Multiple Sclerosis and Related Disorders 5 (2016) 12–26

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

Systematic review and meta-analysis of interventions for depression and anxiety in persons with multiple sclerosis

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ARTICLE INFO

Article history:
Received 15 August 2015
Received in revised form
9 October 2015
Accepted 16 October 2015

Keywords:
Multiple sclerosis
Depression
Anxiety
Treatment
Systematic review
Meta-analysis

ABSTRACT

Background: Depression and anxiety are common in persons with multiple sclerosis (MS), and adversely affect fatigue, medication adherence, and quality of life. Though effective treatments for depression and anxiety exist in the general population, their applicability in the MS population has not been definitively established.
Objective: To determine the overall effect of psychological and pharmacological treatments for depression or anxiety in persons with MS.
Methods: We searched the Medline, EMBASE, PsycINFO, PsycARTICLES Full Text, Cochrane Central Register of Controlled Trials, CINAHL, Web of Science, and Scopus databases using systematic review methodology from database inception until March 25, 2015. Two independent reviewers screened abstracts, extracted data, and assessed risk of bias and strength of evidence. We included controlled clinical trials reporting on the effect of pharmacological or psychological interventions for depression or anxiety in a sample of persons with MS. We calculated standardized mean differences (SMD) and pooled using random effects meta-analysis.
Results: Of 1753 abstracts screened, 21 articles reporting on 13 unique clinical trials met the inclusion criteria. Depression severity improved in nine psychological trials of depression treatment ($N=307$; SMD: -0.45 (95% CI: -0.74, -0.16)). The severity of depression also improved in three pharmacological trials of depression treatment (SMD: -0.63 ($N=165$; 95%CI: -1.07, -0.20)). For anxiety, only a single trial examined psychological therapy for injection phobia and reported no statistically significant improvement.
Conclusion: Pharmacological and psychological treatments for depression were effective in reducing depressive symptoms in MS. The data are insufficient to determine the effectiveness of treatments for anxiety.

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http://dx.doi.org/10.1016/j.msard.2015.10.004

1. Introduction

Psychiatric comorbidity is common in persons with multiple sclerosis (MS), with a lifetime prevalence of depression as high as 24% (Marrie et al., 2015); and of anxiety disorders as high as 21.9% (Marrie et al., 2015). Depression and anxiety are associated with more fatigue (Brown et al., 2009), lower quality of life (Fruehwald et al., 2001; Janssens et al., 2003), and reduced adherence to disease-modifying therapy (DiMatteo et al., 2000; Turner et al., 2009). Although the adverse effects of depression and anxiety in MS are well-recognized, they remain undertreated. Well-developed evidence to guide the treatment of depression and anxiety in MS is lacking (Minden et al., 2014), therefore health care providers must rely on the general psychiatry and psychology literature for treatment recommendations. Effective treatments for depression and anxiety exist in general and medical populations (van Straten et al., 2010; Gartlehner et al., 2011; Roshanaei-Moghaddam et al., 2011; Cuijpers et al., 2013, 2014; Hunsley et al., 2014; Bandelow et al., 2015), but MS-specific considerations, such as cognitive impairment, fatigue, and urinary retention, may affect the safety, tolerability and effectiveness of treatments tested in the general population. Therefore disease-specific investigations of interventions to reduce depression and anxiety in MS are essential (Koch et al., 2011; Minden et al., 2014).

The aim of this systematic review and meta-analysis was to summarize, critically appraise, and quantify the findings of controlled trials of pharmacological and psychological interventions for depression and anxiety in persons with MS.

2. Methods

Using an *a priori* published protocol (Fiest et al., 2015), we conducted this systematic review following the Cochrane Handbook for Systematic Reviews, and reported the findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Moher et al., 2009; Chandler et al., 2013).

2.1. Populations, interventions, comparators, settings and study designs

We included studies meeting these criteria: (1) randomized controlled trial conducted in any setting; (2) published in any language; and (3) conducted in a depressed or anxious population of adults with MS. Definite diagnoses of MS were required based on the prevailing criteria used when the trial was conducted. Depression and anxiety could have been defined by a clinical interview, or by self-report using a screening tool. Otherwise, we did not pre-specify criteria regarding the definition of depression or anxiety, but rather evaluated which approaches were used by individual trials to identify the specific instruments used. We excluded trials if the study population was <18 years old.

2.2. Outcome measures

To ensure relevant, patient-oriented outcomes were examined, we held meetings with primary care providers and individuals living with MS. Based on recommendations from these stakeholders, the primary research question was: “What is the efficacy of pharmacological and psychological treatments for depression or anxiety in persons with MS?”. We compared the severity of depression and/or anxiety on any tool at post-assessment between the treatment and control groups using the standardized mean difference (SMD) of depression and/or anxiety scores. Secondary outcomes were: differences in participant's quality of life and fatigue, proportion of participants achieving remission of depression or anxiety, and participants achieving at least a 50% reduction in depressive or anxious symptoms. The final research question was “What is the tolerability of pharmacological or psychological treatment for depression or anxiety in MS?” for which we examined the drop-out rate and any side effects.

2.3. Search strategy

An Information Specialist (M.F.) developed the search strategies in consultation with experts in neurologic disease (J.M., R.A.M.) and psychiatric disorders (S.P., J.W., L.G., K.F., J.S., J.B.). We searched the Cochrane Database of Systematic Reviews for related systematic reviews, and searched the following databases for randomized controlled trials and systematic reviews: Medline, EMBASE, PsycINFO, PsycARTICLES Full Text, Cochrane Central Register of Controlled Trials, CINAHL, Web of Science, and Scopus. Clinicaltrials.gov and the WHO trial register were also searched for completed or ongoing trials. We identified additional abstracts by scanning the reference lists of systematic reviews, and of the trials which met the inclusion criteria for this review. Databases were searched from inception date to March 25, 2015 without language limits. For Medline, we used the Cochrane Highly Sensitive Search Strategy; variations of this filter, or other validated filters, were used for other databases(Appendix A).

2.4. Study selection

Two reviewers (K.F. and R.A.M.) independently screened titles and abstracts in two phases using EPPI-Reviewer (Thomas et al., 2010). In the first phase, titles and abstracts were reviewed to ensure they were conducted in a population with MS and depression or anxiety, and in the second phase we identified which were clinical trials. These reviewers independently reviewed full text articles from the two-phase abstraction; disagreements were resolved by discussion.

2.5. Data abstraction

The two reviewers independently extracted data using a data collection tool developed by the author team and implemented in EPPI-Reviewer (Appendix B). The following data elements were extracted: study design, inclusion criteria for the study population with respect to demographic or disease characteristics (e.g. age, sex, disease course), approach to identifying depression/anxiety (e.g. diagnostic interview, self-report questionnaire) including the instruments used, interventions used, items related to the risk of bias assessment (see below), and any efficacy or safety outcomes. When multiple papers reported on the same trial, we gathered all unique information (as above) from each publication. We sought translation for non-English articles.

