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Differential effects of behavioral interventions with a graded physical activity component in patients suffering from Chronic Fatigue (Syndrome): An updated systematic review and meta-analysis

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HIGHLIGHTS

- Interventions including physical activity have beneficial effects on chronic fatigue.
- The number of trials is modest and there is heterogeneity between them.
- Type of setting and provider of treatment moderate fatigue severity effect sizes.
- Minimal direct contact interventions are promising.

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ABSTRACT

An updated systematic review and meta-analysis was conducted to (1) evaluate the effects of behavioral and psychological interventions containing a graded physical activity component upon fatigue severity, physical functioning, physical activity and psychological distress, and to (2) examine potential moderator effects of trial characteristics (type of control, setting, provider, length of treatment, psychological component, flexibility in physical activity, and minimal face to face patient–provider contact). Pertinent content of selected studies was extracted and rated on a scale of methodological quality. Sixteen randomized controlled trials (N = 2004) were included in the meta-analyses. Significant small to medium effect sizes (Hedge's $g = 0.25$ to $g = 0.66$) were found for all outcomes at post-treatment (M = 5.2 months) and follow-up (M = 11.7 months), with the exception of physical activity at post-treatment ($g = 0.11$). The largest effects were found for fatigue severity ($g = 0.61$ to $g = 0.66$). Subgroup analyses revealed that minimal contact interventions had additional beneficial effects upon fatigue ($g = 0.96$) and depression ($g = 0.85$). Interventions provided by psychologists-psychotherapists and interventions conducted in secondary–tertiary settings also resulted in more beneficial effects on fatigue. We found some indication of publication bias. The small number of studies and variability between them are limitations of this study. Future research should explore additional moderating effects in order to improve the effectiveness of interventions.

Contents

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1. Introduction

Chronic Fatigue (or Idiopathic Chronic Fatigue—ICF) is a condition characterized by the presence of new onset unexplained persistent fatigue (lasting for at least 6 months) that is not alleviated by rest, is debilitating and leads to significant functional impairment. Commonly, these patients experience additional rheumatologic and neuropsychiatric symptoms (Afari & Buchwald, 2003; Lehman, Lehman, Hemphill, Mandel, & Cooper, 2002). When at least four of these symptoms are present (i.e. unrefreshing sleep, lengthy malaise after exertion lasting for over 24 h, impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain without swelling or redness and headaches of a new type or severity) it is diagnosed as Chronic Fatigue Syndrome (CFS; or Myalgic Encephalomyelitis—ME) according to the widely used Centres for Disease Control and Prevention (CDC) criteria (Fukuda et al., 1994). Another set of diagnostic criteria commonly used is the Oxford Criteria (Sharpe, 1991), which differs from the CDC criteria in that the Oxford Criteria requires mental fatigue to be present, but do not require the presence of additional somatic symptoms. A panel of experts has recently proposed a new international consensus criterion (Carruthers et al., 2011), which does not require the presence of fatigue for at least 6 months, but requires the presence of post-exertional malaise as well as the presence of at least three symptoms related to neurological impairments (e.g. headaches), three immune, genito-urinary symptoms and/or gastro-intestinal (e.g. nausea), and one symptom related to energy production/transport impairments (e.g. subnormal body temperature). In addition, diagnosis of CFS is exclusionary, i.e. thorough full medical history and examinations are first conducted to rule out other medical conditions that could explain the symptoms.

The prevalence of CFS/ME is reported to be in between 0.007% and 2.6% in general population samples, varying according to several factors such as the criteria used to diagnose CFS/ME (Ranjith, 2005). It is more common in younger adults and among women (Afari & Buchwald, 2003). In terms of prognosis, full recovery rates are low, but it is common for patients to experience an improvement in symptom severity (Cairns & Hotpof, 2005). CFS/ME has been associated with a high use of health care resources (McCrone, Darbishire, Ridsdale, & Seed, 2003; Sabes-Figuera et al., 2010). The functional impairment and inability to work commonly found in these patients represent an important socio-economic burden (Fernandez et al., 2009; Sabes-Figuera et al., 2010).

1.1. Physical activity and chronic fatigue

Several studies emphasize the fact that lack of physical activity and prolonged physical inactivity (rest) can result in physical deconditioning as well as in other physiological and psychosocial consequences that may perpetuate fatigue and physical disability (Clark, Clark, & White, 2005; Fulcher & White, 2000; Nijs, Wallman, & Paul, 2011b). It has therefore been recommended that CFS/ME patients engage in physical activity/exercise instead of refraining from it (National Institute for Health and Clinical Excellence, 2007). Physical activity that is too vigorous can however perpetuate fatigue symptoms (Nijs, Paul, & Wallman, 2008; Nijs, Wallman, & Paul, 2011b). Patients' perceptions and expectations with respect to symptom exacerbation as a consequence of physical exertion can lead to fear of physical activity (Clark et al., 2005; Nijs et al., 2008; Prins, Van der Meer, & Bleijenberg, 2006) and explain the reduced levels of physical activity found in patients with chronic fatigue (Nijs et al., 2011a). Not surprisingly, it is common to find a “boom-and-bust pattern”

(or all-or-nothing behavior) in these patients, which is the systematic alternation between periods of over-activity (when feeling good) and, as a consequence of that, feeling extremely fatigued and having to rest for longer periods of time. For these reasons, physical activity should be balanced, gradually introduced and offered with caution to CFS/ME patients (Clark et al., 2005; National Institute for Health and Clinical Excellence, 2007; Nijs, Wallman, & Paul, 2011b).

Graded Exercise Therapy (GET) has been recommended as a treatment for CFS/ME patients (National Institute for Health and Clinical Excellence, 2007). GET is based on the assumption that aerobic exercise (e.g. brisk walking) or physical activity (e.g. housework, gardening) must be initiated at a level (intensity and frequency) that doesn't exacerbate symptoms and must be gradually increased until patients reach an optimal level of activity. GET follows the exercise prescription guidelines of the American College of Sports Medicine (2013), tailored to each patient's initial level of physical capacity. Most GET interventions follow a similar protocol (Fulcher & White, 1998). GET is usually delivered by an exercise physiologist or physical therapist, and consists of supervised aerobic exercise sessions and/or home-based aerobic exercise prescription (e.g. walking). GET focuses on avoiding overexertion by advising patients not to exceed the recommended levels of physical activity/exercise. At the same time, in most GET interventions patients are encouraged not to reduce or stop doing physical activity/exercise when symptoms get worse. Recent approaches to GET have advocated that flexibility in graded exercise programs according to individual tolerance levels can be beneficial for CFS/ME patients. This implies that exercise can be reduced or even stopped when symptoms get worse (Nijs et al., 2008; Wallman, Morton, Goodman, Grove, & Guilfoyle, 2004). A Cochrane review (Edmonds, McGuire, & Price, 2004), and a recent meta-analysis (Castell, Kazantsis, & Moss.Morris, 2011) reported beneficial effects of GET on fatigue severity and functional impairment in patients with chronic fatigue. GET is also used in the treatment of other fatigue-related syndromes such as Fibromyalgia (ACSM, 2013; Carville et al., 2008).

Because of the benefits of physical activity for patients suffering from CFS/ME, a large number of Cognitive Behavioural Therapy (CBT) trials have incorporated a graded physical activity/exercise component. The primary focus of CBT for these patients is on challenging cognitions and behaviors related to the perpetuation of fatigue (e.g. somatic illness attributions). Patients are encouraged to engage in a gradual increase of physical activity and to balance daily activities (e.g. activity and rest). In addition, sleep management is usually addressed and patients are supported to set goals for functional recovery. The positive effects of CBT upon chronic fatigue management have been shown in a Cochrane review (Price, Mitchell, Tidy, & Hunot, 2008) and in two meta-analyses (Castell et al., 2011; Malouff, Thorsteinsson, Rooke, Bhullar, & Schutte, 2008). Some CBT approaches distinguish between relative-active patients (characterized by an alternation of over-activity and rest) and low-active patients and intervene accordingly (Bleijenberg, Prins, & Bazelmans, 2003).

Another recent approach to CFS is multidisciplinary rehabilitation, consisting of a combination of treatments such as CBT, a gradual increase in physical activity/exercise, balancing daily physical activities and rest according to the patients' symptoms, increasing awareness of the body and its relation to psychological well-being, and social/functional reintegration, tailored to patients' needs and goals (Cox, 1999; Thomas, Sadlier, & Smith, 2008; Vos-Vromans et al., 2012). As there is a lack of evaluation studies of this approach, it is difficult to draw conclusions with respect to its effects.

1.2. Previous meta-analyses

Two meta-analyses tried to compare the efficacy of physical activity interventions to psychological interventions in patients with chronic fatigue. The first one, conducted by Malouff et al. (2008) reviewed the effects of CBT, including 12 trials (1371 patients). Overall, there was a medium effect size ($d = 0.48$) for fatigue. A comparison of interventions containing only a (graded) activity component to interventions containing, next to activity, a cognitive component, did not yield significant differential effects ($d = 0.60$ and $d = 0.43$, respectively). Other moderator analyses (treatment format, type of comparison group, sample type, diagnostic criteria used, number of hours of treatment, number of sessions, and number of months of follow-up) also did not result in significant differential effects.

