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Examining the effectiveness of acetylcholinesterase inhibitors and stimulant-based medications for cognitive dysfunction in multiple sclerosis: A systematic review and meta-analysis

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ABSTRACT

We sought to examine the effectiveness of acetylcholinesterase inhibitors (AChEIs) and stimulant-based medications for improving cognitive performance in patients with multiple sclerosis (MS). An electronic database search was conducted on 25th March 2017. Eligible studies were double-blind, randomised, placebo-controlled trials that examined the efficacy of compounds that act primarily as AChEIs or stimulants (administered daily for ≥1 week) on cognitive outcome measures in patients with MS. Where suitable data was reported, we generated effect sizes and corresponding 95% confidence intervals and performed meta-analyses using random-effects models to investigate the effectiveness of these drug types across cognitive domains. Sixteen trials were included in the systematic review, with eleven trials (N = 734 MS patients) providing sufficient data for meta-analysis. Whilst there was only a limited pool of relatively small trials and a number of different compounds, we found that collectively, both AChEIs (donepezil and rivastigmine) and stimulants (methylphenidate, modafinil, l-amphetamine sulfate and lisdexamfetamine dimesylate) offered no significant benefits over placebo on measures of processing speed, working memory, verbal fluency, verbal memory, visuospatial memory or executive functioning.

1. Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disorder of the central nervous system (CNS), histopathologically characterised by demyelination and axonal degeneration (Compston and Coles, 2008). Cognitive dysfunction is present in up to 70% of patients with MS and has been reported at all stages and in all subtypes of the disease (Langdon, 2011; Prakash et al., 2008; Ruet et al., 2013a). Deficits are most commonly reported in processing speed, memory and executive function (Chiaravalloti and DeLuca, 2008), and are thought to arise as a result of the diffuse white and grey matter damage associated with the disease (Rocca et al., 2015). Cognitive dysfunction is a leading cause of disability in MS and is associated with unemployment (Honarmand et al., 2011; Strober et al., 2012), problems in daily functioning (Goverover et al., 2016; Rao et al., 1991), increased caregiver burden (Figved et al., 2007; Labiano-Fontcuberta et al., 2014) and worse quality of life (Phillips et al., 2011; Ruet et al., 2013b). Despite a wealth of recent research in this area, there are currently no regulatory approved treatments for the amelioration of cognitive deficits in MS.

'Pro-cognitive' drugs hold much promise and have been shown to improve cognitive performance in a range of psychiatric and neurological disorders, as well as in healthy volunteers (Linssen et al., 2014; Sahakian and Morein-Zamir, 2015; Turner et al., 2003). These could potentially be administered as an adjunct to standard disease modifying therapies (DMTs) in people with MS in an effort to limit cognitive dysfunction. Pharmacological agents that act primarily as acetylcholinesterase inhibitors (AChEIs) or as CNS stimulants are the two types of adjunctive pharmacotherapies that have been the most heavily researched in relation to cognition among people with MS (Amato et al., 2013; Christodoulou et al., 2008; Roy et al., 2016). AChEIs are designed to increase and sustain brain levels of acetylcholine, a neurotransmitter that facilitates learning and memory (Colović et al., 2013; Hasselmo, 2006). Three AChEIs (donepezil, rivastigmine and galantamine) have been shown to be effective and are currently approved to treat cognitive dysfunction associated with Alzheimer's disease (Birks, 2006; National Institute for Clinical Excellence (NICE), 2011), leading

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to speculation that they may also enhance cognition in people with other neurodegenerative conditions. Authors have proposed that impaired cholinergic function may contribute to cognitive deficits in MS due to disruption of cholinergic pathways and reduced axonal transport of acetylcholine (Christodoulou et al., 2008), suggesting these drugs may exert pro-cognitive effects in this population.

Compounds which act primarily as CNS stimulants (such as methylphenidate, amphetamine and modafinil) are a group of drugs that promote wakefulness and alertness (Ng and O'Brien et al., 2009). These have traditionally been associated with the treatment of attention deficit hyperactivity disorder, as well as sleep disorders such as narcolepsy (Heal et al., 2013). However, these have also been trialled in an effort to improve fatigue in patients with MS (e.g. Rammohan et al., 2002). This is among the most common and disabling symptoms of MS (Krupp, 2003), and may be a potential driver of cognitive dysfunction in this population. These drugs have also been hypothesised to have potential pro-cognitive effects, particularly for measures of processing speed and working memory (Ford-Johnson et al., 2016; Morrow et al., 2009).