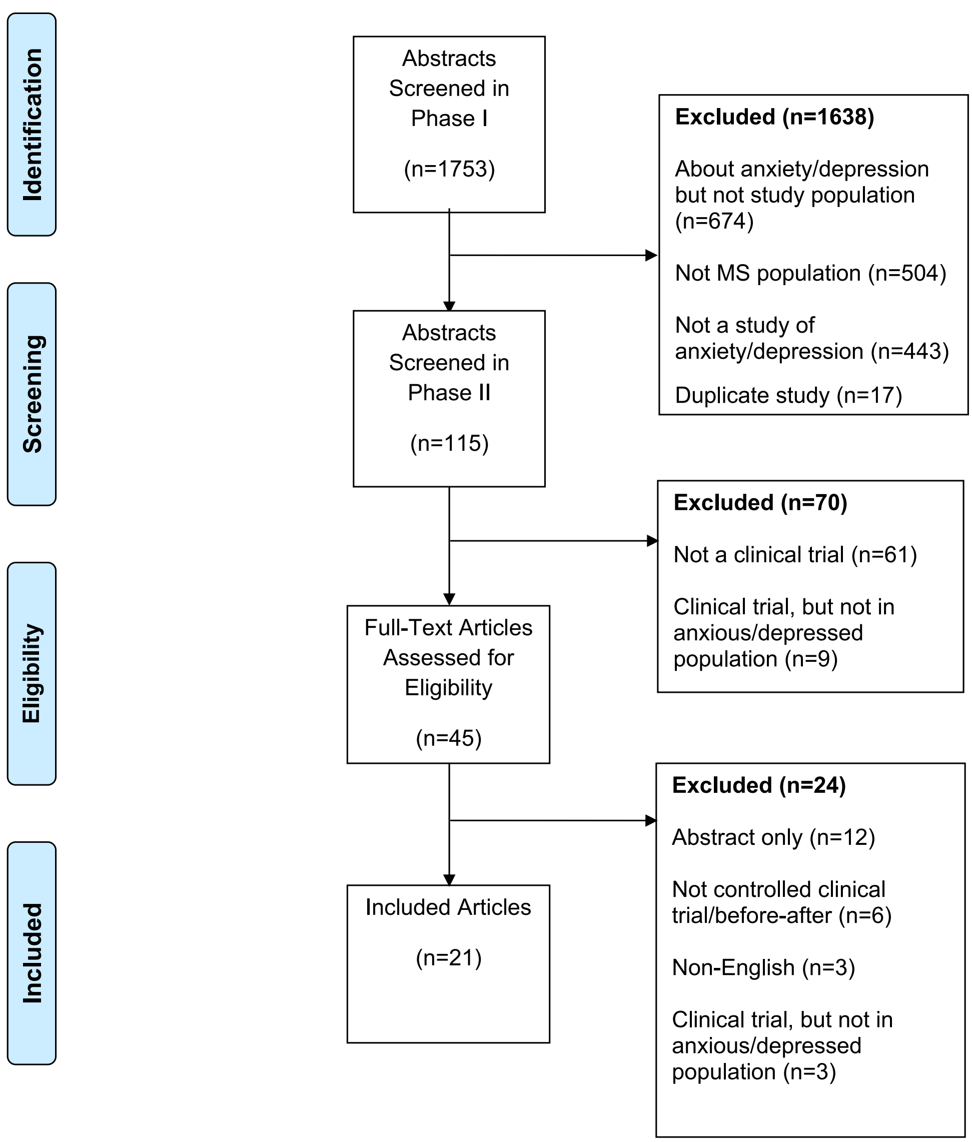

Fig. 1. Study Flow Diagram.

Table 1
Description of included studies.

Author (year) Recruitment context	Study information	Psychiatric co-morbidity information	Intervention: Intervention	Intervention: Comparator	Intervention: Duration	Outcomes: Primary outcome measures	Outcomes: Secondary outcome measures	Outcomes: Outcome	Outcomes: Tolerability
Bombardier (2013)[a] University of Washington Western Regional MS Centre **Setting** Specialty Clinic *University of Washington MS Clinic*	**Study design** Randomized controlled trial **Study population** Disease course *EDSS ≤ 5.5* **Age**: 18–70	**DSM classification** Dysthymic disorder Major depression *Based on SCID* **Screening tool** Patient Health Questionnaire-9 (PHQ-9) *≥ 10 on PHQ-9 or score of 2 or more on questions 1 or 2 (anhedonia or depressed mood)*	**Psychological** Counseling *Motivational interviewing and goal-setting for physical activity* **Provider delivering intervention** Counselor	Waitlist control	12 weeks	***Hamilton Rating Scale for Depression*** Positive and Negative Affect Scale		Remission response rate ≥ 50% at end of treatment Difference in proportion of treatment responders	Rate of adverse effects *MS-related checklist of 22 symptoms*
Kratz (2014)[a] University of Washington Western Regional MS Centre	Supplementary analysis related to Bombardier 2013 study described above.							Positive and negative affect as mediators of effect of physical activity on depression	
Ehde (2008) University of Washington Western Regional MS Centre	**Study design** Randomized controlled trial **Age**: ≥ 18 **Disease stability required pre-enrollment** No use of corticosteroids in prior 2 weeks	**DSM classification** Dysthymic disorder Major depression *Based on SCID* **Screening tool** CES-D *≥ 16*	**Pharmacologic** Paroxetine to 10 mg daily increasing to 40 mg daily **Provider delivering intervention** Psychiatrist	Placebo	12 weeks	***Hamilton Rating Scale for Depression***	Hamilton Anxiety Rating Scale Modified Fatigue Impact Scale	Remission response rate ≥ 50% at end of treatment Difference in proportion of treatment responders	Rate of adverse effects
Cooper (2011) Sheffield Teaching Hospitals NHS Foundation Trust MS Clinic **Setting** Online (from home) Specialty Clinic *Sheffield Clinical Trials Research Unit*	**Study design** Randomized controlled trial **Study population** *EDSS < 8.5* **Disease course** Relapsing remitting MS Secondary progressive MS **Age**: ≥ 18	**Screening tool** Beck Depression Inventory *≥ 14 on two consecutive occasions*	**Psychological** Cognitive behavioral therapy *Computerized CBT- "Beating the Blues"*	Treatment as usual	8 weeks, outcomes at 21 weeks	***Beck Depression Inventory-II*** Patient Health Questionnaire-9	Generalized Anxiety Disorder 7-item Short Form- 36	Difference in mean scores	Discontinuation rate
Forman (2010) Queen's Medical Center, Nottingham & Local MS Society **Setting** University	**Study design** Randomized controlled trial	**Screening tool** Hospital Anxiety and Depression Scale (HADS) *≥ 8 on either HADS scale* General Health Questionnaire-12 (GHQ) *≥ 3 on GHQ*	**Psychological** Cognitive behavioral therapy *Group, In person* **Provider delivering intervention** Clinical neuropsychologist	Waitlist control	12 weeks	***Hospital Anxiety and Depression Scale*** General Health Questionnaire-12	Hospital Anxiety and Depression Scale Short Form-36	Differences in Area Under the Curve	Discontinuation rate
Lincoln (2011)[b] Nottingham University Hospitals NHS Trust	**Study design** Randomized controlled trial	**Screening tool** Hospital Anxiety and Depression Scale (HADS)	**Psychological** Cognitive behavioral therapy *Adjustment group, In Person*	Waitlist control	6 sessions over 12 weeks	Beck Depression Inventory-II	Hospital Anxiety and Depression Scale	Differences in Area Under the Curve	Discontinuation rate