The meta-analysis by Castell et al. (2011) compared the effects of GET ($n = 5$) vs. CBT ($n = 16$) trials upon the following outcomes: fatigue severity, functional impairment, and psychological distress (anxiety and depression). Both types of intervention presented similar overall post-treatment effects ($g = 0.28$ and $g = 0.33$, respectively) for CFS patients. The overall effect sizes for anxiety and depression were however higher within the CBT subset. In addition, the authors also examined potential moderator effects of study characteristics that were previously analyzed in the Malouff et al. (2008) meta-analysis (type of comparison group, treatment format, number of hours of treatment, and diagnostic criteria used) as well as treatment setting, and treatment duration. Number of treatment hours was a significant predictor of treatment effects, but accounted only for a small proportion of the variance of the effects (Castell et al., 2011).

There are a number of limitations in both meta-analyses (Castell et al., 2011; Malouff et al., 2008) that are worth mentioning. First, in the Malouff et al. (2008) study the authors aimed to evaluate the effects of CBT interventions, but also considered trials with an emphasis on GET as a type of CBT as they included them in the overall effect. Second, in the comparison between “activity treatments” and “activity plus cognitive treatments”, the authors included studies in the “activity treatments” category that had a cognitive component (e.g. Powell, Bentall, Nye, & Edwards, 2001). In the meta-analysis conducted by Castell et al. (2011), this same trial was included in the group of CBT trials. Third, in the Castell et al. (2011), potential moderators were analyzed only for the group of CBT trials, due to low heterogeneity found in the GET group. In addition, several of the CBT trials included graded exercise components, limiting the conclusions that can be drawn from a comparison between CBT and GET interventions. Finally, Malouff et al. (2008) did not distinguish between post-treatment and follow-up results and only post-treatment effects were presented in Castell et al. (2011).

1.3. Focus of the systematic review and meta-analysis

In this study, we intend to address some of these limitations and extend the scope of the meta-analysis in the following ways. First, no meta-analysis has yet assessed the effects of behavioral and psychological interventions on physical activity among CFS/ME patients, which is a key behavior targeted in interventions for chronic fatigue management. Second, there are a number of recently published trials assessing the effects of GET, CBT with a graded exercise component, and rehabilitation approaches that were not included in the previous reviews and meta-analyses. Third, several interventions targeting CFS/ME patients present specific treatment characteristics that have not yet been taken into account as moderators: (1) flexibility in physical activity/exercise levels and goals, in accordance with patients' exercise tolerance (Nijs, Wallman, & Paul, 2011b); and (2) minimal contact interventions as compared to more intensive interventions. Based on recent systematic reviews on minimal contact and self-help treatments (Ahl, Mikocka-Walus, Gordon, & Andrews, 2013; Cuijpers, Donker, van Strale, Li, & Andersson, 2010; Haug, Nordgreen, Ost, & Havik, 2012; Pajak, Lackner, & Kamboj, 2013), we considered minimal-contact interventions as self-management interventions that consisted of a maximum of three initial face-to-face sessions followed by remote additional guidance and feedback during the treatment period (e.g. by email, telephone). Usually these interventions also provide patient manuals with information and assignments related to disease management. Most CBT and GET interventions are typically resource-intensive, as they usually require considerable direct provider-patient contact. Recent

reviews have revealed that minimal contact interventions are promising for the treatment of various psychological (e.g. Haug et al., 2012) and physical symptoms (e.g. Pajak et al., 2013). In addition, recent controlled trials of minimal contact interventions in CFS/ME showed promising results (e.g. Tummers, Knoop, van Dam, & Bleijenberg, 2012).

The aims of the current systematic review and meta-analysis are thus:

1— To determine the overall effect of behavioral interventions with a graded physical activity/exercise component on fatigue severity, physical functioning/functional impairment, physical activity and physical capacity, as well as psychological distress (anxiety and depression); both at post-treatment and at follow-up, among patients with ICF and CFS/ME.
2— To examine whether the effects on these outcomes are moderated by the type of care provided to the control condition, the treatment setting, the treatment provider, and the length of treatment.
3— To examine if treatment effects are influenced by the presence of a psychological component in the treatment, by flexibility in physical activity levels or goals, and by the amount of contact between provider and patient (intensive versus minimal contact).

2. Methods

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (Liberati et al., 2009) statement and APA's Meta-Analysis Reporting Methods (APA Publications and Communications Board Working Group on Journal Article Reporting Standards, 2008).

2.1. Eligibility criteria

2.1.1. Types of participants

Studies were included if they were conducted in adult patients presenting (Idiopathic) Chronic Fatigue or Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME).

2.1.2. Types of interventions

Studies had to include an arm of a behavioral and/or psychological intervention with a graded physical activity/exercise component, targeting chronic fatigue management.

2.1.3. Types of comparisons

Studies had to include a control condition, consisting of usual care, waiting list control, or another type of intervention (e.g. relaxation).

2.1.4. Types of outcomes

Studies had to present statistical data allowing the calculation of effect sizes (in the published study or provided by the author(s) upon request), on at least one of the following outcomes — fatigue severity, functional impairment/physical functioning, physical activity and/or physical capacity, and psychological distress (depression and/or anxiety), measured at baseline (pre-treatment), at post-treatment and/or at follow-up.

2.1.5. Types of studies

Studies were included if they were randomized controlled trials (RCTs) published in peer review journals in English.

There were no restrictions with respect to the type of diagnostic criteria used, setting, format and source of delivery of the intervention, as well as with respect to the length of the intervention and follow-up measurement point(s).

2.2. Search strategy and study selection

Initially, electronic databases (MEDLINE, Cochrane Database of Clinical Trials, PsychINFO and Web of Science) were searched for relevant articles published between 1988 and 2013 to coincide with the first diagnosis criteria for CFS (Holmes et al., 1988). A comprehensive search strategy was used, with the combination of the following keywords: chronic fatigue or unexplained chronic fatigue or Idiopathic Chronic Fatigue or Chronic Fatigue Syndrome or CFS or Myalgic Encephalomyelitis or ME, psychological or cognitive or behavior or CBT or graded exercise therapy or exercise or physical activity or aerobic or rehabilitation, and treatment or intervention or trial or RCT (complete search strategies can be obtained from the authors). Next, content pages of key journals were browsed (e.g. *Journal of Psychosomatic Research*). Finally, reference lists from previous review articles and included studies were hand searched to find additional studies (Appendix A).

One author (MM) and an independent researcher (AC) read the titles and abstracts retrieved. If the studies appeared to meet the inclusion criteria, full texts were obtained and reviewed by the first author (MM). A second author (SM) checked and approved the final selection of studies.

2.3. Coding of study characteristics

Characteristics from selected studies were coded using a pre-specified form developed by the authors (Complete coding form is available from the authors). The following information was extracted from each selected study: 1) bibliographic information (authors, year of publication, country and reference); 2) type of diagnostic criteria (CDC, Oxford, other); 3) sample characteristics (sample size, gender, age); 4) setting (primary care, secondary–tertiary, university setting); 5) provider (psychologist/psychotherapist, exercise physiologist, physical therapist, nurse, occupational therapist, other); 6) type of care provided to the intervention group (graded physical activity/exercise therapy, cognitive-behavioral treatment, rehabilitation treatment, other behavioral and psychological approaches); 7) type of care provided to the control group (passive control — waiting list control, treatment as usual, other; active control — relaxation/flexibility, counseling, other); 8) format of delivery (individual or group; face-to-face, telephone, email); 9) length of intervention and number of patient–provider sessions, 10) drop-out rate, 11) outcomes assessed (fatigue severity, physical functioning/impairment, physical activity, physical capacity, depression, anxiety, other); 12) measures used to assess outcomes (type and name of measure); and 13) average assessment points (baseline, post-treatment — after the termination of the treatment, follow-up — assessment conducted in a later point in time after the termination of the trial).

In addition, the following characteristics were coded: i) presence vs. absence of a psychological component within the intervention (e.g. cognitive behavioral therapy); ii) presence vs. absence of flexibility in setting physical activity/exercise levels or goals; iii) whether the intervention was a minimal or a more intensive intervention in terms of direct (face to face) contact hours. These characteristics were coded as 1 (yes) and 0 (no). (Complete coding form can be obtained from the authors).

Two researchers (MM and MJG) independently coded the potential moderators (aforementioned categories 4, 5, 6, 7, i, ii, iii). For the remaining information the first 5 trials were cross-verified. Disagreements in coding were resolved by consensus between the two coders. A third researcher (SM, VDG) resolved any remaining disagreements. The average inter-rater agreement was very good (Cohen's kappa = 0.84).

2.4. Quality and risk of bias assessment

The methodological quality of the included trials was assessed using a 29-item modified version of the Cochrane Collaboration Depression, Anxiety and Neurosis Review Group (CCDAN) quality rating scale (Lackner, Mesmer, Morley, Dowzer, & Hamilton, 2004; Moncrieff,

Churchill, Drummond, & McGuire, 2001), validated by Lackner et al. (2004). The scale assesses characteristics of both internal and external validity of trials. Each item is scored 0 (not done and/or not reported), 1 (done and/or reported to some extent) or 2 (adequately done and/or adequately reported), with the exception of items 23 (Interests declared) and 29 (Consecutive subjects), which are scored 0 or 2. Total scores range from 0 to 58; higher scores indicate higher methodological quality. Risk of bias (high/low/uncertain) was classified based on the following items from this scale: Selection bias — concealment of allocation (item 6); detection bias — blinding of assessors (item 13); attrition bias (incomplete outcome data) — information on attrition (item 16) and inclusion of drop-outs in analyses (item 19), following the guidelines contained in the Cochrane collaboration's tool for assessing risk of bias (Higgins et al., 2011).

