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Psychological interventions for enhancing adherence to disease-modifying therapies (DMTs) in multiple sclerosis (Protocol)

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[Intervention Protocol]

Psychological interventions for enhancing adherence to disease-modifying therapies (DMTs) in multiple sclerosis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of psychological interventions designed to improve adherence to disease-modifying therapies (DMTs) in adults with multiple sclerosis (MS) in terms of adherence. This will be considered in relation to levels of adherence in a comparison group.

Secondary objectives are to assess the impact of interventions on potential predictors of adherence such as motivation, self-efficacy beliefs and healthcare engagement to DMTs adherence.

BACKGROUND

Description of the condition

Among the autoimmune diseases of the central nervous system (CNS), multiple sclerosis (MS) is the most common inflammatory neurologic disease among young and middle-aged adults. MS is caused by a complex array of genetic and environmental factors that contribute to an increased prevalence among females born in temperate climates (Courtney 2009). Patients typically present with a relapsing-remitting course of the disease that is characterised by periodic exacerbations, followed by recovery and stretches of relative stability (Lublin 1996). Eventually, most patients convert to a secondary progressive course that is characterised by a gradual accumulation of disability (Confavreux 2006). Lifespan is minimally impacted in MS; however, the disease contributes to physical, emotional, and cognitive symptoms that substantially reduce participants' overall quality of life (Amato 2001; Benedict 2005). Although there is no cure for MS, several disease-modifying therapies (DMTs) have been shown to reduce the number and severity

of exacerbations, as well as slow disease progression and improve quality of life (Castro-Borrero 2012; Kieseier 2008). DMTs represent a broad class of drugs that are designed to alter immune system functioning, reduce the occurrence of MS relapses and slow disease progression. Different therapies are available for the treatment of multiple sclerosis including immunosuppressants, immunomodulators, and monoclonal antibodies. The benefits of therapy are preventive and not directly observed by patients. Randomised trials show that DMTs contribute to a 33% to 68% reduction in relapse rates, a 35% to 83% reduction in new central nervous system lesion activity, and up to a 50% reduction in disability progression (Bosch-Capblanch 2007; Freedman 2008; Goodin 2008; Johnson 2009; Linker 2008). A recent study show that DMTs significantly decreased new cortical lesion development and cortical atrophy progression compared with untreated patients, with faster and more pronounced effects seen with subcutaneous interferon (IFN) beta-1a than with intramuscular IFN beta-1a or glatiramer acetate (GA) (Calabrese 2012). Absolute risk reductions for MS exacerbations range from 11% to 43% with the average number of patients needed to treat to prevent one exacerbation ranging from two to nine (Zakaria 2015).

Natalizumab and IFNß-1 are superior to all other treatments for preventing clinical relapses and disability progression in the short term (24 months) in people with relapsing-remitting MS (RRMS). The IFNß-1b (Betaseron), GA, and mitoxantrone are also effective, with moderate-quality data, for preventing relapse and disability progression in RRMS in the short term (Filippini 2013). Another recent Cochrane review assessing the benefits and the extent of adverse events associated with 15 disease-modifying drugs showed that alemtuzumab, natalizumab, and fingolimod are more effective than other drugs for preventing relapses (Tramacere 2015). For preventing irreversible disability worsening in the short term (24 months), only natalizumab shows a beneficial effect on the basis of moderate-quality evidence. Despite evidence of efficacy for natalizumab, participants must also confront the possibility of more severe adverse events (SAE), including the risk of death due to progressive multifocal leukoencephalopathy (PML). Other SAE including thrombosis of the jugular vein and allergic reactions leading to treatment discontinuation were found in some studies. However, the treatments for which information on SAEs were available included in this review were associated with a statistically non-significant higher proportion of people with at least one SAE compared with placebo (Tramacere 2015).

Unfortunately, typical of many chronic diseases, a near majority of people with MS may not receive the benefits of the DMTs due to poor adherence (Bruce 2011), which can take many forms. People with MS may disregard their healthcare providers' recommendations, discontinue treatments prematurely, miss doses, or have difficulty following treatment instructions. Several actuarial research studies suggest that between 30% and 50 % of people with MS prematurely discontinue their DMTs (Giovannoni 2012; Reynolds 2010; Tan 2011; Wong 2011). Moreover, among people who continue to take DMTs, a fifth may miss more than 20% of their prescribed doses (Bruce 2010a). As a result, these people have an increased risk of experiencing exacerbations, new brain lesions, and worsening disability (Freedman 2008).