Table 1 (*continued*)

Author (year)	**Study information**	**Psychiatric co-morbidity information**	**Intervention**			**Outcomes**			
Recruitment context			**Intervention**	**Comparator**	**Duration**	**Primary outcome measures**	**Secondary outcome measures**	**Outcome**	**Tolerability**
Setting Clinical trials unit at University	**Disease stability required pre-enrollment** Duration *At least 12 months*	*≥ 8 on either HADS scale* General Health Questionnaire-12 (GHQ) *≥ 3 on GHQ*	**Provider delivering intervention** Psychologist			***Hospital Anxiety and Depression Scale*** General Health Questionnaire-12	EQ5D		
Humphreys (2013)[b] Nottingham University Hospitals NHS Trust	Supplementary analysis related to Lincoln study described above.							Cost effectiveness assessed with service use questionnaire	
Larcombe (1984) Multiple Sclerosis Community Centre & General Hospital **Setting** Specialty Clinic	**Study design** Randomized controlled trial **Age:** 20–65	**Screening tool/Survey** Beck Depression Inventory *≥ 20* Definite or probable depression per Feighner criteria (Feighner et al., 1972)	**Psychological** Cognitive behavioral therapy **Provider delivering intervention** Graduate Student therapist	Waitlist control	6 weeks	Beck Depression Inventory ***Hamilton Rating Scale for Depression***		Difference in mean scores	
Mohr (2000)[c] Kaiser Permanente Medical Care Program of Northern California **Setting** Home	**Study design** Randomized controlled trial **Disease course** Relapsing remitting MS	**Screening tool** Profile of Mood States *≥ 15*	**Psychological** Cognitive behavioral therapy *By telephone* **Provider delivering intervention** Doctoral/post-doctoral psychology students	Treatment as usual (2 patients continues medications, 1 continued therapy- no other mental health care received)	8 weeks	***Profile of Mood States (POMS) Depression-Dejection Scale***		Difference in mean scores	Discontinuation rate
Mohr (2001)[c] Kaiser Permanente Medical Care Program of Northern California	Supplementary analysis related to Mohr 2000 study described above.						Nonspecific OKT3-stimulated production of IFN-gamma with and without IL-10 suppression Antigen-stimulated production of IFN-gamma T-cell proliferative responses (no antigen, MBP, MOG, phytohemagglutinin)		
Mohr (2003)[c] Kaiser Permanente Medical Care Program of Northern California	Supplementary analysis related to Mohr 2000 study described above.						FAI (Total score Global Fatigue Severity Fatigue Consequences Responsiveness to Rest/Sleep Situation-specific fatigue)		
Mohr (2003)[c] Kaiser Permanente Medical Care Program of Northern California	Supplementary analysis related to Mohr 2000 study described above.						MRI: T2 weighted, proton density total lesion volume and divided by lobe, subdivided into right and left hemispheres		
Mohr (2004)[c]	Supplementary analysis						Arizona Social Support		

Kaiser Permanente Medical Care Program of Northern California	related to Mohr 2000 study described above.						Interview Schedule in subgroup (social support as a buffer of the effects of change in depression on IFN-gamma production)		
Mohr (2004)[c] Kaiser Permanente Medical Care Program of Northern California	Supplementary analysis related to Mohr 2000 study described above.						Arizona Social Support Interview Schedule Ambulation Index		
Mohr (2001) University of California San Francisco Multiple Sclerosis Centre **Setting** Specialty Clinic	**Study design** Randomized controlled trial **Disease course** Relapsing remitting MS Secondary progressive MS **Disease stability** **required pre-enrollment** No corticosteroids in the previous 14 days No initiation of interferon in previous 2 months No current MS relapse	**DSM classification** Major Depressive Disorder *Based on Structured Clinical Interview for DSM-IV (SCID)* **Screening tool** Beck Depression Inventory (BDI) *≥ 16 BDI* Hamilton Rating Scale for Depression *≥ 16 HDRS*	**Pharmacologic** Sertraline 50 mg per day until 200 mg daily or remission **Psychological** Cognitive behavioral therapy **Provider delivering intervention** Neurologist Psychologist	Supportive-expressive group therapy	16 weeks	Beck Depression Inventory (BDI) *BDI-18 removing fatigue, work difficulty, health concerns* ***Hamilton Rating Scale for Depression*** Structured Clinical Interview for DSM-IV		Difference in mean scores	Discontinuation rate
Mohr (2005) University of California San Francisco (UCSF) Multiple Sclerosis Centre & UCSF Behavioral Medicine Research Centre **Setting** Specialty Clinic	**Study design** Randomized controlled trial **Study population** Not demented Prescribed interferon-beta1a for at least 3 months **Disease course** Relapsing remitting MS **Disease stability required pre-enrollment** Not in acute exacerbation	**DSM classification** Specific phobia *Blood-injection-injury type* *Based on* Structured Clinical Interview for DSM-IV (SCID)	**Psychological** Cognitive behavioral therapy *Self-injection anxiety therapy, In person* **Provider delivering intervention** Nurse	Telephone support	6 sessions	Structured Clinical Interview for DSM-IV		Difference in proportion of treatment responders Improved vs. not (clinical judgment) Ability to successfully inject	
Mohr (2005) USA National MS Society Mailing List	**Study design** Randomized controlled trial **Study population** Functional impairment resulting in limitations in activity (score of ≥ 3 on Guy's Neurological Disability Scale)	**DSM classification** Dysthymic disorder Major depression *Based on Structured Clinical Interview for DSM-IV (SCID)* **Screening tool** Beck Depression Inventory-II	**Psychological** Cognitive behavioral therapy *By telephone* **Provider delivering intervention** Psychologist	Telephone-administered supportive emotion-focused therapy	16 weeks	Beck Depression Inventory-II ***Hamilton Rating Scale for Depression*** Structured Clinical Interview for DSM-IV		Difference in proportion of treatment responders	Discontinuation rate

Table 1 (*continued*)