Discrepancies in quality rating were resolved by consensus between the two coders (MM and MJG). Overall, inter-rater agreement on the 29 items of the methodological quality scale was satisfactory (Cohen's kappa = 0.68).

2.4.1. Data extraction

Effect sizes (ES) were the standardized mean difference [(mean a − mean b / pooled change SD)] with Hedge's *g* correction for small samples (Hedges, 1981). To calculate effect sizes for selected outcomes, we extracted sample sizes and baseline, post-treatment and/or follow-up means and standard deviations (SD) for the intervention and control groups. Authors of included studies were contacted when necessary to retrieve missing data in published reports. If this information remained unavailable, the following alternative information was extracted to calculate the effect sizes: 1) post-treatment and/or follow-up means, SD and sample size for each group; 2) Mean difference, 95% confidence interval and samples size for independent group comparisons 3) sample size and *p* value for independent group comparison, and 4) raw difference in means and confidence limits for independent groups. When reported in the original trials, we used data from intention-to-treat analyses. If there was more than one follow-up assessment point available, the longest period available without crossovers was chosen. This was the case for four trials (Deale, Chalder, Marks, & Wessely, 1997; Fulcher & White, 1997; Powell et al., 2001; Sharpe et al., 1996). In one study the pooled (post-treatment and follow-up) mean and SD was used for the effects of the intervention on physical activity at follow-up, as this was the only statistical information available (O'Dowd, Gladwell, Rogers, Hollinghurst, & Gregory, 2006). For the study by White et al. (2011) in which more than one intervention arm (vs. one control group) were included in the meta-analyses, composite effect sizes were computed. When several measures were reported for the same outcome (e.g. physical functioning/impairment), we chose the measure most commonly used across the studies included.

In the case of studies presenting two or more intervention arms meeting eligibility criteria, the following choices were made regarding the selection of the intervention arms for inclusion in the meta-analysis: 1) for the trial conducted by Jason et al. (2007) the *Cognitive-Behavioral Therapy* intervention arm with a graded aerobic physical activity component was selected; 2) for the trial conducted by White et al. (2011) the *Graded Exercise Therapy* and the *Cognitive behavioral Therapy* intervention arms were selected, since the other intervention arm (*Adaptive Pacing*) was not an exercise oriented intervention; 3) for the study conducted by Powell et al. (2001), there were three intervention arms differing in treatment-dose (Minimum intervention, Telephone intervention and Maximum intervention). Because there were no significant differences in the effect sizes between the three intervention arms, the less intensive arm — *Minimum Intervention* — was chosen. Regarding control comparisons, in the case of the trial conducted by Jason et al. (2007), the *Active Relaxation* condition was chosen as the control comparison due to its similarities with other control conditions included in this meta-analysis.

2.5. Data analyses

Analyses were conducted using the Comprehensive Meta-Analysis Software version 2.2 (Borenstein, Hedges, Higgins, & Rothstein, 2005). We conducted separate meta-analyses for each outcome (fatigue severity, functional impairment/physical functioning, physical activity and physical capacity, depression and anxiety) and for each measurement point (post-treatment and follow-up). All outcome variables were continuous.

Meta-analyses were conducted using the recommended random-effects model, in which the summary effect is an estimate of the mean of a distribution of effect sizes (Borenstein, Hedges, Higgins, & Rothstein, 2009); the only exceptions were the analyses for the effects of the interventions upon physical activity and physical capacity at post-treatment and follow-up, in which the fixed-effect model was used, due to the limited number of studies (<5 studies) available for the analysis (Borenstein et al., 2009). Effect sizes (ES) were the standardized mean difference with Hedge's *g* correction (Hedges, 1981), interpreted according to Cohen's (Cohen, 1992) guidelines (values of 0.20, 0.50 and 0.80 correspond to small, medium and large effect sizes). Z-values and corresponding *p*-values were considered as indicator of the significance of the effect. We also inspected the standard residuals (i.e. how much each study differs from the overall effect) for outliers (>1.96).

Meta-analyses were inspected for heterogeneity using: 1) Cochran's *Q* statistic (Cochran, 1954), for which a significant *p*-value (<.05) demonstrates that studies don't share a common effect size (i.e. there is heterogeneity in the effect sizes between studies); and 2) I^2 statistic (Higgins et al., 2003) that assesses the proportion of observed dispersion that is due to real differences in the true effect sizes. The I^2 ranges from 0 to 100%, with values of 25%, 50% and 75% reflecting low, moderate and high heterogeneity (Higgins et al., 2003).

Whenever heterogeneity of effect sizes was observed (Q $p < .05$ or $I^2 \geq 50\%$), subgroup analyses were conducted to examine whether effect sizes varied according to the following potential moderators (categorical variables): type of control group (coded as passive or active); setting (coded as primary care, secondary–tertiary care, university setting); provider of the treatment (coded as psychologist, psychiatrist or psychotherapist, exercise physiologist or physical therapist, and nurse); psychological intervention component (coded as yes or no); flexibility in physical activity program (coded as yes or no); and minimal contact (coded as yes or no). Subgroup analyses were conducted using mixed-effect models (Borenstein et al., 2009). Between-groups *Q* statistic and corresponding *p*-values was used to compare the mean effect across subgroups, when there were at least three studies in each subgroup. Due to statistical power effects on the significance of *p*-values, we also considered within-groups estimate points (Hedge's *g*), confidence intervals (CI), and the I^2 statistic (Borenstein et al., 2009). Further, meta-regression analyses using random-effect models were conducted to analyze the moderation effect of the continuous variable length of treatment (in weeks) on treatment effect. Meta-regressions were analyzed based on the *Z*-value and associated *p*-value of the slope and were only conducted for the outcomes presenting at least ten studies (Borenstein et al., 2009).

For both types of moderator analyses (subgroups and meta-regression), adjusted R^2 was used to examine how much of the true variance was explained by the moderators. Adjusted R^2 was calculated based on the two estimates for T^2 (variance of the true effects) using the formula: $R^2 = 1 - \left(\frac{T^2_{within\ or\ unexplained}}{T^2_{total}}\right)$ (Borenstein et al., 2009). Due to the limited number of studies, especially at the follow-up measurement, these analyses were conducted for the longest period of assessment available (post-treatment or follow-up).

2.6. Sensitivity analyses

Sensitivity analyses were carried out to explore whether treatment effects were affected by methodological quality and risk of bias. The effect of total methodological quality on the magnitude of the effect size was analyzed by means of meta-regression (using the aforementioned approach). Publication bias was examined using the following approaches: 1) visual inspection of funnel plot for asymmetry; 2) Egger's test (Sterne & Egger, 2001) to confirm the visual impression; and 3) Duval and Tweedie's 'trim and fill' method (Duval & Tweedie, 2000), which allows the estimation of an adjusted effect size taking into account possible missing studies.

To confirm the validity of the results obtained, primary analyses were repeated excluding 1) studies presenting a high/uncertain risk of bias across categories, 2) studies presenting less strict diagnostic criteria (e.g. persistent fatigue for less than 6 months), and 3) studies in which the intervention and comparison conditions included additional pharmacological treatment for CFS.

3. Results

3.1. Description of included studies

A total of 214 potentially relevant articles (after removing duplicates) were identified in the literature search and additional hand searches. After the screening of titles and abstracts 168 studies were excluded. Common reasons for exclusion were the study design, the target population, and type of treatment provided. The remaining 46 eligible studies were reviewed, which resulted in the inclusion of 26 studies reporting on 16 trials in the present meta-analysis (see Fig. 1; references of excluded studies and reasons for exclusion are presented in Appendix B). Tables 1 and 2 show the characteristics of the trials included in the meta-analysis.

3.1.1. Study characteristics

Most studies were conducted in the United Kingdom ($n = 9$) and the Netherlands ($n = 3$), in secondary–tertiary care settings (e.g. specialized CFS clinics) (n = 11) or in primary care ($n = 3$).

3.1.2. Participant characteristics

In total, 2004 participants were included in the meta-analysis, with a mean age of 39 years; approximately 75% were women. Most trials included CFS patients diagnosed according to the Oxford or/and the CDC criteria. The exceptions were (1) the study conducted by Ridsdale, Hurley, King, McCrone, and Donaldson (2012) targeting patients with a complaint of persistent unexplained fatigue of at least 3 months, and (2) the trial conducted by Prins et al. (2001), which included patients with ICF. In seven studies, severity of the disease, established on the basis of cut-off scores for fatigue severity and functional impairment/physical functioning scales, was an additional criterion for patient inclusion in the trial. Drop-out percentages in intervention conditions ranged from 0% (Wallman et al., 2004) to 35% in the trial conducted by Prins et al. (2001), which was one of the trials that lasted for a longer period of time (8 months) and consisted of a high number of sessions (16 sessions).