Relatively little research has examined factors that contribute to poor DMT adherence in MS, but researchers have argued that people with MS and others with chronic illness may be at especially high risk of premature treatment discontinuation and poor long-term adherence because treatments do not typically reduce acute symptoms (Bruce 2011). Thus, while people with MS are less likely to develop future symptoms when on medication, they do not experience any improvements in their daily activities while on the medications. In fact, frequently, they experience side-effects from the medications, and may therefore feel they are experiencing a reduction in quality of life without any apparent benefit. Side-effects such as stomach upset, flu-like symptoms, injection site reactions can make adherence challenging and almost all of the drugs included in a recent Cochrane review were associated with a higher proportion of participants who withdrew due to adverse events compared to placebo (Tramacere 2015). Studies of discontinuation and adherence maintenance have found that DMT side-effects and perceived lack of DMT efficacy are among the most consistent predictors of adherence in MS (Jokubaitis 2013; Rinon 2011; Turner 2007). Complacency has also been evident among people who have reported being "too busy" to adhere (Bruce 2011; Devonshire 2011; Hancock 2011). Other barriers that have been shown to be associated with poor adherence include medication costs, lack of provider support, and neuropsychiatric disability (including negative affect, fatigue, cognitive impairment, and needle phobia) (Bruce 2010a; Bruce 2010b; Koudriavtseva 2012; Mohr 1999; Patti 2010; Rinon 2011).

The fact that patients frequently discontinue treatments suggests that there is patient dissatisfaction with current DMTs. Indeed, the frequent use of complementary and alternative medicines (by an estimated 57% to 70% of patients with MS) also supports the view that conventional therapies are not adequately meeting patient needs (Giovannoni 2012; Nayak 2003; Page 2003). Indeed, there are reasonable motives for some people to decline the use of DMTs. With the increased availability of various evidence-based treatments, it is important that people have access to adequate information in order to make informed choices and minimise the possible negative effects of treatment. In this context, it is imperative to evaluate which strategies are most effective to enhance informed choice and subsequent adherence (Foster 2012; Köpke 2014; Stacey 2014).

Description of the intervention

Adherence interventions typically use educational, psychological and/or behavioural techniques to help people follow agreed-upon treatment recommendations. A variety of different strategies have been suggested for improving adherence in MS, including struc-

tured education programs, regular nurse assistance, and psychological interventions (Berger 2005; Nieuwlaat 2014). These interventions are designed to help people overcome common barriers to poor adherence and typically include face-to-face, individual or group therapy, telephone, or web-based contacts. Easthal's meta-analysis (Easthall 2013), showed that cognitive-based behaviour change techniques are effective interventions in eliciting improvements in medication adherence and are likely to be greater than the behavioural and educational interventions largely used in current practice. Evidence is limited on whether these approaches are broadly applicable or affect long-term medication adherence and health outcomes (Viswanathan 2012).

Adherence interventions are usually multi-modal or 'complex' (Craig 2008), in that they include several components that may or may not interact. These could incorporate a combination of educational, psychological and behavioural techniques to support people with MS to follow agreed-upon treatment recommendations. Our focus in this review is whether these complex interventions work in their entirety but, we will extract detailed descriptions (where available) of the individual intervention components and process and contextual factors in line with guidance for the description and reporting of trials of complex interventions (Hoffman 2014; Möhler 2012).

We will include interventions mostly, or wholly, based on psychological theories and practice, which aim to improve adherence to DMTs. Experimental interventions will include those focusing on initiation of a DMT for the first time and those which are re-initiating a DMT, as well as increasing the percentage of prescribed doses taken, in those already taking a DMT. We will include all kinds of strategies and all modalities to deliver them.

The comparison group could include standard treatment, no intervention, placebo treatment or another active intervention aimed to increase adherence to DMTs. Standard treatment varies across sites and countries; it usually consists of basic education about symptom management, information and support, options for pharmacologic and nonpharmacologic management, family issues, instruction for self-administration, and information on the incidence and management of side-effects. We will consider all modalities to deliver them.

How the intervention might work

The focus of this review is on psychological interventions that aim to improve adherence directly by increasing participants' motivation to adhere to recommendations to take DMT. Motivational interventions may attempt to enhance the perceived importance and benefits of DMT and address potential barriers. In addition, the interventions may work by providing education and increasing participants' self-efficacy and skills to use treatment as prescribed. We will also consider interventions that directly or indirectly increase adherence to DMTs such as cognitive-behavioural interventions to teach anxiety-reduction skills, challenge phobic anxiety through exposure, and address maladaptive thoughts through cognitive restructuring. A combination of these approaches may improve adherence by both increasing patient motivation and offering supports that help people overcome barriers to change.