Author (year) Recruitment context	Study information	Psychiatric co-morbidity information	Intervention: Intervention	Intervention: Comparator	Intervention: Duration	Outcomes: Primary outcome measures	Outcomes: Secondary outcome measures	Outcomes: Outcome	Outcomes: Tolerability
Setting Specialty Clinic	**Disease stability required pre-enrollment** Not currently experiencing an MS exacerbation **Age**: $\geq$ 18	$\geq$ *16* Hamilton Rating Scale for Depression $\geq$ *14*							
Beckner (2007)[d] USA National MS Society Mailing List	Supplementary analysis related to Baron 2011 study described below.							Role of alliance in therapy outcomes Social support as a moderator for response to telephone administered psychotherapy	
Baron (2011)[d] USA National MS Society **Setting** Home	**Study design** Randomized controlled trial **Study population** Functional limitation defined as $\geq$ 3 on Guy's Neurological Disability Scale **Disease stability required pre-enrollment** Exclude current relapse **Age**: $\geq$ 18	**DSM classification** Major depression *Based on Structured Clinical Interview for DSM-IV (SCID)* **Screening tool** Beck Depression Inventory-II $\geq$ *16* Hamilton Rating Scale for Depression $\geq$ *14*	**Psychological** Cognitive behavioral therapy *By Phone* **Provider delivering intervention** Psychologist	Telephone-administered supportive emotion-focused therapy	16 weeks	Beck Depression Inventory-II Hospital Anxiety and Depression Scale Hamilton Rating Scale for Depression Structured Clinical Interview for DSM-IV	Short Form-36	Difference in mean scores	
Nordin (2012) Lund University Hospital Department of Neurology **Setting** Specialty Clinic	**Study design** Randomized controlled trial **Disease stability required pre-enrollment** No to moderate functional disability (< 6.0 on EDSS)	**Screening tool** Beck Depression Inventory $\geq$ *10* Hospital Anxiety and Depression Scale (HADS) $\geq$ *9 on one or both HADS scales*	**Psychological** Cognitive behavioral therapy (Acceptance and commitment therapy) **Provider delivering intervention** Psychologist	Relaxation training	15 weeks	Beck Depression Inventory ***Hospital Anxiety and Depression Scale***		Difference in mean scores	
Schiffer (1990) University of Rochester Multiple Sclerosis Research Group **Setting** Specialty Clinic	**Study design** Randomized controlled trial	**DSM classification** Major depression *Based on the Schedule for Affective Disorders and Schizophrenia Interview*	**Pharmacologic** Desipramine 25 mg increased to 75 mg BID **Provider delivering intervention** Neurologist	Placebo	5 weeks	Beck Depression Inventory ***Hamilton Rating Scale for Depression***		Difference in mean scores Improved vs. not (clinical judgment)	Discontinuation rate Rate of adverse effects

Note: Bold Italicized font in primary outcome column indicates scale used for meta-analysis.

[a] Reporting results from the same trial.
[b] Reporting results from the same trial.
[c] Reporting results from the same trial.
[d] Reporting results from the same trial.

2.6. Risk of bias assessment

The two reviewers independently evaluated the internal validity of the trials using the Cochrane Collaboration's Risk of Bias tool (Supplemental methods) (Higgins et al., 2011). The strength of evidence for the primary outcomes was graded as low, moderate or high using the approach described by the GRADE working group (Supplemental methods) (Guyatt et al., 2008).

2.7. Data synthesis and analysis

We summarized the findings using descriptive statistics, including mean, median, standard deviation (SD), interquartile range (IQR), and frequencies (percent). Since studies measured depressive symptoms using multiple tools, the effect estimates for most outcomes were pooled using the SMD, where the effect size is represented in units of SD. Negative SMDs indicate a difference in results favoring the intervention; an SMD of 0.20 is considered small, 0.50 medium, and ≥ 0.80 a large effect (Cohen, 1988). For the secondary objectives related to depression remission and symptom reduction, odds ratios (OR) with 95% confidence intervals (95%CI) were used to estimate the magnitude of effect.

When studies used multiple measures of the same outcome (e.g. Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) for depression), we analyzed one estimate using predetermined criteria (see supplemental methods). We pooled the data using random-effects models in Review Manager 5.3 (The Cochrane Collaboration, 2014) overall, and stratified by type of comparison group (active vs. inactive). Estimates were calculated as SMDs or OR and the accompanying 95%CI. We quantified the amount of heterogeneity using the *I*-squared (I^2) statistic, and its significance determined based on the accompanying *Q p* -value (Higgins et al., 2003). I^2 is calculated using *Q* according to the following: $I^2=100\%*(Q\text{-degrees of freedom})/Q$ (Higgins et al., 2003). A value of 0% indicates no observed heterogeneity, and increasing values represent greater amounts of heterogeneity; values of 25%, 50%, and 75%, indicate low, moderate, and high levels of heterogeneity, respectively (Higgins et al., 2003). Publication bias was assessed in R (R, 2014) using funnel plots, Begg's rank test (Begg and Mazumdar, 1994) or Egger's regression tests (Egger and Smith, 1997).

3. Results

3.1. Results of the search

We screened 1753 unique abstracts, excluding 1638 in the first phase. Over 40% (674/1638) were excluded because depression or anxiety were not inclusion criteria for the study population, approximately 30% (504/1638) were not studies of the MS population, while 27% (443/1638) were not studies of depression or anxiety (Fig. 1). We reviewed the full-text of 45 manuscripts. Of these, 21 articles reporting on 13 unique clinical trials met the final inclusion criteria (Table 1). Abstracts which were deemed potentially relevant for which full-text did not exist are shown in Table 2. Relevant unpublished trials found on clinicaltrials.gov and the WHO trials register were also tabulated (Table 3).

3.2. Description of studies

The 13 randomized controlled trials were published from 1984 to 2014, and conducted in the United States ($n=8$; 61.5%) (Schiffer and Wineman, 1990; Mohr et al., 2000, 2001, 2005a, 2005b; Ehde et al., 2008; Baron et al., 2011; Bombardier et al., 2013), England ($n=4$; 30.8%) (Larcombe and Wilson, 1984; Forman and Lincoln, 2010; Cooper et al., 2011; Lincoln et al., 2011), and Sweden ($n=1$; 7.7%) (Nordin and Rorsman, 2012) (Table 1). The number of participants enrolled ranged from 20 to 151 (median: 40, IQR: 99). Most trials examined the effects of psychotherapy interventions ($n=10$; 76.9%) (Larcombe and Wilson, 1984; Mohr et al., 2000, 2001; Mohr et al., 2003a, 2003b, 2004, 2005a, 2005b; Mohr and Genain, 2004; Beckner et al., 2007; Forman and Lincoln, 2010; Baron et al., 2011; Cooper et al., 2011; Lincoln et al., 2011; Nordin and Rorsman, 2012; Bombardier et al., 2013; Humphreys et al., 2013; Kratz et al., 2014); two investigated pharmacotherapy alone (15.4%) (Schiffer and Wineman, 1990; Ehde et al., 2008); and one examined pharmacotherapy and psychotherapy interventions (7.7%) (Mohr et al., 2001). Twelve studies examined depression, and one studied anxiety (Mohr et al., 2005a). The primary outcome of the 12 included studies was the effect of the intervention on depression or depressive symptoms, with the main outcome of the remaining trial being the effect on injection anxiety (Mohr et al., 2005a). Inclusion criteria for the trials were varied, with some studies restricting inclusion to those of a certain age, disease course, or disability status (Table 1).