3.1.3. Outcome measures

Ten RCTs (Deale et al., 1997; Fulcher & White, 1997; Moss-Morris, Sharon, Tobin, & Baldi, 2005; O'Dowd et al., 2006; Powell et al., 2001; Ridsdale et al., 2012; Wallman et al., 2004; Wearden, Dowrick, Chew-Graham, Bentall, & Dunn, 2010; Wearden et al., 1998; White et al., 2011) assessed fatigue severity using the Chalder Fatigue Scale (Chalder et al., 1993). In three other trials (Knoop, Van der Meer, & Bleijenberg, 2008; Prins et al., 2001; Tummers et al., 2012) fatigue severity was assessed with the Checklist of Individual Strength (Vercoulen, Alberets, & Bleijenberg, 1999). One study (Jason et al., 2007) used the Fatigue Severity Scale (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) and another trial (Sharpe et al., 1996) used a single-item to assess fatigue.

Of the thirteen studies assessing functional impairment/physical functioning, eleven studies (Deale et al., 1997; Fulcher & White, 1997; Jason et al., 2007; Knoop et al., 2008; Moss-Morris et al., 2005; Núñez et al., 2011; O'Dowd et al., 2006; Powell et al., 2001; Tummers et al., 2012; Wearden et al., 2010; White et al., 2011) used the Short Form Health Survey-36 (Ware & Sherbourne, 1992), one trial (Ridsdale et al., 2012) used the Work and Social Adjustment Scale (Mundt, Marks, Shear, & Greist, 2002) and another study (Prins et al., 2001) used the Sickness Impact Profile (Bergner, Bobbitt, Carter, & Gilson, 1981). Physical activity was assessed in seven trials, by means of actigraphy (Knoop et al., 2008; Prins et al., 2001, reported in Wiborg,

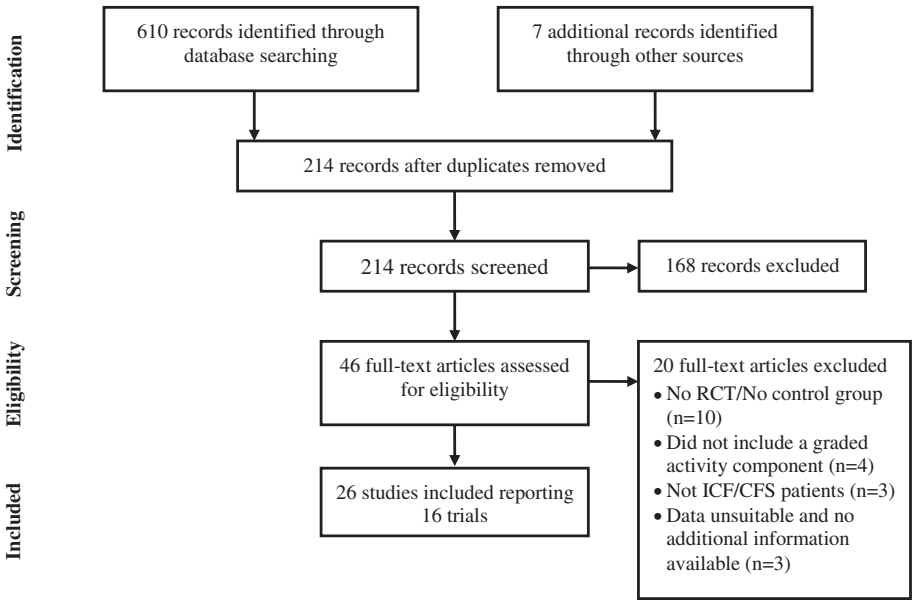

Fig. 1. Flowchart of studies.

Table 1
Details of included studies.

[a]First author, year, country	Population[b]/diagnostic criteria	[c]Sample size/% women	[d]Drop-out (%)	Setting	Provider	[e]Intervention condition	Control condition	Number and format of sessions/length (weeks)	[f]Assessment points (months)	[g]Outcomes
Fulcher & White, 1997 UK	CF/Oxford	66/74%	12	Secondary–tertiary care	Exercise physiologist	GET	Flexibility + Relaxation**	12 face to face sessions/12 weeks	PT = 3	FAT, PF, PA, DEP
Wearden et al., 1998 UK	CFS/ Oxford	68/70.5%	32	Secondary–tertiary care	Physical therapist	GET + drug placebo	Exercise placebo + drug placebo**	8 face to face sessions/26 weeks	PT = 6.5	FAT, PA, DEP, ANX
Wallman et al., 2004; Wallman, Morton, Goodman, & Grove, 2005 AU	CFS/ CDC	61/76.5%	0	University setting	Exercise physiologist	GET	Flexibility + relaxation**	1 face to face + 6 telephone calls/12 weeks	PT = 3–4	FAT, PA, DEP, ANX
Moss-Morris et al., 2005 NZ	CFS/CDC	49/71%	12	Secondary–tertiary care	Psychologist	GET	Treatment as usual*	12 face to face sessions/12 weeks	PT = 3	FAT, PF, PA
[h]White, Sharpe, Chalder, DeCesare, & Walyin, 2007; White et al., 2011, UK	CFS/Oxford + severity	320/76.5%	6	Secondary–tertiary care	Physical therapist, Exercise physiologist	GET	Treatment as usual*	14 face to face sessions/23 weeks	PT = 6 FU = 13	FAT, PF, PA, DEP, ANX
Ridsdale et al., 2012 UK	CFS/CF > 3 M	146/79%	27	Primary care	Physical therapist	GET	Treatment as usual*	8 face to face sessions + 2 telephone calls/24 weeks	PT = 6 FU = 12	FAT, PF, DEP, ANX
Powell et al., 2001; Powell, Bentall, Nye, & Edwards, 2004; Bentall, Powell, Nye, & Edwards, 2002. UK	CFS/Oxford + severity	71/73%	13	Secondary–tertiary care	Psychologist	Pragmatic rehabilitation	Treatment as usual*	2 face to face sessions + 2 telephone calls/12 weeks	PT = 3 FU = 12	FAT, PF, DEP, ANX
Wearden et al., 2006, 2010, 2012; Wearden & Emsley, 2013, UK	CFS/Oxford + severity	195/77%	15	Primary care (home visits)	Nurse	Pragmatic rehabilitation	Treatment as usual*	5 home visits + 5 telephone calls/18 weeks	PT = 5 FU = 17	FAT, PF, PA, DEP, ANX
Sharpe et al., 1996 UK	CFS/Oxford + severity	60/68.5%	0	Secondary–tertiary care	Psychologist	CBT with graded exercise	Treatment as usual*	16 face to face sessions/16 weeks	PT = 5 FU = 12	FAT, PA, DEP, ANX
Deale et al., 1997, Deale, Huasain, Chalder, & Wessely, 2001, UK	CFS/CDC and oxford	60/68.5%	10	Secondary–tertiary care	Psychologist	CBT with graded exercise	Active relaxation**	13 face to face sessions/16–24 weeks	PT = 6 FU = 12	FAT, PF, DEP
Prins et al., 2001 Wiborg et al., 2010 NL	ICF/CDC + severity	180/70.5%	35	Secondary–tertiary care	Psychotherapist	CBT with graded exercise	Treatment as usual*	16 face to face sessions/32 weeks	PT = 8 FU = 14	FAT, PF, PA
O'Dowd et al., 2006 UK	CFS/CDC	103/62.5%	17	Primary care	Psychologist Physical & occupation therapist	CBT with graded exercise	Treatment as usual*	8 face to face group sessions/16 weeks	PT = 6 FU = 12	FAT, PF, PA, DEP, ANX
Jason et al., 2007, USA	CFS/CDC	57/83.3%	20	n/a	Nurse	CBT with graded exercise	Active relaxation**	13 face to face sessions/26 weeks	FU = 12	FAT, PF, PA, DEP, ANX
[h]White et al., 2007, 2011, UK	CFS/Oxford + severity	321/78%	7.5	Secondary–tertiary care	Psychologist/nurse therapist	CBT with graded exercise	Treatment as usual*	14 face to face sessions/23 weeks	PT = 6 FU = 13	FAT, PF, PA, DEP, ANX
Knoop et al., 2008, Tummers, Knoop, & Bleijenberg, 2010 Wiborg et al., 2010 NL	CFS CDC + severity	169/79%	0.07	Secondary–tertiary care	Psychotherapist	CBT with graded exercise	Waiting list*	1 face to face session + email or telephone calls every 2 weeks/≥16 weeks	PT = 6	FAT, PF, PA
Tummers et al., 2012, 2013 NL	CFS CDC + severity	123/78%	11	Secondary–tertiary care	Psychiatric nurse	CBT with graded exercise	Waiting list*	1 face to face session + email every 2 weeks/≥20 weeks	PT = 6	FAT, PF
Núñez et al., 2011, Spain	CFS/CDC	115/89.4%	0.05	Secondary–tertiary care	Psychologist Physical therapist	Multiconvergent therapy + medication	Exercise counseling + medication**	9 face to face group session + 36 group sessions/24 weeks	FU = 12	PF

n/a = information not available.
[a] AU = Australia; NL = The Netherlands; NZ = New Zealand; UK = United Kingdom; US = United States of America.
[b] CF = Chronic Fatigue; CFS = Chronic Fatigue Syndrome; ICF = Idiopathic Chronic Fatigue.
[c] Sample characteristics at baseline.
[d] Percentage of withdrawal in intervention condition.
[e] GET = Graded Exercise Therapy; CBT = Cognitive-behavioral therapy.
[f] Measurement periods included in the meta-analyses (months from baseline): PT = Post-treatment; FU = Follow-up.
[g] FAT = Fatigue severity; PA = Physical activity; PF = Physical functioning; DEP = Depression; ANX = Anxiety.
[h] Trial presenting two intervention arms included in the meta-analysis.
* Passive control group.
** Active control group.