Why it is important to do this review

Adherence to DMTs is essential to maximise treatment benefit and to ensure the cost-effectiveness of treatments. Enhancing adherence has the potential to lead to improved health outcomes among people with MS. Little is known ab)out the types or efficacy of adherence interventions that have been used in MS. No published systematic reviews address this specific question to date. A Cochrane Review (Nieuwlaat 2014) assessed the results of randomised controlled trials (RCTs) of interventions to help people adhere to prescribed medications, however adherence to DMT treatments by people with MS is not addressed in this review and it does not focus specifically on psychological interventions.

OBJECTIVES

To assess the effects of psychological interventions designed to improve adherence to disease-modifying therapies (DMTs) in adults with multiple sclerosis (MS) in terms of adherence. This will be considered in relation to levels of adherence in a comparison group.

Secondary objectives are to assess the impact of interventions on potential predictors of adherence such as motivation, self-efficacy beliefs and healthcare engagement to DMTs adherence.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and cluster-RCTs in which a psychological intervention addressing adherence to DMT in adults is compared to standard treatment, no treatment/placebo treatment or another active intervention and where adherence is assessed. We will not consider a follow-up period as an exclusion criterion. Cross-over trials will also be included.

Types of participants

We will include adults (18 years and over) diagnosed with all types of clinically definite MS (regardless of psychiatric comorbidities

or level of disability) and clinically Isolated syndrome (CIS), defined according to the Poser (Poser 1983) and revised McDonald (McDonald 2001; Polman 2005; Polman 2011) criteria. The revised McDonald criteria for MS diagnosis will be applied when people have experienced a typical CIS (or progressive paraparesis/cerebellar/cognitive syndrome in the case of suspected primary progressive MS (PPMS). Participants could include those starting on any form of DMT for the first time or those who are re-initiating a DMT, regardless of the amount of prior use of therapy. Studies that include people with MS and people with other health conditions will be excluded unless the results for people with MS have been presented separately.

Types of interventions

We will include interventions, mostly or wholly based on psychological theories and practice, which aim to improve adherence to DMTs versus standard treatment, no intervention, placebo treatment or another intervention. Interventions could include those focusing on initiation of a DMT for the first time and those who are re-initiating a DMT, as well as improving adherence amongst those already taking DMTs. Interventions can address patients, providers and care givers.

Types of outcome measures

Primary outcomes

The primary outcome of the review will be adherence to DMTs; adherence will be evaluated in terms of percentage of:

- percentage of doses taken;
- percentage above a threshold of number of doses;
- proportion of participants starting DMT;
- proportion of participants stopping medication; and
- others used in the literature on adherence to DMTs in people with MS.

We will examine short-term (less than three months after randomisation) and long-term (greater than three months after randomisation) outcomes separately. We will include studies with a measure of adherence regardless if it is a primary or secondary outcome in the studies.

Secondary outcomes

We will also include outcomes related to :

- motivation to adhere;
- self-efficacy to adhere; and
- healthcare engagement (e.g. attending a neurology appointment to discuss re-initiation of DMTs).

We will include adverse effects of the adherence interventions such as increased anxiety or needle pricks/infections in the context of needle phobia interventions (but not adverse effects of the DMT treatments themselves as this is not the focus of the current review).

Search methods for identification of studies

Electronic searches

The Information Specialist will search the Trials Register of the Cochrane Multiple Sclerosis and Rare Diseases of the CNS Group, which, among other sources, contains trials from:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2016, most recent issue);
- MEDLINE (PubMed) (1966 to date);
- Embase (Embase.com) (1974 to date);
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost) (1981 to date);
- Latin American and Caribbean Health Science Information Database (LILACS) (Bireme) (1982 to date);
- ClinicalTrials.gov (http://clinicaltrials.gov); and
- World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch).

Information on the Group's Trials Register and details of search strategies used to identify trials can be found in the 'Specialised Register' section within the Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System Group's module.
The keywords that we will use to search for trials for this review are listed in Appendix 1.

Searching other resources

In addition we will:

- screen reference lists and published reviews for additional trials;
- search dissertations and theses from System for Information on grey Literature in Europe (Single) and conference proceedings, congress abstracts, reports, professional society meetings and websites of the main MS associations;
- contact researchers working on this topic and especially lead authors of identified trials to identify studies;
- Search for meeting abstracts from MS associations to identify other published or unpublished peer-reviewed trials.

