impairment in persons with relapsing-remitting MS.

3.2.6 Tryptophan

Tryptophan is a naturally occurring essential amino acid and precursor for serotonin ("Drug monograph: Tryptophan," 2021). It has been suggested that CI in MS may be mediated by serotonergic dysregulation (Boadle-Biber, 1993; Cowen & Sherwood, 2013); as such, increasing the availability of tryptophan may normalize serotonin metabolism and in turn neuropsychological dysfunction (Lieben et al., 2018).

Table 37. Study Examining Tryptophan for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Lieben et al. 2018 *Intake of tryptophan-enriched whey protein acutely enhances recall of positive loaded words in patients with multiple sclerosis* USA **RCT Crossover** PEDro=7 N$_{Initial}$=32, N$_{Final}$=31	**Population:** *Non-depressed mood (n=17):* Mean age=44yr; Sex: males=6, females=11; Disease course: RRMS=16, SPMS=1; Mean EDSS=2.47; Mean disease duration=9.9yr. *Depressed mood (n=15):* Mean age=44yr; Sex: males=3, females=12; Disease course: RRMS=13, SPMS=2; Mean EDSS=3.50; Mean disease duration=6.7yr. **Intervention:** Participants were stratified into 2 groups based on the presence or absence of depressed mood. Participants then received mixtures containing 40g of a whey protein with or without additional tryptophan (TRP; low, medium, or high) in a randomized order. The mixture was consumed in maximally 10min during each test session, and test sessions were separated by at least 1wk. Cognitive assessments were performed 3hr after dietary intake. **Cognitive Outcomes/Outcome Measures:** Affective Memory Test (AMT); Trail Making Test (TMT-A, B); Stroop Colour-Word Task (SCWT).	1. Immediately after dietary intake, there was a higher total number of correctly recalled words on the AMT in the low TRP condition compared to the whey-only condition (p<0.001), with improvement being based on an increase in recalled positive and neutral words (p=0.001 and p<0.001, respectively). 2. The total number of correctly recalled words on the AMT 30min after presentation (delayed recall) was similar between dose conditions, although the delayed recall of positive words was higher in the low TRP condition compared to the whey-only condition (p=0.004). 3. The number of correctly recognized words and the delayed recognition accuracy scores on the AMT were higher in the low TRP condition compared to the whey-only condition (p=0.04). 4. The reaction times of correctly recognized words on the AMT were not affected by TRP supplementation. 5. There was no difference between dose conditions in terms of performance on the TMT. 6. There was a faster performance for color naming on the SCWT in the medium TRP condition compared to the whey-only condition (p=0.048), although this did not affect the overall SCWT interference score.

Discussion

One study has examined the effect of dietary tryptophan enrichment on cognitive function in PwMS. Lieben et al. (2018) conducted a RCT crossover in which participants received mixtures containing a whey-based protein alone or with additional tryptophan (in a low, medium, or high ratio) in a randomized order. Cognitive assessments were performed three hours after dietary intake, including the Affective Memory Test, Trail Making Test, and Stroop Color-Word Task. Following dietary intake, the low tryptophan condition demonstrated significant improvements on the Affective Memory Test compared to the whey-only condition, but there were no differences between dose conditions in terms of performance on the Trail Making Test or overall Stroop Color-Word Task. The effect of a tryptophan-enriched diet was irrespective of the presence of depressed mood. However, baseline values of cognitive performance were not measured prior to dietary intake; as such, a potential placebo effect cannot be ruled out. A further

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limitation of this study is that longer-term effects of dietary tryptophan enrichment on cognition were not examined.

Conclusion

There is level 1b evidence that a tryptophan-enriched whey-based diet compared to a whey-based diet alone may acutely improve memory, but not processing speed, or cognitive flexibility and interference (one randomized controlled trial; Lieben et al. 2018).

> A tryptophan-enriched whey-based diet may acutely improve memory, but not other cognitive functions, in persons with MS.

3.2.7 Vitamin D

Vitamin D deficiency has been associated with cognitive dysfunction (Llewellyn, Langa, & Lang, 2009), providing support for a role of vitamin D supplementation in cognitive functioning and beyond bone homeostasis (Darwish et al., 2017).