Knoop, Stulemeijer, Prins, & Bleijenberg, 2010), the six-minute walking test (Jason et al., 2007; Sharpe et al., 1996; White et al., 2011), the incremental shuttle walking test (O'Dowd et al., 2006), and a timed step test (Wearden & Emsley, 2013). Physical capacity was assessed in four trials (Fulcher & White, 1997; Moss-Morris et al., 2005; Wallman et al., 2004; Wearden et al., 1998) by means of laboratory physical capacity measures (e.g. oxygen consumption).

Eleven studies assessed psychological distress (depression and/or anxiety). Nine of these (Fulcher & White, 1997; O'Dowd et al., 2006; Powell et al., 2001; Ridsdale et al., 2012; Sharpe et al., 1996; Wallman et al., 2004; Wearden et al., 1998, 2010; White et al., 2011) used the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983), two RCTs (Deale et al., 1997; Jason et al., 2007) used the Beck Depression Inventory (Beck, Steer, & Brown, 1996), and the Beck Anxiety Inventory (Hewitt & Norton, 1993) was used in one trial (Jason et al., 2007).

3.1.4. Intervention characteristics

In six trials the intervention group received Graded Exercise Therapy (GET), which consisted of exercise prescription (aerobic activities) adapted to the patient's physical capacity assessed at baseline (e.g. 40% of $V0_2$ max) taking into account a gradual increase in the duration and intensity of aerobic activities (e.g. walking). Patients were recommended not to exceed the levels of exercise agreed upon beforehand by the therapist and patient in order to avoid overexertion, and to maintain these levels if symptoms got worse. The exception was the graded exercise program conducted by Wallman et al. (2004) in which patients were advised to reduce their activity levels if symptoms got worse (i.e. flexibility in physical activity levels-pacing). GET interventions consisted of supervised aerobic exercise sessions and/or home-based exercise prescription. The number of sessions ranged from 8 to 14 sessions, lasting for 12 to 24 weeks, with the exception of one trial which had only 1 face-to-face session and 6 telephone contacts (Wallman et al., 2004). One GET trial presented a booster session after the end of the intervention (White et al., 2011). GET interventions were conducted by exercise physiologists and/or physical therapists, except in one trial (Moss-Morris et al., 2005) where the intervention was delivered by psychologists. In one of the trials both intervention and control groups included a placebo drug component (Wearden et al., 1998).

Two trials (Powell et al., 2001; Wearden et al., 2010) consisted of Pragmatic Rehabilitation, an educational treatment providing patients with an explanatory model for their symptoms (i.e. a model integrating physical deconditioning, circadian dysrhythmia and disturbed sleep patterns). The program, collaboratively established by therapist and patient, included a home-based graded exercise program, normalization of sleep patterns, and practicing rest and relaxation. The treatment also included an educational support manual. The trial conducted by Powell et al. (2001) was delivered by psychologists and provided minimal contact to patients, consisting of 2 face-to-face sessions and 2 brief telephone contacts (plus access to a telephone helpline), lasting for 12 weeks. The trial conducted by Wearden et al. (2010) was delivered by nurses, had 5 face-to-face home visits and five additional telephone contacts, lasting for 18 weeks.

In eight trials the intervention condition (and one of the intervention arms of the trial by White et al., 2011) consisted of Cognitive-Behavioral Therapy (CBT) with a graded physical activity/exercise component. In general, these interventions challenge cognitions and behaviors related to the perpetuation of fatigue and aim at increasing patients' sense of control over symptoms. Patients are encouraged to engage in a gradual increase of exercise levels, sleep management is addressed and patients are supported to set personal recovery goals (e.g. work). Two of these RCTs (Knoop et al., 2008; Tummers et al., 2012) were minimal contact CBT interventions, consisting of patient (self-help) CBT-based manuals (with assignments) and regular email or telephone contacts to provide feedback. In addition, these two CBT interventions distinguished between relatively active (characterized by an alternation of overactivity and rest) and low active patients. The first group of patients was initially encouraged to balance their daily activities and rest, and both patient groups were supported to gradually increase their physical activity levels (Bleijenberg et al., 2003). With the exception of these two trials, the number of face-to-face CBT sessions ranged from 8 to 16 sessions, with a duration of 16 to 32 weeks. Four interventions were conducted by psychologists/psychotherapists (Deale et al., 1997; Knoop et al., 2008; Prins et al., 2001; Sharpe et al., 1996). Two interventions were conducted by nurses (Tummers et al., 2012; Wearden et al., 2010). One trial was delivered by a team consisting of psychologists/psychotherapists, physical therapists and occupational therapists (O'Dowd et al., 2006), and another by psychotherapists and nurse therapists (White et al., 2011). Only one intervention was delivered in a group format (O'Dowd et al., 2006).

Finally, one study (Núñez et al., 2011) consisted of a multidisciplinary treatment (called multiconvergent therapy), combining CBT and GET group sessions and pharmacological treatment (painkillers and non-steroidal anti-inflammatory drugs). The CBT component of this trial also included progressive muscle relaxation, assertiveness training, and memory and attention training. The GET component included aerobic exercise (walking) carried out according to the protocols and also included relaxation and flexibility training.

3.1.5. Control condition characteristics

The type of control conditions differed across trials. Ten RCTs compared the intervention arms against passive control groups, such as waiting list (Knoop et al., 2008; Tummers et al., 2012), or treatment as usual (Moss-Morris et al., 2005; O'Dowd et al., 2006; Powell et al., 2001; Prins et al., 2001; Ridsdale et al., 2012; Sharpe et al., 1996; Wearden et al., 2010; White et al., 2011).

The remaining six trials had active control groups, presenting a structure/format similar to the intervention arms. In two of these trials, control groups received flexibility and relaxation training, conducted either at home (Wallman et al., 2004) or in the same setting and with the same provider as the intervention arm (Fulcher & White, 1997). In both trials, control subjects were encouraged to avoid doing other physical activities. In two other RCTs patients in the control group received relaxation training (Deale et al., 1997; Jason et al., 2007), which consisted of progressive muscle relaxation, imagery and rapid relaxation skills (e.g. breathing focus). No advice was given on rest or physical activities. In the trial conducted by Wearden et al. (1998) participants in the control group received an exercise placebo (advice to do physical activity when capable and to rest when needed) and a drug placebo (similar to the intervention arm). In another trial patients received advice (called exercise counseling) on doing aerobic activities and stretching exercises at home (Núñez et al., 2011).

3.2. Quality of the studies and risk of bias

Table 2 shows the quality of the trials and risk of bias (for the detailed classification of each item see Appendix C). The quality of the trials varied, with scores ranging from 29 to 51. The trial conducted by Núñez et al. (2011) showed the lowest quality score, and presented a high or uncertain risk of bias on all criteria. In relation to attrition bias, most studies presented adequate drop-out information and inclusion. Thirteen trials reported an adequate method of concealment, nine studies did not report details on blinding of assessors, and five presented high risk of bias.

3.3. Synthesis of results

Table 3 shows the overall results of the meta-analysis for all outcomes at post-treatment and follow-up (the forest plots are presented in Appendix D). Table 4 presents the results of the subgroup analysis for all outcomes for the longest period of assessment available.

Table 2
Classification on methodological quality, risk of bias and moderators of included interventions.

Study ID		Risk of bias						
	Total methodological quality[a]	Allocation concealment	Assessor blinded	Inclusion drop-outs	Dropout information	Psychological component	Minimal contact interventions[b]	Physical activity flexibility
Fulcher	37	Low	High	Low	Low	No	No	No
Wearden et al. (1998)	41	Low	High	Low	Low	No	No	No
Wallman	32	Unclear	Unclear	Low	Low	No	Yes*	Yes
Moss-Morris	33	Low	Unclear	Low	Low	No	No	No
White	51	Low	High	Low	Low	No (GET arm) Yes (CBT arm)	No	No
Ridsdale	41	Low	Unclear	Low	Low	No	No	No
Powell	41	Low	High	Low	Low	Yes	Yes	Yes
Wearden et al. (2010)	49	Low	Unclear	Low	Low	Yes	No**	Yes
Sharpe	42	Low	Unclear	Low	Low	Yes	No	No
Deale	42	Low	Unclear	Low	Low	Yes	No	No
Prins	44	Low	Unclear	Low	Low	Yes	No	Yes
O'Dowd	47	Low	Low	Low	Low	Yes	No	Yes
Jason	30	Unclear	Unclear	Unclear	High	Yes	No	No
Knoop	35	Low	Unclear	Low	Low	Yes	Yes	Yes
Tummers	40	Low	High	Low	Low	Yes	Yes	Yes
Nunez	29	Unclear	Unclear	High	Unclear	Yes	No	No

[a] Range 0–58.
[b] In contrast to more intensive interventions.
* Did not provide a patient (self-help) manual.
** Provided a patient (self-help) manual and direct-contact was provided through home visits.