Data collection and analysis

Selection of studies

We will assess studies according to the methods highlighted in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Two review authors, one a content expert (AC, MCG), will independently screen titles and abstracts identified from the search for their relevance for inclusion in the review. Studies will be reviewed for relevance based on study design, types of participants and interventions. The full-text publications of those deemed either eligible or potentially eligible will be obtained as well are for those where it is unclear. We will identify and exclude duplicates and will collate multiple reports of the same study so that each study is the unit of interest rather than reports. The two review authors will independently screen the full-text publications and identify studies for inclusion in the review according to the predetermined eligibility criteria. Eligibility criteria will be assessed in a prespecified order. Reasons for exclusion of studies will be recorded in the table 'Characteristics of excluded studies'. Disagreements about whether a study should be included will be resolved by discussion among the two review authors (AC, MCG) and, if necessary, a third review author (KG) will be consulted to arbitrate.
Review authors will not be masked to the name(s) of the author(s) institution(s) or publication source at any level of the review.

Data extraction and management

Data extraction will be undertaken by a content expert and a methodologist (JB, PWT). We will design a data extraction form. Data will be extracted independently using the bespoke form. We will extract the following information from the included studies.

- Date, country and clinical setting of trial.
- Study design.
- Rationale: aim of the intervention (e.g. DMT initiation or re-initiation, or both).
- Eligibility criteria.
- Participant characteristics (e.g. age, gender, years since diagnosis, type of MS, degree of disability, psychiatric diagnosis).
- Description of intervention (intent (e.g. reduce needle phobia, increase confidence etc.) duration, frequency, how delivered, who delivered, format of delivery, training of person delivering, whether adapted for MS, whether concomitant interventions were given).
- Type of comparison group(s) and, if appropriate, description of the duration, frequency, how delivered, who delivered, format of delivery, training of person delivering, whether adapted for MS, and whether concomitant interventions were given.
- Comparability of baseline characteristics between treatment and control groups.
- Description of follow-up.
- Outcomes measured, whether primary or secondary, and when they were recorded.
- Number enrolled in trial and in each group.
- Presence of sample size calculation.
- Numbers included at each follow-up in each group.
- Attempts at masking.
- Description of randomisation and allocation concealment.
- Intention-to-treat principle - whether participants were analysed in the group to which they were originally assigned, number and reasons for dropout and withdrawal in each group, and missing data assumptions used in the analysis. If data have been analysed separately using both intention-to-treat and per protocol approaches, preference will be given to the former.
- For nominal outcomes (denominator and numerator in each category for each group).
- For interval and ordinal data (N, mean, standard deviation (SD) for each group) or (N, median, interquartile range (IQR) or range) as appropriate.
- Notes: funding source and any potential conflicts of interest for the authors.

Once data have been extracted, descriptive information on clinical populations, interventions and outcomes will be passed to the Clinical Heterogeneity Group to review. This review will be undertaken blinded to study results. The Clinical Heterogeneity Group will decide which studies are similar enough in clinical and methodological content for combination in a meta-analysis to make sense, and will consist of three revIew authors members of the team (ST, DC, AC) with expertise in psychological interventions.
We will include studies reported as full text, those published as abstract only, and unpublished data. We will contact Chief Investigators to provide additional (unpublished) relevant information if necessary. One review author (PT) will enter the extracted data into RevMan software (Review Manager 2015) and a second review author (ST) will cross-check the data entry.
All studies that meet the inclusion criteria will be summarised in the 'Characteristics of included studies' table provided in RevMan software (Review Manager 2015) developed by Cochrane and will include details related to design, participants, interventions and outcomes

Assessment of risk of bias in included studies

Two review authors (AC, ST) will independently assess the risk of bias in included studies with any disagreements resolved by discussion or arbitration by a third review author (PT). The risk assessment for each included study will be presented in the 'Risk of bias' table. We will contact the study authors for additional information about the study methods as necessary.
Two review authors (ST, PWT) will assess the included articles (without masking of source and authorship) for study quality us-

ing Cochrane's tool for assessing risk of bias Chapter 8 (Higgins 2011b) that encompasses the following domains: random sequence generation, allocation concealment, masking of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting and 'other' sources of bias. A judgment of yes indicates a low risk of bias, no a high risk of bias and unclear either unclear or unknown risk of bias. However, masking patients and clinicians to treatment allocation is typically not possible in trials of psychological interventions. For this domain, our assessment of blinding will include only the outcome assessors (i.e. it will not include participant-reported outcomes). We will also consider whether the intervention was standardised and the validity and reliability of outcome measures. For each study and for each outcome, risk of bias will be summarised across domains (excluding domains of blinding of participants and personnel and excluding participant reported outcomes) using a classification of low risk (low risk of bias in all key domains), high risk (high risk of bias in at least one key domain) and unclear risk (unclear risk in at least one key domain). A 'Summary of findings' table will be created for the primary outcome of adherence and will be rated in accordance with methods of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group approach (Guyatt 2008).
When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Measures of treatment effect