Table 38. Study Examining Vitamin D for Cognitive Impairment in Multiple Sclerosis

Author Year Title Country Research Design PEDro Sample Size	Methods	Results
Darwish et al. 2017 *Effect of vitamin D replacement on cognition in multiple sclerosis patients* Lebanon **Pre-Post** N$_{Initial}$=88, N$_{Final}$=61	**Population:** *Sufficient 25(OH)D (n=47):* Mean age=37.2yr; Sex: males=20, females=27; Disease course: RRMS or CIS; Mean EDSS=1.1; Mean disease duration=5.7yr. *Deficient 25 (OH)D (n=41):* Mean age=35.3yr; Sex: males=20, females=21; Disease course: RRMS or CIS; Mean EDSS=1.6; Mean disease duration=4.8yr. **Intervention:** Patients were tested for serum levels of 25 hydroxyvitamin D (25(OH)D). Subjects were categorized into sufficient (25(OH)D >35ng/ml) and deficient (25(OH)D <25ng/ml) groups. The deficient group underwent high dose vitamin D$_3$ supplementation for 3mo. The sufficient group continued their usual treatment. Assessments were performed at baseline and after supplementation. **Cognitive Outcomes/Outcome Measures:** Montreal Cognitive Assessment (MoCA); Symbol Digit Modalities Test (SDMT); Brief Visuospatial Memory Test-Revised (BVMT-R): Delayed recall, trials composite score; Stroop Test.	1. The deficient 25(OH)D group improved significantly on the BVMT-delayed recall (p=0.02) and the MoCA (p=0.006) after therapy. 2. The sufficient 25(OH)D group improved significantly on the BVMT-delayed recall (p=0.02) after therapy, but not the MoCA (p=0.08). 3. No significant change was observed on the SDMT or Stroop Test scores after therapy for either group. 4. Both groups showed improvement on the BVMT-Trials Composite score after treatment (p=0.003 for the sufficient group; p=0.004 for the deficient group).

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Discussion

One study by Darwish et al. (2017) examined the effects of replenishing Vitamin D on cognitive function in PwMS who were deficient at baseline. Participants were divided into two groups, one labelled Vitamin D deficient who were supplemented for three months, and the other labelled Vitamin D sufficient who continued their usual treatment. Whether the two groups were significantly different at baseline was not discussed. The deficient group demonstrated a statistically significant improvement on mild CI (Montreal Cognitive Assessment) and visuospatial memory (BVMT-R) over the three-month treatment period, while the sufficient group improved significantly on visuospatial memory. However, this was analyzed using repeat measures t-tests and the change over time between the two groups was not examined.

Conclusion

There is level 4 evidence that vitamin D may improve mild cognitive impairment and visuospatial memory, but not visual processing speed, or cognitive interference and mental flexibility (one pre-post study; Darwish et al. 2017).

> Preliminary evidence suggests that vitamin D may improve mild cognitive impairment and visuospatial memory, but not other cognitive functions, in persons with MS.

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4.0 Evidence Statement Summary

There are no pharmacological interventions for the treatment or prevention of cognitive impairment in MS supported by level 1a evidence (at least two high quality RCTs).

There is level 1b evidence that the following interventions may benefit cognition in MS on one or more cognitive outcomes:

- MS disease modifying therapies
- Amphetamine products
- Immediate release 4-aminopyridine
- Simvastatin
- Tryptophan
- *Achillea millefolium*

There is level 1a evidence that the following interventions do not benefit cognition in MS on one or more cognitive outcomes:

- Amantadine
- Donepezil
- Memantine
- Rivastigmine
- *Ginkgo biloba*
- Dalfampridine

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Level of Evidence Statements (listed in alphabetical order by product)

Achillea millefolium

There is level 1b evidence that Achillea millefolium as an add-on therapy compared to placebo may improve auditory processing speed and verbal learning and memory in persons with relapsing-remitting MS, but not general cognition or executive functioning at 12 months (one randomized controlled trial; Ayoobi et al. 2019).

Amantadine

There is level 1a evidence that amantadine compared to placebo may not improve cognitive function (two randomized controlled trials; Cohen et al. 2019, Geisler et al. 1996).

There is level 1b evidence that pemoline compared to amantadine or placebo may not improve cognitive function (one randomized controlled trial; Geisler et al. 1996).