3.3.1. Effects on fatigue severity

Fatigue severity data was available for 14 trials at post-treatment (varying from 3 to 8 months after baseline) and for 9 trials at follow-up (varying from 12 to 17 months after baseline). Significant medium effect sizes were found for fatigue severity at post-treatment (g = 0.61; 95% CI 0.44–0.78) and follow-up (g = 0.66; 95% CI 0.38–0.93). At both assessment points, the effects varied widely from study to study. The trial conducted by Powell et al. (2001) showed the largest effect sizes (g = 1.83 and g = 2.08, respectively). The standard residuals showed these values were outliers (3.21 and 3.018, respectively). The results of the overall effect sizes if this study was removed would vary within 0.08 and 0.15 from the initial point estimate, respectively, which means this study had a large impact on the overall effect at both time points. The smallest effects were found in the trial conducted by Deale et al. (1997) at post-treatment (g = 0.28) and the trial by Ridsdale et al. (2012) at follow-up (g = 0.10).

There was evidence of moderate to high heterogeneity between trials at both assessment points (Q = 37.94, p < 0.001; I^2 = 66%, and Q = 43.97, p < 0.001; I^2 = 82%, respectively), indicating that the variance could not be explained by sampling error alone (Table 3). For this reason, we examined the potential moderators of variance in effect sizes for the combined post-treatment and follow-up data (k = 15, g = 0.66, Z = 6.98, p < 0.001; 95% CI 0.47–0.85; Q = 49.59, p < 0.001; I^2 = 72%). Interventions conducted in secondary–tertiary settings, interventions delivered by psychologists or psychotherapists, and interventions providing minimal contact (versus more intensive contact), showed higher effects upon fatigue severity (p = 0.01, p < 0.05, p < 0.05, respectively) and explained 29%, 33% and 25% of the variance in fatigue severity, respectively. In addition, the overall effect sizes for interventions containing a psychological component and allowing flexibility in physical activity levels/goals were larger, but also presented high levels of heterogeneity (Table 4).

3.3.2. Effects on functional impairment/physical functioning

Eleven trials at post-treatment (3–8 months) and eight trials at follow-up (12–17 months) presented data for the effects of interventions on functional impairment/physical functioning (Table 3). Combined effect sizes were g = 0.29 (95% CI 0.13–0.44) at post-treatment and g = 0.38 (95% CI 0.13–0.64) at follow-up. At both assessment points, the effects varied widely from study to study. The trial conducted by Deale et al. (1997) showed the largest effect sizes at both assessment points (g = 0.92 and g = 1.35, respectively). The standard residuals of this trial revealed it was an outlier (2.03 and 2.44, respectively). If removed the overall effect size would drop to g = 0.25 and g = 0.28. The trial conducted by O'Dowd et al. (2006) showed negative effects (g = −0.20) at post-treatment and the trial conducted by Núñez et al. (2011) showed a negative effect (g = −0.10) at follow-up.

The results for functional impairment/physical functioning showed evidence of moderate to high heterogeneity between trials (Q = 21.46, p < 0.05; I^2 = 53% and Q = 30.24, p < 0.001; I^2 = 77%, respectively). Subsequent subgroup and meta-regression analyses were conducted for the longest period of assessment available (k = 13, g = 0.35, Z = 4.41, p < 0.001; 95% CI 0.19–0.51; Q = 29.92, p < 0.05; I^2 = 60%). There were no significant associations between study characteristics and the effect sizes of the interventions (Table 4), indicating that none of the variance in the treatments effects on functional impairment/physical functioning was explained by the moderators analyzed (adjusted R^2 = 0%).

3.3.3. Effects on physical activity and physical capacity

The overall effect size for physical activity at post-treatment was not significant (k = 4, 5–8 months; g = 0.11; 95% CI −0.07–0.28). The trial by Sharpe et al. (1996) showed the largest and the only significant effect size (g = 0.63) on physical activity, with a standard residual of 2.13. If removed, overall effect size would drop to g = 0.04. At follow-up, we found a significant small effect size (k = 5, 12–17 months; g = 0.28; 95% CI 0.15–0.40; Table 3). At follow-up, the trial of Sharpe et al. (1996) showed the largest effect size (g = 0.73) and the trial by Wearden et al. (2010) the lowest effect (g = 0.11). There was considerable heterogeneity between trials at post-treatment (Q = 4.64, p = 0.20; I^2 = 35%) and no evidence of heterogeneity at follow-up (Q = 4.49, p = 0.35; I^2 = 11%). The overall effect size for physical capacity at post-treatment was small but significant (k = 4, 3–6 months; g = 0.27; 95% CI 0.00–0.54). There was evidence of heterogeneity between trials (Q = 10.90, p < 0.01; I^2 = 73%). The trial conducted by Moss-Morris et al. (2005) showed a negative effect (g = −0.97), that is considered an outlier effect (standard residual: −3.27). If this trial was removed, the overall effect would increase to g = 0.43.

Due to the limited number of trials, data for both physical activity and physical capacity at the longest available period of assessment were combined to conduct moderator analyses. Combining physical

activity and physical capacity assessments resulted in a small but significant effect size with moderate heterogeneity between trials ($k = 11$, $g = 0.25$, $Z = 2.62$, $p < 0.01$; 95% CI 0.06–0.43; $Q = 24.20$, $p < 0.01$; $I^2 = 59\%$). Due to the limited number of trials, subgroup comparisons were conducted only for the following characteristics: 1) type of control group, 2) presence of a psychological component and 3) flexibility in physical activity/exercise program. There were no significant associations between these characteristics and the effect size of the interventions upon physical activity/physical capacity, indicating that none of the variance in this combined outcome variable was explained by these characteristics (adjusted $R^2 = 0\%$).

3.3.4. Effects on depression

Data was available for ten trials at post-treatment (3–6 months) and seven trials at follow-up (12–17 months). Overall, interventions yielded significant effect sizes on depression levels at post-treatment ($g = 0.41$; 95% CI 0.22–0.59) and follow-up ($g = 0.37$; 95% CI 0.17–0.58). At both assessment points, the trial conducted by Powell et al. (2001) showed the largest effect sizes ($g = 0.93$ and $g = 1.12$, respectively). At follow-up, the standard residual of this trial was 2.50. The overall effect, if this study was removed, decreased to $g = 0.29$. At post-treatment the smallest effect sizes were found in the trial conducted by Fulcher and White (1997) ($g = 0.03$), in which patients were excluded at baseline if presenting a psychiatric disorder. If removed the overall effect would increase to $g = 0.44$. At follow-up, the smallest effect was found for the trial conducted by Jason et al. (2007) ($g = 0.08$).

For depression there was evidence of considerable heterogeneity between studies ($Q = 16.56$, $p = 0.06$; $I^2 = 46\%$, and $Q = 12.59$, $p = <0.05$; $I^2 = 52\%$, respectively) (Table 3). Subsequent subgroup analyses and meta-regression analyses were conducted for the longest available period of assessment ($k = 12, g = 0.35, Z = 4.00, p < 0.001$; 95% CI 0.18–0.53; $Q = 27.20, p < 0.001$; $I^2 = 60\%$). There were no significant moderator effects for type of control condition, type of setting, treatment provider, and presence of a psychological component. Interventions with minimal direct patient-provider contact had significantly higher effects upon depression ($p = <0.001$), and all of the heterogeneity was explained (adjusted $R^2 = 100\%$. In addition, meta-regression showed a marginal association between depression and length of the intervention (slope: $-0.03, Z = -1.74, p = 0.08$). Furthermore, there was a marginal moderator effect for flexibility in physical activity levels ($p < 0.10$; adjusted $R^2 = 9\%$).

3.3.5. Effects on anxiety

Small but significant effects were found for anxiety at post-treatment ($k = 7$, 3–6 months; $g = 0.28$; 95% CI 0.13–0.43) and follow-up ($k = 6$, 12–17 months; $g = 0.25$; 95% CI 0.14–0.37) (see Table 3). At post-treatment, the trial conducted by Wallman et al. (2004) showed the largest effect size ($g = 0.57$) and the trial by Wearden et al. (1998) showed the smallest ($g = 0.12$). At follow-up, the trial conducted by Powell et al. (2001) showed the largest effect size ($g = 0.52$) and the smallest effect was found in the trial conducted by Sharpe et al. (1996) (g = 0.07). There was no evidence of heterogeneity between the trials on both assessment points ($Q = 2.70$, $p = 0.85$; $I^2 = 0\%$ and $Q = 2.50$, $p = 0.86$; $I^2 = 0\%$, respectively). For that reason, no further moderator analyses were conducted.

3.4. Sensitivity analyses

Meta-regressions with respect to methodological quality did not reveal any significant slope for any of the outcomes assessed (Table 4). Visual inspection of the funnel plots revealed asymmetry for fatigue severity. Egger's test showed a significant asymmetric funnel plot at post-treatment (intercept: 2.36, 95% CI 0.29–4.42, $p = 0.03$). After adjustment with the trim-and-fill procedure the magnitude of the effect sizes decreased from g = 0.61 to g = 0.40 at post-treatment (95% CI 0.21–0.59; number of trimmed studies = 5). At follow-up, inspection of the funnel plot for fatigue severity showed the presence of asymmetry, although Egger's test did not indicate a significant asymmetric plot (intercept: 2.37, 95% CI −1.75–6.49, $p = 0.22$). After adjustment the point estimate dropped from g = 0.66 to g = 0.46 (95% CI 0.14–0.77; number of trimmed studies = 2). Furthermore, inspection of the funnel plot of the effects for physical impairment/functioning at post-treatment revealed the presence of asymmetry. Egger's test did not show a significant asymmetric funnel plot (intercept: 0.25, 95% CI −2.47–2.97, $p = 0.84$). After adjustment with the trim-and-fill procedures, the magnitude of the effect dropped from g = 0.29 to g = 0.23 (95% CI 0.07–0.39, number of trimmed studies = 2). We also found presence of asymmetry for physical capacity at post-treatment. Egger's test indicated an asymmetric funnel plot (intercept: −8.79, 95% CI −17.31–0.28, $p = 0.05$). After adjustment the point estimate dropped from g = 0.27 to g = 0.18 (95% CI −0.06–0.42, number of trimmed studies = 1). There was no indication of asymmetry for other outcomes.