All data will be entered and analysed in RevMan software (Review Manager 2015). We will perform statistical analyses using the statistical software provided by Cochrane. For continuous variables, we will calculate mean differences (MDs) or standardised mean differences (SMDs) with 95% confidence intervals (CIs) and for dichotomous variables we will present risk ratios (RRs) with 95% CIs and number needed to treat for an additional beneficial outcome (NNTB) (such as percentage above a threshold of number of doses or
proportion starting DMT) or number needed to treat for an additional harmful outcome (NNTH) (such as proportion stopping medication). Where the same outcome measure is expressed as a continuous variable in some studies and dichotomous in others, we will initially analyse them separately, but we will also conduct an additional analysis transforming the effect size estimates from the latter to SMDs in order to facilitate a meta-analysis. Where the same outcome variable is expressed in both continuous and dichotomous forms within the same study, we will prioritise the former. We will undertake meta-analysis only when the studies are sufficiently homogeneous in terms of participants, interventions and outcomes to provide a meaningful summary.

Unit of analysis issues

In the case of cluster-randomised trials to avoid unit of analysis errors, we will adjust the results when the unit of analysis is presented as the total number of individual participants rather than the number of clusters using the mean cluster size and the intracluster correlation coefficient (ICC), (Higgins 2011b). If the ICC is not available, we will impute it using estimates from other studies or general recommendations. If there is uncertainty about what value to use, we will conduct a sensitivity analysis trying a variety of plausible values. For cross-over trials we will use the pre-cross over results only. For trials where there have been multiple treatment attempts per participant, we will use participant (rather than treatment attempt) as the unit of analysis. For trials with more than two arms (either multiple treatment arms or multiple comparator arms), the Clinical Heterogeneity Group will consider which arms can be combined into pair-wise comparisons or whether intervention arms are dissimilar enough that they should be included in separate meta-analyses. This will ensure that individual trial arms are not included more than once in each meta-analysis.

Dealing with missing data

If trial level data are missing or inadequate, we will contact the primary authors (by email, letter or telephone) to obtain additional information or further clarification.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by considering the characteristics of participants, interventions, study designs and outcomes. We will attempt to blind this group to study results.
For each set of clinically/methodologically homogenous studies, we will examine statistical heterogeneity by visually inspecting whether the CIs overlap on the forest plot, (if used, see below), with poor overlap indicating the presence of heterogeneity), by using the Chi^2 statistic (significance level of 0.1) and using the I^2 statistic (Higgins 2011a). We will perform meta-analysis using random-effects models where there is substantial statistical heterogeneity ($I^2 > 50\%$).

Assessment of reporting biases

If we are able to pool more than 10 trials, we will use funnel plots to explore the possibility of publication bias. A comprehensive search strategy, which includes searching for unpublished studies (grey literature), and searching trials registers (see Search methods for identification of studies) will be used to minimise reporting biases. We will contact the authors for the full data or the reason for not publishing the data, where data are not reported or published in full.

Data synthesis

We will present a narrative synthesis of the included studies describing major characteristics and results. If studies are sufficiently similar in terms of participants, eligibility criteria, interventions (type and intent) and outcomes (including the time frame of follow-up), as determined by the Clinical Heterogeneity Group, we will consider meta-analysis as described in the assessment of heterogeneity section. See section on Measures of treatment effect for details of analysis

Subgroup analysis and investigation of heterogeneity

Results from studies will only be pooled if blinded assessment of clinical and methodological heterogeneity determines that they are similar enough. If there are sufficient studies, it is anticipated that the main analysis will consist of a series of meta-analyses on subgroups of clinically and methodologically homogenous studies. However, we will also use meta-regression techniques to see whether study level characteristics (such as type of intervention) impact on effect size.

Sensitivity analysis

A sensitivity analysis will be conducted when one or more studies have a high risk of introducing bias (for example inadequate data, withdrawals by more than 40% of the participants, nearly total non-adherence to the protocol, or very poor or non-adjusted comparability in the baseline criteria).