Amphetamine products

There is level 1b evidence that mixed amphetamine salts, extended release compared to placebo may improve visual processing speed, but not auditory processing speed (one randomized controlled trial; Morrow & Rosehart 2015).

There is level 1b evidence that lisdexamfetamine dimesylate compared to placebo may improve visual processing speed, and verbal learning and memory, but not auditory processing speed, visuospatial memory, or subjective impact on daily activities (one randomized controlled trial; Morrow et al. 2013).

There is level 1b evidence that l-amphetamine compared to placebo may improve verbal and visuospatial memory (one randomized controlled trial; Morrow et al. 2009; Sumowski et al. 2011).

There is level 1b evidence that l-amphetamine compared to placebo may not improve auditory processing speed, visual processing speed, or subjective ratings of cognition (one randomized controlled trial; Morrow et al. 2009).

Boswellia Serrata/Papyrifera

There is level 1b evidence that Boswellia serrata compared to placebo may improve verbal memory and learning, and visuospatial memory, but not visual processing speed, executive function, verbal fluency, auditory processing speed, or spatial processing, in persons with relapsing-remitting MS (one randomized controlled trial; Majdinasab et al. 2016).

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There is level 1b evidence that Boswellia papyrifera compared to placebo may improve visuospatial memory, but not verbal memory and learning or visual processing speed, in persons with relapsing-remitting MS (one randomized controlled trial; Sedighi et al. 2014).

Dalfampridine/Fampridine

There is level 1a evidence that dalfampridine compared to placebo may not improve verbal learning and memory, visuospatial memory, or executive function after 12 weeks of treatment (two randomized controlled trials; De Giglio et al. 2019; Satchidanand et al. 2020).

There is level 1b evidence that dalfampridine compared to placebo may not improve verbal fluency after 12 weeks of treatment (one randomized controlled trial; De Giglio et al. 2019).

There is level 1b evidence that slow-release fampridine compared to placebo may not acutely improve auditory processing speed (one randomized controlled trial; Morrow et al. 2017) or visual processing speed (one randomized controlled trial; Jensen et al. 2016) or attention, with the exception of improving phasic alertness (one randomized controlled trial; Broicher et al. 2018).

There is level 1b evidence that immediate release 4-aminopyridine compared to placebo may improve working memory, verbal fluency, executive function and visuospatial skills, but not other cognitive functions, in persons with relapsing-remitting MS (one randomized controlled trial; Arreola-Mora et al. 2019).

There is level 4 evidence that slow-release fampridine may not improve visuospatial or verbal memory long-term (one pre-post study; Bakirtzis et al. 2018).

There is conflicting evidence regarding whether dalfampridine compared to placebo improves visual and auditory processing speed after 12 weeks of treatment (two randomized controlled trials; De Giglio et al. 2019; Satchidanand et al. 2020).

Disease Modifying Therapies

Level 1b

There is level 1b evidence that daclizumab may be more effective at improving and preventing worsening of processing speed compared to interferon beta 1a after 92 weeks of treatment in relapsing-remitting MS (from one randomized controlled trial; Benedict et al. 2018). Daclizumab is no longer available.

There is level 1b evidence that fingolimod or injectable disease modifying therapies may <u>maintain</u> verbal processing speed at 48 weeks (one open label randomized controlled trial; Cree et al. 2018).

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There is level 1b evidence that glatiramer acetate compared to placebo may not improve cognitive impairment in persons with relapsing-remitting MS (one randomized controlled trial; Weinstein et al. 1999).

There is level 1b evidence that interferon beta 1a compared to placebo may be more effective for reducing cognitive deterioration in persons with relapsing MS (one randomized controlled trial; Fischer et al. 2000).

There is level 1b evidence that interferon beta 1a compared to interferon beta 1b may not be more effective for improving visual processing speed in persons with relapsing-remitting MS (one randomized controlled trial and one prospective controlled trial; Mokhber et al. 2014; Melanson et al. 2010).

There is level 1b evidence that high dose estroprogestins in combination with interferon beta may be more effective for protecting against cognitive decline compared to interferon beta alone in females with relapsing-remitting MS, but may not be more effective than low dose estroprogestins combined with interferon beta (one randomized controlled trial; De Giglio et al. 2017).