Single-dose pilot studies of these pharmacological agents have reported some beneficial effects on cognitive outcomes (Benedict et al., 2008; Bruce et al., 2012; Huolman et al., 2011), though the long-term benefits of sustained use of these drugs in patients with MS remain unclear. Results of individual studies involving daily use of these medications to date have been mixed, though many of the studies in this area have been small and potentially underpowered to detect treatment effects. While previous reviews have narratively discussed this literature (e.g. Amato et al., 2013; Christodoulou et al., 2008; Roy et al., 2016), the collective results of these trials have not been examined statistically using meta-analytic techniques. Thus, we sought to combine previous data to establish whether daily use of AChEIs and stimulant-based medications are efficacious for improving domain-specific aspects of cognitive function in people with MS.

2. Method

This review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2.1. Study inclusion criteria

Eligible studies were double-blind, randomised, placebo-controlled trials that examined the efficacy of AChEIs or CNS stimulants administered to patients with a diagnosis of MS, as defined by the Poser or McDonald criteria (McDonald et al., 2001; Poser et al., 1983). For the purposes of this review, eligible stimulant-based medications included methylphenidate, modafinil and amphetamine-based compounds, all of which are primarily associated with increased alertness. Studies were required to report cognitive outcome measures and to involve daily administration of the study drug continuously for at least seven days. In order to be included in the meta-analyses, studies were required to use a parallel group design and provide sufficient data to calculate an effect size. Crossover trials were eligible for inclusion in the meta-analyses, providing baseline and outcome data from the two groups were reported prior to the crossover component.

No restrictions were placed on the dose or route of administration of the study drug, or the age of patients or phenotype of MS for inclusion. Single-session studies in which participants completed cognitive measures after receiving a single dose of an experimental drug (or varying doses thereof) and review articles were excluded from this review. Where information was duplicated across multiple publications, only the original article was included in the meta-analyses. Medications that are no longer widely available due to safety concerns were not included. No language restrictions were placed on studies for inclusion.

2.2. Search strategy

On 25th March 2017, we conducted an electronic database search of Ovid MEDLINE, PsycINFO, Embase and the Cochrane Central Register of Controlled Trials (from inception) using the following keyword search terms: "multiple sclerosis" and "cogniti*" and "trial" and "pharmaco*" or "cholinesterase" or "donepezil" or "rivastigmine" or "galantamine" or "physostigmine" or "stimulant" or "modafinil" or "amphetamine" or "methylphenidate". We also searched the ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) databases using the search terms "multiple sclerosis" and "cognition" in an effort to identify unpublished studies and ongoing research. In addition, a search of Google Scholar was conducted and the reference lists of retrieved articles were also reviewed to identify any additional relevant studies.

2.3. Study selection and data extraction

Two of the authors (J.C. and A.T.) independently screened articles for eligibility. There were no disagreements regarding the inclusion of studies in this review. A standardised data extraction spreadsheet was used for all eligible studies to record: (1) study characteristics (authors, year of publication, country where the work was performed); (2) cognitive domains assessed and measures used; (3) sample demographics (sample size, sex, age, years of education); (4) MS disease characteristics (disease duration, disease course, medication use and degree of physical disability); (5) trial design (study drug, maximum daily dose, treatment duration, eligibility criteria, study sites, randomisation procedures, whether intention-to-treat analyses were performed, treatment compliance, attrition, adverse events); (6) cognitive performance for the treatment and placebo groups (mean pre- and post-intervention scores and/or change scores and associated standard deviations, or other relevant statistics). Where necessary, we contacted study authors for unreported data in an effort to calculate effect sizes.

2.4. Risk of bias

We evaluated studies included in the meta-analyses using the Cochrane Collaboration's 'Risk of bias' tool (Higgins et al., 2011). This assesses six aspects of trial methodology that could potentially introduce different sources of bias; sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting.

2.5. Statistical analysis

Data analyses were performed using Comprehensive Meta-Analysis version 3.0 (Borenstein et al., 2007). In order to determine whether AChEIs or CNS stimulants were effective for improving cognitive performance, we examined the differences in mean pre-to-post intervention change scores between the treatment and placebo groups. Standardised mean difference effect size estimates were calculated for cognitive performance using Hedges' g. This represents the difference between the means of the treatment and placebo groups, divided by the pooled standard deviation and weighted for sample size. We used the change scores and associated standard deviations reported in the articles where these were provided. Where these were not reported, the mean change score for each condition was calculated by subtracting mean baseline task scores from those at the post-treatment assessment. The associated standard deviations were imputed as recommended by the Cochrane Handbook (Higgins and Green, 2011). The correlation coefficient used to calculate these was 0.7, however, sensitivity analyses indicated that varying this had no impact on the overall findings. We also performed additional sensitivity analyses using post-treatment group means (where reported) instead of change scores in the meta-