3.3. Interventions and assessments

Depressive and anxiety disorders were identified in the 13 unique included trials using screening tools or clinical interviews. For depression, six of the studies (Larcombe and Wilson, 1984; Mohr et al., 2000; Forman and Lincoln, 2010; Cooper et al., 2011; Lincoln et al., 2011; Nordin and Rorsman, 2012) used only symptom-based measures to determine eligibility, including the BDI ($n=3$)(Larcombe and Wilson, 1984; Cooper et al., 2011; Nordin and Rorsman, 2012), the HADS ($n=3$) (Forman and Lincoln, 2010; Lincoln et al., 2011; Nordin and Rorsman, 2012), the General Health Questionnaire ($n=2$) (Forman and Lincoln, 2010; Lincoln et al., 2011), and the Profile of Mood States ($n=1$) (Mohr et al., 2000). Three of these studies used two scales (Forman and Lincoln, 2010; Lincoln et al., 2011; Nordin and Rorsman, 2012). Five studies (Mohr et al., 2001; Mohr et al., 2005; Ehde, et al., 2008; Baron, et al., 2011; Bombardier, et al., 2013) used the structured clinical interview for DSM-IV (SCID), and symptom-based measures [BDI (n=3) (Mohr et al., 2001, 2005b; Baron et al., 2011), Hamilton Rating Scale for Depression (HRSD) (n=3) (Mohr et al., 2001; Mohr et al., 2005; Baron et al., 2011), Centers for Epidemiologic Studies Depression Scale (CES-D) ($n=1$) (Ehde et al., 2008), and the Patient Health Questionnaire-9 (PHQ-9) ($n=1$) (Bombardier et al., 2013)]. The remaining trial used solely the Schedule for Affective Disorders and Schizophrenia to diagnose depression (Schiffer and Wineman, 1990). The single trial reporting anxiety as the primary outcome used the SCID to diagnose a blood-injection-injury specific phobia (Mohr et al., 2005a).

The active treatment phase of all interventions ranged in duration from 6 to 16 weeks (median: 12, percentile25-percentile 75: 8–15) (Table 1). The psychological interventions employed included cognitive behavioral therapy (CBT): i.e. group or individual; computerized, telephone, or in person; $n=8$), acceptance and commitment therapy, and telephone-delivered physical activity counseling (with motivational interviewing). The comparator groups were most often treatment as usual ($n=2$) or wait-list control ($n=4$). The two pharmacological interventions compared paroxetine or desipramine to placebo. The single trial combining psychological and pharmacological interventions used sertraline, CBT, and supportive-expressive group therapy.

Instruments used to assess outcomes varied across studies, including those for depression or anxiety, fatigue, quality of life, and disease-specific outcomes (e.g. disability) (Table 1). The most commonly used tools to assess changes in depression were the BDI

Table 2
Abstract only studies.

Author (year)	Study information	Psychiatric comorbidity information	Intervention			Outcomes			
			Intervention	**Comparator**	**Duration**	**Primary outcome**	**Secondary outcomes**	**Outcome measures**	**Tolerability**
Bogosian (2014)	**Study design** Randomized controlled trial **Disease course** Primary progressive MS Secondary progressive MS	Distress	**Psychological** Mindfulness-based intervention *Group Therapy*	Waitlist control	8 weeks			Difference in mean scores	
Fischer (2013)	**Study design** Randomized controlled trial **Age**: 18–65	Self-reported need for depression therapy	**Psychological** Mindfulness-based intervention *Internet-based (Deprexis)*	Waitlist control	9 weeks	Beck Depression Inventory-II		Difference in scores	Discontinuation rate
Gaede (2013)	**Study design** Randomized controlled trial		**Psychological** Deep transcranial magnetic stimulation *Left Prefrontal Cortex or Motor Cortex*	Sham control	18 sessions over 6 weeks	Beck Depression Inventory	Fatigue Severity Scale	Difference in scores	
Kiropoulos (2014)	**Study design** Randomized controlle d trial **Disease course** Relapsing remitting MS	Experiencing depressive symptoms	**Psychological** Cognitive behavioral therapy *Tailored* **Provider delivering intervention** Clinical Psychologist	Treatment as usual	8 sessions			Difference in scores	
Kontou (2014)	**Study design** Randomized controlled trial	**Screening tool** Hospital Anxiety and Depression Scale General Health Questionnaire-12	**Psychological** Adjustment therapy *Individual*	Adjustment therapy *Group*		Hospital Anxiety and Depression Scale General Health Questionnaire-12			
Verrall (2012)	**Study design** Randomized controlled trial	**DSM Classification** Major depression Dysthymia	**Psychological** Physical activity counseling *Primarily by telephone*	Waitlist control	12 weeks			Difference in mean scores Prediction of 12-week outcomes	

Table 3
Ongoing clinical trials.

Lead investigator (status)	**Study information**	**Psychiatric comorbidity information**	**Intervention**			**Outcomes**			
			Intervention	**Comparator**	**Duration**	**Primary outcome**	**Secondary outcomes**	**Outcome measures**	**Tolerability**
Boeschoten (Recruitment Pending) ID: NTR2772	**Study design** Randomized controlled trial **Age**: ≥ 18	**Screening tool** Beck Depression Inventory-II *Score of* ≥ 16	**Psychological** Cognitive behavioral therapy/problem solving therapy *Online*	NR	5 weeks	Beck Depression Inventory-II Inventory of Depressive Symptomatology Hospital Anxiety and Depression Scale	Beck Anxiety Inventory Hospital Anxiety and Depression Scale Fatigue severity scale EQ-5D WQ-VAS		
Cooper (Recruitment Completed) ID: NCT00678496	**Study design** Randomized controlled trial **Age**: ≥ 18	**Screening tool** Beck Depression Inventory-II *Score of* ≥ 14 *on at least 2 occasions*	**Psychological** Cognitive behavioral therapy *In person*	Cognitive behavioral therapy *Computer-based at home* Treatment as usual	8 weeks	Beck Depression Inventory-II Patient Health Questionnaire-9	Generalized Anxiety Disorder-7 Short Form-36	Difference in mean scores	
Meyers (Recruitment Terminated) ID: NCT00151294	**Study design** Randomized controlled trial **Age**: ≥ 18	Mild to moderate depressive symptoms, with or without emotional lability	**Pharmacologic** Escitalopram oxalate	Placebo					
Nazanin (Recruitment Complete) ID: IRTC201405188323N8	**Study design** Randomized controlled trial	“Beck Criteria”	Yoga	Aquatic training	2 months	“Beck”	Fatigue severity scale		
Salari (Recruitment Completed) ID: IRCT2012081010550N1	**Study design** Randomized controlled trial	**Screening tool** Beck Depression Inventory *Score of* ≥ 19	Zinc Sulfate	Placebo	12 weeks	Beck Depression Inventory			
Shinto (Recruitment Completed) ID: NCT00122954	**Study design** Randomized controlled trial **Disease course** Relapsing remitting MS **Age**: 18–65	**Screening tool** Montgomery–Asberg Depression Rating Scale *Score of* ≥ 11 *&* ≤ 30	Fish Oil concentrate	Placebo oil	3 months	Montgomery–Asberg Depression Rating Scale	Short Form-36	50% improvement in scores	

Note: NR= Not reported.

($n=7$) (Larcombe and Wilson, 1984; Schiffer and Wineman, 1990; Mohr et al., 2001; Mohr et al., 2005b; Baron et al., 2011; Cooper et al., 2011; Lincoln et al., 2011), the HRSD ($n=6$) (Larcombe and Wilson, 1984; Schiffer and Wineman, 1990; Mohr et al., 2001; Ehde et al., 2008; Baron et al., 2011; Bombardier et al., 2013), and the HADS ($n=4$) (Mohr et al., 2005b; Forman and Lincoln, 2010; Baron et al., 2011; Lincoln et al., 2011). Most studies ($n=10$) used more than one scale. The single trial on anxiety used clinical judgment and successful self-administration of an injection to assess change between visits (Mohr et al., 2005a).