There is level 1b evidence that interferon beta in combination with either high dose or low dose estroprogestins may not be more effective than interferon-beta alone for improving cognitive function in females with relapsing-remitting MS (one randomized controlled trial; De Giglio et al. 2017).

There is level 1b evidence that natalizumab in combination with interferon beta 1a may not be superior to interferon beta 1a alone over 2 years for delaying a decline in auditory processing speed in persons with relapsing-remitting MS (one randomized controlled trial; Weinstock-Guttman et al. 2012; Rudick et al. 2006).

There is level 1b evidence that natalizumab treatment over 2 years compared to placebo may delay a decline in auditory processing speed in persons with relapsing-remitting MS (one randomized controlled trial; Weinstock-Guttman et al. 2012; Polman et al. 2006).

There is level 1b evidence that ozanimod may improve visual processing speed compared to interferon beta 1a over 12 months in relapsing-remitting MS (one randomized controlled trial; Comi et al. 2019).

Level 2

There is level 2 evidence that fingolimod or interferon beta 1b may improve cognition on a comprehensive cognitive battery over 18 months in relapsing-remitting MS (one open label randomized controlled trial; Comi et. al. 2017).

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There is level 2 evidence that fingolimod, natalizumab, and interferon may not be more effective compared to one another for cognitive stability in persons with relapsing-remitting MS (one prospective controlled trial; Utz et al. 2016).

There is level 2 evidence that interferon beta 1a, interferon beta 1b, and glatiramer acetate may not be more effective compared to one another for cognitive impairment in persons with relapsing-remitting MS (one cohort study; Cinar et al. 2017).

There is level 2 evidence that interferon beta 1b treated healthy controls without MS and people with relapsing-remitting MS improve on cognitive testing, but healthy controls show greater improvement on verbal memory than those with relapsing-remitting MS (one cohort study; Gerschlager et al. 2000).

There is level 2 evidence that different interferon beta (IFN-β) preparations (subcutaneous IFN-β-1a, subcutaneous IFN-β-1b, intramuscular IFN-β-1a) compared to one another may not be more effective for improving visual processing speed in persons with relapsing-remitting MS (one prospective controlled trial; Melanson et al. 2010).

There is level 2 evidence that <u>interferon beta</u> compared to no treatment may improve visuospatial memory, visual processing speed and auditory processing speed, and cognitive reasoning, but not verbal learning and memory, or verbal fluency (one cohort study; Hamdy et al. 2013).

There is level 2 evidence that interferon <u>beta 1b</u> compared to no treatment may improve spatial memory, auditory processing speed, and may have stabilizing effects on verbal fluency in persons with relapsing-remitting MS (one prospective controlled trial; Barak & Achiron 2002).

There is level 2 evidence that interferon <u>beta 1b</u> may improve or stabilize visual processing speed in relapsing-remitting MS (one cohort study; Kleiter et al. 2017).

There is level 2 evidence that interferon <u>beta 1a</u> may improve or stabilize visual processing speed, but not cognitive fatigue symptoms, in relapsing-remitting MS (one cohort study; Rieckmann et al. 2019).

There is level 2 evidence that high-dose interferon <u>beta 1b</u> compared to low dose interferon beta 1b or placebo may improve visual memory, but not verbal memory, processing speed, or selective attention in persons with relapsing-remitting MS (one prospective controlled trial; Pliskin et al. 1996).

There is level 2 evidence that high dose interferon <u>beta 1a</u> compared to low dose may be more effective for protecting against cognitive decline in persons with relapsing-remitting MS (one cohort study; Patti et al. 2009; 2010; 2013).

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There is level 2 evidence that mitoxantrone compared to no treatment may be more effective for cognitive stability (one cohort study; Schröder et al. 2011).

There is level 2 evidence that natalizumab may not be superior to interferon beta at 1 year for <u>improving</u> a global assessment summary score of cognitive tests in persons with relapsing-remitting MS (one prospective controlled trial; Sundgren et al. 2016).

There is level 2 evidence that natalizumab may be more effective for <u>reducing</u> cognitive deterioration compared to interferon beta after a mean of 1.5 years in persons with relapsing-remitting MS (one prospective controlled trial; Portaccio et al. 2013).