'Summary of findings' table

We will present the overall quality of the evidence for each outcome according with the methods of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group (GRADE Working Group 2004) approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias), but also to external validity, such as directness of results (Guyatt 2008). For each comparison, two review authors will independently rate the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' using (GRADEprofiler 2011). We will resolve any discrepancies by consensus, or, if needed, by arbitration by a third review author. For each comparison, we will present a summary of the evidence for the main outcomes in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2008; Schünemann 2011). If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table.

We will create a 'Summary of findings' table using the following outcomes:

- adherence to treatment (DMTs);
- motivation to adhere;
- self-efficacy to adhere;
- healthcare engagement (e.g., attending a neurology appointment to discuss re-initiation of DMTs).

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REFERENCES

Additional references

Amato 2001
Amato MP, Ponziani G, Rossi F, Liedl CL, Stefanile C, Rossi L. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 2001;**7**:340–4.

Benedict 2005
Benedict R, Wahlig E, Bakshi R, Fishman I, Munschauer F, Zivadinov R, et al. Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *Journal of Neurological Sciences* 2005;**231**:29–34.

Berger 2005
Berger BA, Liang H, Hudmon KS. Evaluation of software-based telephone counseling to enhance medication persistency among patients with multiple sclerosis. *Journal of the American Pharmacists Association : JAPhA* 2005;**45**: 466–72.

Bosch-Capblanch 2007
Bosch-Capblanch X, Abba K, Prictor M, Garner P. Contracts between patients and healthcare practitioners for improving patients' adherence to treatment, prevention and health promotion activities. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD004808.pub3]

Bruce 2010a

Bruce JM, Hancock L, Arnett P, Lynch S. Objective adherence monitoring in MS: Initial validation and association with self-report. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 2010;**16**:112–20.

Bruce 2010b

Bruce JM, Hancock L, Lynch S. Treatment adherence in multiple sclerosis: Association with emotional status, personality, and cognition. *Journal of Behavioral Medicine* 2010;**33**:219–27.

Bruce 2011

Bruce JM, Lynch S. Multiple Sclerosis: MS treatment adherence- how to keep patients on medication?. *Nature Reviews Neurology* 2011;**7**:421–2.

Calabrese 2012

Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F, et al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 2012; **18**(4):418-24.

Castro-Borrero 2012

Castro-Borrero W, Graves D, Frohman T, Flores AB, Hardeman P, Logan D, et al. Current and emerging therapies in multiple sclerosis: a systematic review. *Therapeutic Advances in Neurological Disorders* 2012;**5**: 205–20. [DOI: 10.1177/1756285612450936]

Confavreux 2006

Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. *Brain* 2006;**129**:606–16.

Courtney 2009

Courtney AM, Treadaway K, Remington G, Frohman E. Multiple sclerosis. *Medical Clinics of North American* 2009; **93**(2):451–76.

Craig 2008

Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008;**337**:a1655.

Devonshire 2011

Devonshire V, Lapierre Y, Macdonell R, Ramo-Tello C, Patti F, Fontoura P, et al. The Global Adherence Project (GAP): a multicenter observational study on adherence to disease modifying therapies in patients with relapsing remitting multiple sclerosis. *European Journal of Neurology* 2011;**18**:69–77.

Easthall 2013

Easthall C, Song F, Bhattacharya D. A meta-analysis of cognitive-based behaviour change techniques as interventions to improve medication adherence. *BMJ Open* 2013;**3**:e002749.

Filippini 2013

Filippini G, Del Giovane C, Vacchi L, D'Amico R, Di Pietrantonj C, Beecher D, et al. Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2013, Issue 6. [DOI: 10.1002/14651858.CD008933.pub2]

Foster 2012

Forster A, Brown L, Smith J, House A, Knapp P, Wright JJ, et al. Information provision for stroke patients and their caregivers. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: 10.1002/14651858.CD001919.pub3]

Freedman 2008

Freedman MS, Hughes B, Mikol DD, Bennett R, Cuffel B, Divan V, et al. Efficacy of disease-modifying therapies in relapsing remitting multiple sclerosis: a systematic comparison. *European Neurology* 2008;**60**(1):1–11.

Giovannoni 2012

Giovannoni G, Southam E, Wauban E. Systematic review of disease-modifying therapies to assess unmet needs in multiple sclerosis: tolerability and adherence. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 2012;**18**(7): 932–46.

Goodin 2008

Goodin DS. Disease-modifying therapy in multiple sclerosis: update and clinical implications. *Neurology* 2008; **71**:S8–13.

GRADE Working Group 2004

GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004; Vol. 328, issue 7454:1490–4.