3.4. Risk of bias assessment

Of the 13 included studies, 11 had an unclear risk of bias (Appendix C). We adjudicated one trial (Mohr et al., 2001) as having a high risk of bias in two domains (allocation concealment and incomplete outcome data), and one (Mohr et al., 2005a) having a high risk of bias in the allocation concealment domain. We most often adjudicated a low risk of bias in the incomplete outcome data, blinding, and sequence generation domains.

3.5. Primary outcomes

3.5.1. Depression

The severity of depression scores improved in nine psychological studies of depression treatment (SMD: −0.45[95%CI: −0.74, −0.16]) (Fig. 2a). Significant heterogeneity existed between estimates (I^2: 53%, Q p -value = 0.03). The SMD of depression scores in psychological trials did not differ when the data were evaluated in subgroups comparing diagnosis of depression as clinician-rated or self-report ($p=0.69$), or comparing if the intervention was CBT versus another therapy ($p=0.91$). One trial was an outlier, with an estimate five times as large as the others (Larcombe and Wilson, 1984); after removing this trial, the estimated heterogeneity based on I^2 was 0% (Q p -value = 0.89), and psychological interventions maintained a positive effect (SMD: −0.34[95%CI: −0.53, −0.16]). Psychological trials with inactive comparators (e.g. usual care, waitlist control) resulted in an improvement in depressive symptoms (SMD: −0.63[95%CI: −1.07, −0.19]) (Fig. 2b), while those with an active comparator showed no improvement (SMD: −0.18[95% CI: −0.49, 0.13]) (Fig. 2c).

Depression severity improved in the three pharmacological studies of depression treatment in MS (SMD: −0.45[95%CI: −1.07, −0.20]) (Fig. 3a). Heterogeneity was low (I^2 10%, Q p-value = 0.33). There was an improvement in depressive symptoms in trials using an inactive comparator (SMD: −0.87[95%CI: −1.38, −0.35]) (Fig. 3b), though symptoms did not improve in the single trial using an active comparator (SMD: −0.24[95%CI: −0.91,0.43]) (Fig. 3c).

3.5.2. Level of evidence

For the primary outcome of depression, we considered the quality of evidence, based on GRADE ratings, to be moderate (Appendix D). The quality of evidence was moderate in the trial of self-injection anxiety.

3.6. Secondary outcomes

3.6.1. Depression

Two studies (Ehde et al., 2008; Bombardier et al., 2013), one pharmacological and one psychological, reported the proportion of patients achieving a 50% reduction in symptoms. The odds of having a 50% reduction in symptoms did not differ between groups in either trial. We did not pool these due to the differences in the intervention employed.

3.6.2. Anxiety

Anxiety severity did not significantly improve in three psychological trials (Forman and Lincoln, 2010; Lincoln et al., 2011; Nordin and Rorsman, 2012) of depression treatment (SMD: −0.34 [95%CI: −0.84, 0.15]). The amount of heterogeneity present between studies was I^2: 52%, Q p-value = 0.13.

The single trial (Mohr et al., 2005a) of psychological treatment for anxiety was a trial of injection anxiety and showed a non-significant improvement in self-injection anxiety at the end of treatment ($p=0.058$).

3.6.3. Fatigue

In two pharmacological trials (Mohr et al., 2003; Ehde et al., 2008), fatigue scores did not improve (SMD: −0.70[95%CI: −1.17, −0.23]). This model resulted in no statistical heterogeneity – I^2: 0%, Q p-value = 0.85.