There is level 2 evidence that global cognitive performance on the Brief Repeatable Battery improves similarly with natalizumab or fingolimod treatment at two years in persons with relapsing-remitting MS (one cohort study; Preziosa et al. 2020).

There is level 2 evidence that natalizumab is associated with greater improvements in auditory processing speed compared to interferon beta, glatiramer acetate, or dimethyl fumarate in relapsing-remitting MS (one prospective controlled trial; Rorsman et al. 2018).

<div align="center">Level 4</div>

There is level 4 evidence that alemtuzumab may have stabilizing effects on overall cognition and may improve processing speed in persons with relapsing-remitting MS (one pre-post study; Riepl et al. 2018).

There is level 4 evidence that cyclophosphamide combined with methylprednisolone may improve general cognitive impairment, verbal memory, inhibition, and verbal language skills in persons with progressive MS (one pre-post study; Zephir et al. 2005).

There is level 4 evidence that dimethyl fumarate may slow cognitive decline or improve cognitive impairment in persons with relapsing-remitting MS (one pre-post study; Amato et al. 2020).

There is level 4 evidence that interferon <u>beta 1b</u> may stabilize or improve cognitive function in persons with relapsing-remitting MS (one pre-post study; Lanzillo et al. 2006).

There is level 4 evidence that interferon <u>beta 1b</u> may improve cognitive reasoning in persons with relapsing MS (one pre-post study; Flechter et al. 2007).

There is level 4 evidence that interferon <u>beta 1a</u> may improve auditory processing speed in persons with relapsing-remitting MS (two pre-post studies; Mori et al. 2012; Benešová & Tvaroh et al. 2017).

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There is level 4 evidence that natalizumab may <u>stabilize or improve</u> attention and processing speed after 2 years of treatment in persons with relapsing-remitting MS (seven pre-post studies; Perumal et al. 2019; Talmage et al. 2017; Jacques et. al 2016; Kunkel et al. 2015; Mattioli et al. 2015; Iaffaldano et al. 2012; Mattioli et. al. 2011).

There is level 4 evidence that natalizumab treatment <u>may improve</u> attention and processing speed within 4 weeks to six months of starting treatment in persons with relapsing-remitting MS (three pre-post studies; Wilken et al. 2013; Edwards et al. 2012; Lang et al. 2012).

There is level 4 evidence that natalizumab treatment <u>improves or maintains</u> patient reported cognitive function on the Medical Outcomes Scale - Cognitive functioning in persons with relapsing-remitting MS (one pre-post study; Stephenson et al. 2012).

There is level 4 evidence that a decrease in serum osteopontin levels correlates with a globally improved cognitive index score in patients treated with natalizumab for at least one year in persons with relapsing-remitting MS (one pre-post study; Iaffaldano et al. 2014).

There is level 4 evidence that rituximab may improve visual processing speed in persons with relapsing-remitting MS (one pre-post study; de Flon et al. 2017).

There is level 4 evidence that teriflunomide may have stabilizing effects on cognition (one pre-post study; Coyle et al. 2018).

Conflicting evidence

There is conflicting evidence regarding whether or not different interferon beta (IFN-β) preparations (subcutaneous IFN-β-1a, subcutaneous IFN-β-1b, intramuscular IFN-β-1a) compared to one another improve verbal learning and memory, spatial memory, auditory processing speed, and verbal fluency (one randomized controlled trial and one prospective controlled trial; Mokhber et al. 2014; Melanson et al. 2010).

There is conflicting evidence that <u>improvements</u> in attention and processing speed after starting natalizumab treatment may be sustained at 3 years in persons with relapsing-remitting MS (two pre-post studies; Planche et al. 2017; Mattioli et al. 2013).

There is conflicting evidence regarding whether natalizumab <u>improves or maintains</u> cognition consistently across multiple cognitive domains in persons with relapsing-remitting MS (one prospective controlled study; Sundgren et al. 2016; ten pre-post studies; Planche et al. 2017; Jacques et. al 2016; Kunkel et al. 2015; Mattioli et al. 2015; Iaffaldano et. al. 2014; Wilken et al. 2013; Iaffaldano et al. 2012; Edwards et al. 2012; Lang et al. 2012; Mattioli et. al. 2011; one case series; Gudesblatt et al. 2018).