GRADEprofiler 2011 [Computer program]

The GRADEpro Working Group. GRADEprofiler (GRADEpro). Version 3.6. The GRADEpro Working Group, 2011.

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924–6.

Hancock 2011

Hancock L, Bruce JM, Lynch S. Exacerbation history is associated with medication and appointment adherence in MS. *Journal of Behavioral Medicine* 2011;**34**:330–8.

Higgins 2011a

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Higgins 2011b

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hoffman 2014

Hoffmann T, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: Template for Intervention Description and Replication (TIDieR)

checklist and guide. *BMJ (Clinical Research Ed.)* 2014;**348**: g1687.

Johnson 2009
Johnson KP, Due DL. Benefits of glatiramer acetate in the treatment of relapsing-remitting multiple sclerosis. *Expert Review of Pharmacoeconomics & Outcomes Research* 2009;**9**: 205–14.

Jokubaitis 2013
Jokubaitis V, Spelman T, Lechner-Scott J, Barnett M, Shaw C, Vucic S, et al. The Australian Multiple Sclerosis immunotherapy study: a prospective, multicentre study of drug utilisation using the MS base platform. *PLoS One* 2013;**8**(3):e59694.

Kieseier 2008
Kieseier BC, Wiendl H, Leussink VI, Stuve O. Immunomodulatory treatment strategies in multiple sclerosis. *Journal of Neurology* 2008;**255**(Suppl 6):15–21.

Koudriavtseva 2012
Koudriavtseva T, Onesti E, Pestalozza I, Sperduti I, Jandolo B. The importance of physician-patient relationship for improvement of adherence to long-term therapy: data of survey in a cohort of multiple sclerosis patients with mild and moderate disability. *Neurological Sciences* 2012;**33**: 575–84.

Köpke 2014
Köpke S, Solari A, Khan F, Heesen C, Giordano A. Information provision for people with multiple sclerosis. *Cochrane Database of Systematic Reviews* 2014, Issue 4. [DOI: 10.1002/14651858.CD008757.pub2]

Linker 2008
Linker RA, Kieseier BC, Gold R. Identification and development of new therapeutics for multiple sclerosis. *Trends in Pharmacological Sciences* 2008;**29**:558–65.

Lublin 1996
Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: Results of an international survey. *Neurology* 1996;**46**:907–11.

McDonald 2001
McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Annals of Neurology* 2001;**50**:121–7.

Mohr 1999
Mohr DC, Goodkin DE, Masuoka L, Dick LP, Russo D, Eckhardt J, et al. Treatment adherence and patient retention in the first year of a Phase-III clinical trial for the treatment of multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 1999;**5**:192–7.

Möhler 2012
Möhler R, Bartoszek G, Köpke S, Meyer G. Proposed criteria for reporting the development and evaluation of complex interventions in healthcare (CReDECI): guideline development. *International Journal of Nursing Studies* 2012; **49**:40–6.

Nayak 2003
Nayak S, Matheis RJ, Schoenberger NE, Shiflett SC. Use of unconventional therapies by individuals with multiple sclerosis. *Clinical Rehabilitation* 2003;**17**:181–91.

Nieuwlaat 2014
Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews* 2014, Issue 11. [DOI: 10.1002/14651858.CD000011.pub4]

Page 2003
Page SA, Verhoef MJ, Stebbins RA, Metz LM, Levy JC. The use of complementary and alternative therapies by people with multiple sclerosis. *Chronic Diseases in Canada* 2003; **24**:75–9.

Patti 2010
Patti F. Optimizing the benefit of multiple sclerosis therapy: the importance of treatment adherence. *Patient Preference and Adherence* 2010;**4**:1–9.

Polman 2005
Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Annals of Neurology* 2005;**58**(6):840–6.

Polman 2011
Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology* 2011;**69**(2):292–302.

Poser 1983
Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis:guidelines for research protocols. *Annals of Neurology* 1983;**13**(8):227–31.

Review Manager 2015 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2015.

Reynolds 2010
Reynolds MW, Stephen R, Seaman C, Rajagopalan K. Persistence and adherence to disease modifying drugs among patients with multiple sclerosis. *Current Medical Research and Opinion* 2010;**26**:663–74.

Rinon 2011
Rinon A, Buch M, Holley D, Verdun E. The MS Choices Survey: findings of a study assessing physician and patient perspectives on living with and managing multiple sclerosis. *Patient Preference and Adherence* 2011;**5**:629–43.

Schünemann 2011
Schünemann H, Oxman A, Higgins J, Vist G, Glasziou P, Guyatt G. Chapter 11: Presenting results and 'Summary of findings'tables. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version5.1.0 [updated March 2011].