Primary analyses were repeated with the exclusion of the trial by Núñez et al. (2011), which presented a high risk of bias, poor methodological quality (Table 2) and included additional pharmacological treatment in the intervention arm. Excluding this study led to an increase in the magnitude of treatment effects for functional impairment/physical functioning at follow-up from g = 0.38 to g = 0.45. Analyses were also repeated with the exclusion of the trial by Jason et al. (2007) due to high/uncertain risk of bias in all categories. Excluding this trial led only to very small increases in the overall point estimates between 0.01 (physical activity) to 0.04 (depression). The exclusion of the trial conducted by Ridsdale et al. (2012) because of less restrictive diagnostic criteria (complaint of fatigue for more than 3 months), led to an increase

Table 3
Effects of the interventions for each outcome at post-treatment and follow-up.

Outcomes	Assessment point	Sample size	Hedges' g (95% CI)	Z	Q	I^2	No. of trials
Fatigue	Post-treatment	1776	0.61 (0.44–0.78)	6.98**	37.94**	66%	14
	Follow-up	1325	0.66 (0.38–0.93)	4.70**	43.97**	82%	9
Physical functioning	Post-treatment	1612	0.29 (0.13–0.44)	3.70**	21.46*	53%	11
	Follow-up	1216	0.38 (0.13–0.64)	2.98**	30.24**	77%	8
Physical activity	Post-treatment	513	0.11 (−0.07–0.28)	1.21	4.64	35%	4
	Follow-up	773	0.28 (0.15–0.40)	4.18**	4.49	11%	5
[a]Physical capacity	Post-treatment	214	0.27 (0.00–0.54)	1.96*	10.90**	73%	4
Depression	Post-treatment	921	0.41 (0.22–0.59)	4.38**	16.56†	46%	10
	Follow-up	999	0.37 (0.17–0.58)	3.62**	12.59*	52%	7
Anxiety	Post-treatment	686	0.28 (0.13–0.43)	3.67**	2.70	0%	7
	Follow-up	939	0.25 (0.14–0.37)	4.20**	2.50	0%	6

† $p < 0.10$.
* $p < 0.05$.
** $p < 0.01$.
[a] Data available only at post-treatment.

Table 4
Subgroup analysis assessing the effect of study characteristics upon effect size at the longest assessment period available, separated by outcome.

Moderator		Fatigue					Physical functioning					Physical activity					Depression				
		[a]*k*	*g* (95% CI)	Z	*p*[1]	I^2	[a]*k*	*g* (95% CI)	Z	*p*[1]	I^2	[a]*k*	*g* (95% CI)	Z	*p*[1]	I^2	[a]*k*	*g* (95% CI)	Z	*p*[1]	I^2
Control condition	Passive	11	0.65 (0.44–0.86)	3.59**	0.92	78%	10	0.33 (0.16–0.50)	3.86**	0.61	11%	7	0.19 (−0.04–0.41)	1.64†	0.37	73%	8	0.41 (0.22–0.60)	4.22**	0.26	68%
	Active	5	0.63 (0.29–0.97)	6.18**		0%	4	0.43 (0.11–0.74)	2.65**		85%	4	0.37 (0.04–0.71)	2.17*		0%	5	0.21 (−0.08–0.50)	1.42		0%
[b]Setting	Primary	3	0.26 (−0.09–0.60)	1.45	0.01	0%	3	0.15 (−0.14–0.44)	1.02	0.10	0%	2	0.41 (−0.08–0.90)	1.63	n/a	75%	3	0.15 (−0.15–0.45)	0.99	0.12	0%
	Secondary–tertiary	11	0.77 (0.58–0.97)	7.81**		71%	10	0.43 (0.26–0.59)	5.07**		62%	8	0.19 (−0.05–0.43)	1.53		72%	8	0.44 (0.24–0.64)	4.32**		66%
[c]Provider	Nurse	3	0.53 (0.16–0.90)	2.73**	0.02	48%	3	0.21 (−0.12–0.55)	1.24	0.21	0%	2	0.13 (−0.31–0.53)	0.57	n/a	0%	2	0.35 (0.00–0.70)	1.99*	0.14	75%
	Physical therapist, physiologist	5	0.43 (0.14–0.72)	2.90**		28%	3	0.33 (0.01–0.66)	2.01*		57%	4	0.44 (0.16–0.73)	3.03**		0%	5	0.23 (−0.05–0.50)	1.63		0%
	Psychologist, psychotherapist	6	1.00 (0.72–1.28)	6.95**		74%	5	0.59 (0.31–0.86)	4.18**		71%	4	0.06 (−0.23–0.35)	0.39		77%	3	0.71 (0.32–1.11)	3.53**		67%
Psychological component	No	6	0.50 (0.21–0.79)	3.36**	0.22	42%	4	0.33 (0.04–0.62)	2.21*	0.83	35%	5	0.29 (−0.02–0.60)	1.85†	0.72	66%	5	0.23 (−0.03–0.49)	1.72†	0.23	0%
	Yes	10	0.72 (0.51–0.94)	6.52**		76%	10	0.37 (0.19–0.54)	4.00**		65%	7	0.22 (−0.02–0.45)	1.82†		60%	8	0.43 (0.22–0.64)	4.08**		67%
Flexibility in activity	No	9	0.57 (0.33–0.80)	4.70**	0.35	45%	8	0.35 (0.14–0.55)	3.34**	0.93	75%	7	0.25 (−0.02–0.51)	1.82†	0.98	72%	8	0.24 (0.05–0.44)	2.45*	0.08	0%
	Yes	7	0.73 (0.48–0.99)	5.58**		81%	6	0.36 (0.14–0.59)	3.16**		24%	5	0.24 (−0.06–0.54)	1.58		61%	5	0.53 (0.26–0.78)	4.11**		78%
Minimal contact	No	12	0.53 (0.35–0.71)	5.79**	0.03	40%	11	0.32 (0.15–0.49)	3.78**	0.41	60%	10	0.25 (0.04–0.47)	2.31*	n/a	68%	10	0.24 (0.14–0.35)	4.45**	0.00	0%
	Yes	4	0.96 (0.63–1.28)	5.82**		85%	3	0.47 (0.15–0.79)	2.90**		50%	2	0.20 (−0.27–0.67)	0.82		59%	3	0.85 (0.59–1.10)	6.52**		34%
Meta-regressions		*k*	Slope	Z	*p*		*k*	Slope	Z	*p*		*k*	Slope	Z	*p*		*k*	Slope	Z	*p*	
Length of treatment		15	−0.03	−1.63	0.10		13	−0.02	−1.24	0.22		11	−0.01	−0.53	0.60		12	−0.03	−1.74	0.08	
Methodological quality		15	−0.02	−0.97	0.33		13	0.00	0.31	0.76		11	0.01	0.89	0.38		12	−0.01	−0.64	0.52	

n/a = not enough interventions in the subgroup to allow for a comparison.
† $p < 0.10$.
* $p < 0.05$.
** $p < 0.01$.
[1] *p*-Values correspond to subgroup differences in effects.
[a] For the subgroup analyses, the intervention arms of the trial by White et al. (2011) were analyzed using each arm within the study as the unit of analysis.
[b] Wallman et al. (2004) trial was not included as it was the only study conducted in a university laboratory department; Jason et al. (2007) study was not included as no information regarding the exact location setting was provided.
[c] The trials conducted by O'Dowd et al. (2006), Núñez et al. (2011) and the CBT arm of White et al. (2011) were not included because treatments were provided by specialists from multiple fields.

in the overall point estimate for fatigue severity at follow-up (from g = 0.66 to g = 0.73), and to increases of approximately 0.03 for the other outcomes.

4. Discussion

This meta-analysis examined the effectiveness of behavioral and psychological treatments focusing on graded aerobic physical activity/exercise in chronic fatigue patients. Treatments included Graded Exercise Therapy (GET), Cognitive behavioral Therapy (CBT), pragmatic rehabilitation and multicomponent approaches. Sixteen trials assessing fatigue severity, physical functioning /functional impairment, physical activity/physical capacity, and/or psychological distress (depression and anxiety) at post-treatment and/or follow-up, were included. In addition, this meta-analysis analyzed the potential moderating effects of the following trial characteristics: care provided to the control condition, treatment setting, provider of the treatment, length of treatment, whether the intervention included a psychological component (or not), flexibility in setting physical activity levels or goals in accordance with the patients' exercise tolerance, and whether or not the intervention was a minimal (direct face to face) contact intervention.