Donepezil

There is level 1a evidence that donepezil compared to placebo may not improve spatial memory, visual processing speed, auditory processing speed, or verbal fluency (two randomized controlled trials; Krupp et al. 2004; Krupp et al. 2011).

There is level 1b evidence that donepezil compared to placebo may not improve executive function or spatial processing (one randomized controlled trial; Krupp et al. 2011).

There is level 1b evidence that donepezil compared to placebo may not improve problem solving (one randomized controlled trial; Krupp et al. 2004).

Erythropoietin

There is level 1b evidence that erythropoietin compared to placebo may not improve cognitive impairment in persons with primary or secondary progressive MS (one randomized controlled trial; Schreiber et al. 2017).

Fluoxetine

There is level 1b evidence that fluoxetine compared to placebo may not improve cognitive impairment in persons with relapsing-remitting MS (one randomized controlled trial; Cambron et al. 2018).

Ginkgo biloba

There is level 1a evidence that Ginkgo biloba compared to placebo may not improve auditory processing speed, verbal memory and learning, or verbal fluency (two randomized controlled trials; Lovera et al. 2012; Lovera et al. 2007).

There is level 1b evidence that Ginkgo biloba compared to placebo may not improve visual processing speed (one randomized controlled trial; Lovera et al. 2007).

There is conflicting evidence regarding whether or not Ginkgo biloba compared to placebo improves cognitive interference and mental flexibility (two randomized controlled trials; Lovera et al. 2012; Lovera et al. 2007).

Melatonin

There is level 1b evidence that melatonin compared to placebo may not improve auditory processing speed in persons with relapsing-remitting MS but may improve self-reported cognitive fatigue (one randomized controlled trial; Roostaei et al. 2015).

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Memantine

There is level 1a evidence that memantine compared to placebo may not improve cognitive impairment (two randomized controlled trials; Peyro Saint Paul et al. 2016; Lovera et al. 2010).

Methylphenidate

There is level 4 evidence that methylphenidate compared to placebo may improve auditory processing speed in persons with relapsing-remitting MS (one randomized controlled trial; Harel et al. 2009).

Modafinil/Armodafinil

There is level 1b evidence that modafinil compared to placebo may improve working memory on the WAIS-III letter-number sequencing, but not visual processing speed or verbal memory and learning (one randomized controlled trial; Ford-Johnson et al. 2016).

There is level 1b evidence that armodafinil compared to placebo may improve verbal memory, but not visuospatial memory, cognitive interference and mental flexibility, verbal fluency, auditory processing speed, or sustained attention and impulsivity (one randomized controlled trial; Bruce et al. 2012).

Naturopathy

There is level 1b evidence that naturopathic medicine combined with usual care compared to MS education plus usual care or usual care alone is not more effective for improving cognitive impairment in persons with relapsing-remitting MS (one randomized controlled trial; Shinto et al. 2008).

Pemoline

There is level 1b evidence that pemoline compared to amantadine or placebo may not improve cognitive function (one randomized controlled trial; Geisler et al. 1996).

Prucalopride

There is level 1b evidence that prucalopride compared to placebo may not improve cognitive impairment in persons with relapsing-remitting MS (one randomized controlled trial; Cambron et al. 2018).

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Rivastigmine

There is level 1a evidence that rivastigmine compared to placebo may not improve memory or general cognitive impairment (two randomized controlled trials; Mäurer et al. 2013; Shaygannejad et al. 2008).

There is conflicting evidence regarding whether or not rivastigmine compared to placebo improves processing speed (two randomized controlled trials; Huolman et al. 2011; Mäurer et al. 2013).

Simvastatin

There is level 1b evidence that simvastatin compared to placebo may improve executive function, but not other cognitive functions, in persons with secondary progressive MS (one randomized controlled trial; Chan et al. 2017).

Tryptophan

There is level 1b evidence that a tryptophan-enriched whey-based diet compared to a whey-based diet alone may acutely improve memory, but not processing speed, or cognitive flexibility and interference (one randomized controlled trial; Lieben et al. 2018).

Vitamin D

There is level 4 evidence that vitamin D may improve mild cognitive impairment and visuospatial memory, but not visual processing speed, or cognitive interference and mental flexibility (one pre-post study; Darwish et al. 2017).

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