The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Stacey 2014
Stacey D, Légaré F, Col NF, Bennett CL, Barry MJ, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database of Systematic Reviews* 2014, Issue 1. [DOI: 10.1002/14651858.CD001431.pub4]

Tan 2011
Tan H, Cai Q, Agarwal S, Stephenson JJ, Kamat S. Impact of adherence to disease-modifying therapies on clinical and economic outcomes among patients with multiple sclerosis. *Advances in Therapy* 2011;**28**:51–61.

Tramacere 2015
Tramacere I, DelGiovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2015, Issue 9. [DOI: 10.1002/14651858.CD011381.pub2]

Turner 2007
Turner AP, Kivlahan DR, Sloan AP, Haselkorn JK. Predicting ongoing adherence to disease modifying therapies in multiple sclerosis: utility of the health beliefs model. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 2007; **13**:1146–52.

Viswanathan 2012
Viswanathan M, Golin CE, Hones CD, Ashok M, Blalock SJ, Wines RC, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Annals of Internal Medicine* 2012;**157**(11):785–95.

Wong 2011
Wong J, Gomes T, Mamdani M, Manno M, O'Conner P. Adherence to multiple sclerosis disease-modifying therapies in Ontario is low. *Canadian Journal of Neurological Sciences* 2011;**38**(3):429–33.

Zakaria 2015
Zakaria M. Smoke and mirrors: Limited value of relative risk reductions for assessing the benefits of disease-modifying therapies for multiple sclerosis. *Multiple Sclerosis and Related Disorders* 2015;**4**(3):187–91.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Keywords

{Motivational Interviewing} OR {Behavior Therapy} OR {Behaviour Therapy} OR {transtheoretical model} OR {positive psychology interventions} OR {Anger} OR {Art Therapy} OR {Attention} OR {Psychoanalytic Therapy} OR {Cognitive Therapy} OR {Personal Construct Theory} OR {Counseling} OR {Crisis Intervention} OR {Psychotherapy} OR {Depression} OR {Family Therapy} OR {Gestalt Theory} OR {Psychotherapy} OR {Hypnosis} OR {Milieu Therapy} OR {Nondirective Therapy} OR {Problem Solving} OR {Psychoanalysis} OR {Psychodrama} OR {Play Therapy} OR {Self Concept} OR {Self Efficacy} OR {Self Assessment } OR {Social Support} OR {Socio environmental Therapy} OR {psychological stress} OR {anger management} OR {anxiety} OR {art therapy} OR {assertiveness} OR {attention} OR {aversion therapy} OR {biofeedback training} OR {brief therapy} OR {colour therapy} OR {cognitive rehabilitation} OR {concentration} OR {construct theory} OR {counseling} OR {crisis intervention} OR {dance therapy} OR {emotion focusing} OR {executive function} OR {expert patient} OR {exposure} OR {functional analysis} OR {milieu therapy} OR {mood } OR {role play} OR {schema-focussed} OR {self control} OR {self-esteem} OR {self-efficacy} OR {self-image} OR {self management} OR {self monitoring} OR {self talk} OR {self disclosure} OR {self narrative} OR {social support} OR {socio environmental} OR {sociotherapy} OR {supportive therapy} OR {transactional} OR {systemic} OR {client-centred} OR {client-centered} OR {acceptance therapy} OR {commitement therapy} OR {mindfulness-based cognitive therapy} OR {mindfulness-based stress reduction} OR {well-being therapy} **AND** {medication adherence } OR {medication persistence} OR {compliance} OR {persistence} OR {adherence} OR {cooperation} OR {compliance therapy} OR {patient education} OR {reminder systems} OR {decision support techniques} OR {decision making} OR {computer assisted} **AND** {monoclonal antibodies} OR {immunosuppressive agents} OR {neuroprotective agents} OR {disease-modifying therapy} OR {disease-modifying therapies} OR {DMTs}

CONTRIBUTIONS OF AUTHORS

All authors contributed to the protocol design and content, with the exception of Keri Swaggart, who developed and ran the search strategy for the others resources searched.

DECLARATIONS OF INTEREST

AC, MCG, PT and ST are members of the iMSpire (International Multiple Sclerosis Partnership in Research) Special Interest Group.

JB, DC and KJG have received funding for adherence research from the U.S. National MS Society, including a trial examining the efficacy of a psychological

intervention for improving adherence in MS.

JB is also a member of the Novartis unbranded speaker's bureau and the Novartis MS and cognition medical advisory board.

KRS - none.