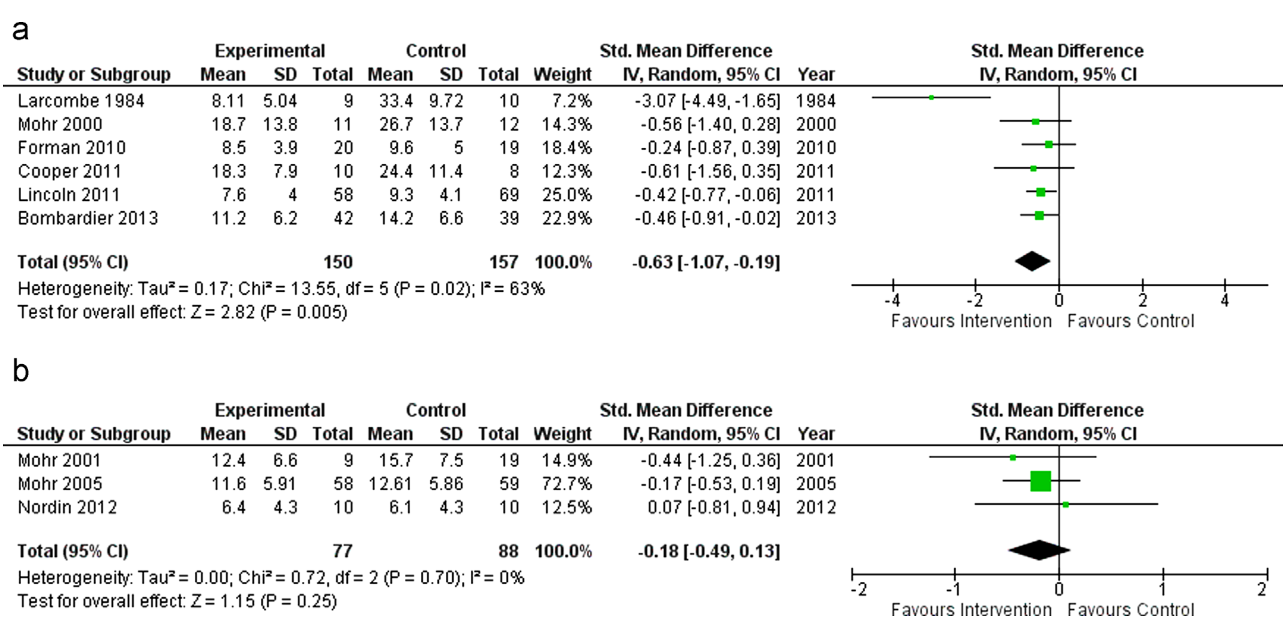

Fig. 2

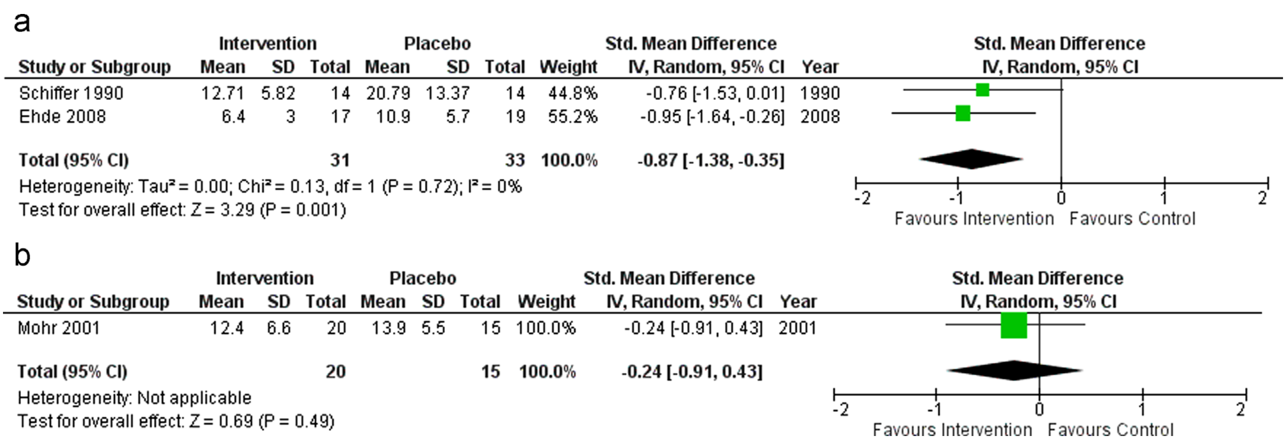

Fig. 3

3.6.4. *Quality of life*

Two trials measured physical and mental aspects of quality of life (Ehde et al., 2008; Forman and Lincoln, 2010), while a third trial used an overall quality of life measure (Lincoln et al., 2011). Physical and mental quality of life, did not significantly improve in two trials (SMD: −0.34[95%CI: −0.86, 0.18]; SMD: −0.30[95%CI: −0.76, 0.16]). There was no significant heterogeneity between estimates of both physical and mental quality of life (Q *p*-values = 0.25 and 0.83, respectively). With the overall quality of life measure, the pooled quality of life SMD (including physical quality of life studies) was −0.21 (95%CI: −0.49, 0.07), and including mental quality of life studies was −0.19 (95%CI: −0.47, 0.08).

3.7. *Tolerability*

Adverse medication effects were reported in two pharmacological intervention studies(Table 4). In the trial comparing desipramine to placebo, the overall prevalence of adverse events was higher in the desipramine group than the placebo group (Schiffer and Wineman, 1990). Dry mouth was reported equally in both groups. Ehde and colleagues found that all adverse events were more common in the paroxetine group, relative to placebo, including nausea, headache, dry mouth, and sexual dysfunction (Ehde et al., 2008). Eleven studies reported the proportion of dropouts; the proportion dropping out in the treatment arm ranged from 0.0% to 31.3% (median[IQR] 11.6% [17.7%]), and in the control arm from 0.0% to 33.3% (median[IQR] 14.6% [15.0%]).

Table 4
Multiple sclerosis study adverse effects.

Study	Drop out (%)				Adverse effect	Rate of adverse effects (%)	
Bombardier (2013)	*Counseling*		*Wait List*				
	5.0		19.0				
Cooper (2011)	*CBT*		*Treatment as usual*				
	16.7		33.3				
Ehde (2008)	*Paroxetine*		*Placebo*			*Paroxetine*	*Placebo*
	22.7		5.0		Nausea	57.1	5.0
					Headache	47.6	10.0
					Dry Mouth	47.6	35.0
					Sexual Dysfunction	23.8	5.0
Forman (2010)	*CBT*		*Wait List*				
	0.0		5.0				
Kratz (2014)	*Counseling*		*Wait List*				
	5.0		19.0				
Lincoln (2011)	*Counseling*		*Wait List*				
	19.5		10.1				
Mohr (2000)	*CBT*		*Treatment as usual*				
	31.3		25.0				
Mohr (2001)	*CBT*	*SEGT*		*Sertraline*			
	5.0	18.0		29.0			
Mohr (2005)	*CBT*		*Telephone Support*				
	26.7		20.0				
Mohr (2005)	*CBT*		*SEFT*				
	6.5		7.8				
Schiffer (1990)	*Desipramine*		*Placebo*			*Desipramine*	*Placebo*
	0.0		0.0		Any adverse event	85.7	50.0
					Postural Hypotension		
					Dry mouth	35.7	35.7
					Constipation		
					Jitteriness		
					Edema		
					Dizziness		
					Rash		

CBT: Cognitive Behavioral Therapy; SEGT: Supportive-Expressive Group Therapy; SEFT: Supportive Emotion-Focused Therapy.

3.8. Publication bias

We did not detect significant publication bias in the pooled SMD of depression scores in pharmacological or psychological trials by Begg's or Egger's tests. The funnel plots appeared symmetrical upon visual inspection. The funnel plots of all secondary outcomes appeared symmetrical and no publication bias was identified on Begg's or Egger's tests.

4. Discussion

We reviewed 13 randomized controlled trials reporting interventions for treating depression and anxiety in MS, predominantly utilizing CBT for depression. Pharmacologic and psychological interventions for depression in depressed persons with MS were generally effective in reducing depressive symptoms.

Most trials focused on psychological interventions for depression were effective in improving symptoms. A meta-analysis of nine well-controlled trials of CBT for major depression in a non-medical sample found a small effect (Hedges' $g=-0.28$; 95%CI: -0.45, -0.12) of CBT (Lynch et al., 2010). Another meta-analysis of psychological treatment for depression in patients with medical conditions reported a moderate effect (Cohen's $d=0.42$, 95%CI: $0.27-0.58$) on improving outcomes, relative to the control group (van Straten et al., 2010). The effect size (SMD= -0.45) found in our study is consistent with this finding, suggesting psychological interventions are at least moderately effective in treating depression in medical conditions. There was a relative dearth of studies investigating pharmacological interventions for depression in MS.

A Cochrane review of pharmacological treatment of depression in MS found no effect in the three trials studied here; the authors of this review analyzed categorical outcomes (e.g. reduction of scores by 7 points or more, any reduction in score), rather than continuous outcomes (Koch et al., 2011), which may explain this difference in conclusions. Few studies investigated pharmacological interventions for depression in MS but they demonstrated effectiveness in reducing depressive symptoms. In the general population, selective serotonin reuptake inhibitors (SSRIs) (relative risk (RR) for improvement: 1.37; 95%CI: 1.21, 1.55) and tricyclic antidepressants (RR for improvement: 1.26; 95%CI: 1.12, 1.42) can be effective in improving depression when compared to placebo (Arroll et al., 2005). Interestingly, the pharmacotherapy studies we reviewed used medications not commonly prescribed for the treatment of depression, which may be poorly tolerated in the MS population. For example, tricyclic antidepressants such as desipramine have anticholinergic side-effects that may exacerbate urinary retention, cognitive changes, and fatigue (Politte et al., 2008; Campbell et al., 2009; Gray et al., 2015). The trial using paroxetine (an SSRI) reported high levels of adverse effects, including nausea, headache, and dry mouth, consistent with its anticholinergic properties. Additional studies using antidepressants that may have better tolerability are needed in the MS population, pointing to the need to consider the adverse effect profile, and concomitant medications when choosing therapy. A recent meta-analysis reported that acute psychological therapy was as effective in preventing depression relapse as sustained pharmacotherapy, and more effective than when pharmacotherapy was discontinued within 6–18 months of initiation (Cuijpers et al., 2013). For these reasons, psychological interventions may be of particular value in the MS population.

Depression was measured using a large number of tools, with little consistency between studies. A recent systematic review of the prevalence of psychiatric comorbidities in MS identified eight different tools used to detect depression; the most common being the BDI (Beck et al., 1961, 1996; Beck and Steer, 1984), HADS (Zigmond and Snaith, 1983), and CES-D (Radloff, 1977). For instruments to be useful in measuring depression, they must be clinically relevant, valid, reliable, and sensitive to change. The NINDS Common Data Elements suggests using the CES-D, but this recommendation was not based on a formal comparison of the psychometric properties of instruments. The American Academy of Neurology (AAN) published guidelines on the assessment and management of psychiatric disorders in MS, specifically evaluating the evidence-base of tools for assessing symptoms and making diagnoses (Minden et al., 2014). They determined that the BDI and a two-question screen may be effective for identifying individuals with depression, but that evidence is insufficient to support or refute the use of the CES-D. Further complicating this issue is the use of self-report and clinician-administered tools to measure depression. The clinical relevance of changes on self-reported symptom-based scales needs to be interpreted in the context of the magnitude of change and severity of symptoms before treatment. The larger effect sizes of clinician-administered tools that we found are similar to those reported in a meta-analysis on effect sizes of tools in trials of psychotherapy for depression (Cuijpers et al., 2010). Our findings suggest that these tools may be more sensitive in the MS population, though they may also be more prone to bias if the clinician performing the assessment was not blinded (as was true for some of the psychological treatment trials reported here). There is a lack of agreement regarding which tool to use to identify depression in MS. Until such time as the psychometric properties of these tools are compared directly and one tool becomes the standard, comparisons of the effectiveness of interventions will be difficult.

As with depression, anxiety negatively impacts quality of life (Dubayova et al., 2013), physical disability (Jones et al., 2014), and sleep quality (Vitkova et al., 2014) in MS. Thoughnumerous studies show that anxiety is almost as common as depression in persons with MS (Korostil and Feinstein, 2007; Beiske et al., 2008; Marrie et al., 2013), we found only one underpowered trial that examined an intervention to reduce anxiety for self-injection (Mohr et al., 2005a); until recently, disease-modifying therapies for MS were only available by injection. We found no controlled studies on the effectiveness of psychological or pharmacological treatments of the most common anxiety disorders in persons with MS, suggesting a need for research in this area. In three of the psychotherapy intervention trials for depression here was no apparent benefit on anxiety reduction when this was examined as an outcome.

We found robust effects of pharmacological treatments in improving symptoms of fatigue in persons with depression. Fatigue is one of the most prevalent symptoms of MS (Minden et al., 2006), and is often considered to be the worst symptom of disease (Fisk et al., 1994). Similarly, fatigue is a common symptom of depression (Marin and Menza, 2004); the overlap of depressive and MS symptoms, along with medication effects, may guide the choice of tool to measure depression. The effect of depression treatments on fatigue in MS warrants further study. Note that depression and anxiety are typically long-term problems and it would be helpful to have more studies with longer follow up periods to understand treatment effectiveness and acceptability over the long term.

Our review was guided by systematic review methodology and studied numerous databases with limited publication restrictions. The strength of the evidence based on the GRADE rubric was rated as moderate in favor of treatment for depression. However, the strength of the inferences made in this review is limited by several factors. While some of the depression trials also measured anxiety symptoms, none explicitly reported comorbidity with respect to proportions of those with an anxiety disorder or elevated anxiety symptoms. The trials also did not evaluate whether the presence of anxiety symptoms influenced the likelihood of response to treatment of depression. Since our analyses did not reveal a reduction of anxiety symptoms with depression interventions, different interventions may be required to achieve anxiety symptom reduction in persons with depression and MS. The risk of bias in the depression trials was rated as unclear due to a lack of reporting on important bias considerations in the primary literature, but 11 of the trials were rated as moderate to high quality lending us to believe these therapies can be used. Psychological trials were ranked lower on the risk of bias and quality of evidence scales because of a lack of blinding inherent in their design. Blinding in these trials may not be feasible or warranted, and methods have been proposed to mitigate these issues in trial design and quality assessment (Boutron et al., 2007). It is important to consider the type of control group used in controlled trials (Mohr et al., 2014; Watts et al., 2015). Pill placebo is an appropriate control for pharmacologic trials, but does not always work for psychological trials as some participants prefer to avoid pharmacotherapy. Waitlist control is an appropriate control for psychological trials, but it produces less change than pill placebo and treatment as usual (Mohr et al., 2009). These factors should be considered when comparing pharmacologic and psychological treatments using the SMD statistic. There was significant heterogeneity between the psychological trials of depression treatments, though after removal of an outlier the heterogeneity was minimized. Finally, eight trials restricted their sample to those persons with relapsing-remitting MS, reducing the generalizability of these findings to the progressive MS population.

We described existing controlled interventions for depression and anxiety in MS, most of which focused on psychological interventions. Those trials that examined pharmacotherapy employed medications that may not be ideal for use in MS. Pharmacologic and psychological interventions reduce symptoms of depression in people with MS. Further studies using SSRI, selective norepinephrine reuptake inhibitors, and newer antidepressant medications are required to determine optimal therapy for depression and anxiety. The benefits of psychological therapies indicate this approach should be more widely considered and accessible for persons with MS.

Funding

This study was funded (in part) by the Canadian Institutes of Health Research (CIHR), a Don Paty Career Development Award from the MS Society of Canada (to R.A.M.), a Manitoba Research Chair from Research Manitoba (to R.A.M., J.S.), and the Bingham Chair in Gastroenterology (to C.B.).

Acknowledgment

Thanks to Michelle Fiander, MLIS (Fiander Consulting) and Tania Gottschalk, B.A., M.Ed., M.Sc. (Librarian, University of Manitoba), who provided assistance regarding the development of the search strategies for this review. Thank you to Dr. Nadina Lincoln and Dr. Ia Rorsman for providing additional information and data from their original publications to allow meta-analyses to be conducted. Thank you to Dr. Reza Vosoughi for his help in journal article translation. We would like to acknowledge the members of the CIHR team on “Defining the burden and managing the effects of psychiatric comorbidity in chronic immunoinflammatory disease”: Dr. Ruth Ann Marrie, M.D., Ph.D. (University of Manitoba), Dr. Charles Bernstein, M.D. (University of Manitoba), Dr. Lindsay Berrigan, Ph.D. (St. Francis Xavier University), Dr. James Bolton, M.D. (University of Manitoba), Dr. John Fisk, Ph.D. (Dalhousie University), Dr. Lesley Graff, Ph.D. (University of Manitoba), Dr. Carol Hitchon, M.D., M.Sc. (University of Manitoba), Dr. Alan Katz, M.B., Ch.B. (University of Manitoba), Dr. Lisa Lix, Ph.D. (University of Manitoba), Dr. James Marriot, M.D., M.Sc. (University of Manitoba), Dr. Scott Patten, M.D., Ph.D. (University of Calgary), Dr. Jitender Sareen, M.D. (University of Manitoba), Dr. John Walker, Ph. D. (University of Manitoba), Dr. Ryan Zarychanski, M.D., M.Sc. (University of Manitoba), Dr. Alexander Singer, M.D. (University of Manitoba), and Dr. Christine Peschken, M.D., M.Sc. (University of Manitoba).

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.msard.2015.10.004.

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