4.1. Fatigue

Our results indicate that interventions focusing on graded physical activity/exercise have beneficial effects on chronic fatigue management, which is in accordance with the results from previous reviews (Castell et al., 2011; Edmonds et al., 2004; Malouff et al., 2008; Price et al., 2008). Interventions had a moderate impact on fatigue severity at post-treatment ($g = 0.61$) and at follow-up ($g = 0.66$). The post-treatment result obtained was somewhat similar to the results found Malouff et al. (2008) [Physical fatigue: $d = 0.81$; mixed (physical and mental) fatigue: $d = 0.52$], and higher than the effect sizes reported by Castell et al. (2011; GET: $g = 0.41$; CBT: $g = 0.36$). Treatment effects varied widely between studies and subsequent subgroup comparisons revealed that several trial characteristics were significant moderators of the effect of the interventions on fatigue severity. Interventions conducted in secondary–tertiary settings had a higher effect on fatigue severity reduction than interventions conducted at primary care. Castell et al. (2011) also found the lowest intervention effect in primary care trials. It is however important to point out that of the studies included in our meta-analysis, only three studies were conducted in primary care settings, each of them with clearly distinct features. One trial, the Pragmatic Rehabilitation trial, was conducted by nurses who did home visits (Wearden et al., 2010), another was a GET trial conducted by physical therapists (Ridsdale et al., 2012), and the last one was a CBT trial with a graded exercise component delivered by several health care specialists to groups of patients (O'Dowd et al., 2006). Interventions delivered by psychologists or psychotherapists were more effective in reducing fatigue severity. Previous meta-analyses did not examine this moderator effect. The high heterogeneity found in this subgroup and the limited number of trials is a limitation to this finding. Furthermore, other moderators may also explain part of this result, such as the fact that interventions conducted by psychologists/psychotherapists were mainly conducted in secondary care, in which a larger effect was found. Likewise, the magnitude of the effect of the interventions delivered by physical therapists or physiologists was similar to the effect of GET interventions on fatigue severity. Other possible explanations for this finding may be related to the level of training and experience of the providers as well as the therapeutic relation that was established with patients (Castell et al., 2011; Huibers et al., 2004; Wearden et al., 2010). More research is clearly needed to analyze this potential moderator effect. Finally, minimal contact self-management interventions, consisting of a maximum of 3 face-to-face sessions, providing additional remote guidance and in many cases including patient (self-help) manuals, were associated with larger effects on fatigue severity. This result is in line with recent research that pointed at the beneficial effects of minimal contact interventions on psychological (Haug et al., 2012) and physical symptoms (Pajak et al., 2013). Furthermore, in a recent trial directly comparing CBT delivered face-to-face to CBT delivered by telephone (with an initial face-to- face session), similar beneficial effects were found on fatigue, social adjustment and physical functioning in CFS/ME patients (Burgess, Andiappan, & Chalder, 2012).

4.2. Functional impairment

Regarding functional impairment/physical functioning, there were small treatment effects at both assessment points ($g = 0.29$ and $g = 0.38$), which is in line with the results from a previous meta-analysis (e.g. Castell et al., 2011). Again, we found that intervention effects varied widely between studies and that some interventions had no significant effects on physical functioning/functional impairment. None of the moderators explained the observed variance in treatment effect.

4.3. Physical activity

This is the first meta-analysis assessing the impact of interventions with a graded activity/exercise component on physical activity and physical capacity. We found few studies reporting on the effects of interventions on physical activity/capacity. At post-treatment, interventions had a trivial effect on physical activity ($g = 0.11$) and a small effect on physical capacity and post-treatment ($g = 0.27$). At follow-up, overall effect on physical activity was also of small magnitude ($g = 0.28$). None of the moderators explained the observed variance in treatments effect. However, due to the limited number of studies, these analyses were only conducted for some of the potential moderators. One of the possible reasons for the small effects found may be the heterogeneous measurement of physical activity/physical capacity. Some studies made use of actigraphy to assess daily physical activity, while others relied on walking tests or on physiological measures to assess cardiorespiratory fitness. We also found considerable heterogeneity between studies using a similar exercise testing protocol; this result was however influenced by the negative results found in one trial (Moss-Morris et al., 2005).

The small effect of existing (psychological and behavioral) interventions targeting physical activity and physical capacity may point at the fact that alternative ways of promoting physical activity, e.g. making use of motivational counseling and self-regulation approaches (e.g. Janssen, Gucht, Exel, & Maes, 2013; Knittle et al., 2015) may be more successful in changing this health behavior. The discrepancy that was found in this meta-analysis between the effects found for fatigue severity and for physical activity could indicate that the mere increase of physical activity does not necessary lead to improved outcomes in terms of chronic fatigue management. Flexibility in physical activity levels or goals combined with pacing (balance between activities and rest) may be equally important for chronic fatigue management (Nijs et al., 2008). It could also be hypothesized that the effect of the interventions on fatigue cannot be explained by changes in physical activity and/or physical capacity. In fact, previous mediation analyses did not find a mediation effect of physical activity assessed by means of objective measures, but these trials also had trivial effects upon physical activity (Moss-Morris et al., 2005; Wearden & Emsley, 2013; Wiborg et al., 2010). It has been suggested that the positive effects of behavioral and psychological interventions on CFS/ME may be explained by changes in cognitions associated with progress in physical activity behavior (Knoop, Prins, Moss-Morris, & Bleijenbeg, 2010). By perceiving an increase in physical activity without exacerbation, patients may feel more in control of their fatigue, present with less fear avoidance beliefs, focus less on fatigue and bodily symptoms and increased self-efficacy, with in turn, can lead to positive effects on fatigue management, and this has been shown in some recent mediation analyses conducted in GET and CBT trials (Heins, Knoop, Burk, & Bleijenberg, 2013; Wearden,

Dunn, Dowrick, & Morriss, 2012; Wiborg, Knoop, Frank, & Bleijenberg, 2012). Furthermore, in a recent mediation analysis of the PACE trial (Chalder, Goldsmith, White, Sharpe, & Pickles, 2015), both fear avoidance beliefs and improved exercise tolerance mediated the effects of GET interventions on fatigue severity and physical functioning, pointing to the importance of both cognitive and behavioral aspects of CFS/ME management.

4.4. Psychological distress

For depression, small effect sizes were found at both assessment points ($g = 0.41$ and $g = 0.37$), slightly higher than the effect sizes found in previous reviews (Castell et al., 2011; Edmonds et al., 2004). Interventions with minimal face to face contact were associated with larger effect sizes, and a marginal significant effect was found for the length of the intervention. Interventions that allowed for flexibility in physical activity levels presented higher effects on depression. Finally, small effect sizes were found for anxiety at both assessment points ($g = 0.28$ and $g = 0.25$). The magnitude of the effects is higher than what was found in a previous meta-analysis (Castell et al., 2011; GET: $g = 0.01$; CBT: $g = 0.15$). Our results should however be interpreted with care as only a small number of studies were included in the analyses for anxiety at both assessment points. It may be the case that patients with more severe psychological distress or co-existing mood disorders will benefit more from additional emotional regulation approaches (e.g. CBT for mood disorders). In fact, two recent trials have found that depressive symptoms were a significant moderator of treatment effects (Tummers, Knoop, van Dam, & Bleijenberg, 2013; Wearden et al., 2012). Future reviews could address the potential moderator effect of psychological distress in a wide range of trials.

4.5. Additional considerations on moderators of treatment effects

For all outcomes, heterogeneity in effect sizes was not associated with type of care provided to the control condition (passive vs. active) as was found in previous meta-analyses (Castell et al., 2011; Malouff et al., 2008). Similarly, a flexible approach to physical activity levels or goals was not significantly associated with higher effect sizes, except for the marginal effect found for depression. We did not find a significant difference in effects between interventions focusing only on physical activity or also containing a psychological component, but results point to a greater effect of this last type of treatment on both fatigue and depression. Finally, heterogeneity in treatment effects was not associated with the length of treatment for any of the outcomes.

4.6. Limitations and suggestions for future research

The present meta-analysis has a number of limitations. First, although interventions have shown beneficial effects for most outcomes, we found a high level of heterogeneity between studies that could not be (fully) accounted for by the moderators that we examined. The limited number of trials included in this review limits the conclusions that can be drawn from the moderator analyses, because non-significant effects may be due to low statistical power (Borenstein et al., 2009). Future studies should continue to explore other potential moderators that can account for differences between trial results. Among these are patient and disease-related characteristics (e.g. illness duration, severity of disease, mood disorders, avoidance or all-or-nothing behaviors), treatment features (e.g. physical activity, flexible graded activity + pacing) or design-related moderators such as single-center vs. multi-center trials.

Second, sensitivity analysis revealed some indication of publication bias for the outcomes fatigue severity, physical functioning and physical capacity. The existence of unpublished trials with negative results could have reduced the effect sizes for some of the outcomes analyzed. Adjusted effect sizes and re-analysis excluding trials with low methodological quality, did not alter the significance of the effect sizes, with the exception of physical capacity. In addition, the sample size of many trials included in this meta-analysis was small, which constitutes a methodological limitation (Borenstein et al., 2009).

Third, promising recent trials adopting a multidisciplinary rehabilitation treatment approach, could not be included because they were non-randomized and/or did not provide enough statistical information. The only study on multidisciplinary rehabilitation that was included (Núñez et al., 2011) was characterized by poor methodological quality.

Fourth, most of the coding of intervention characteristics was based on the intervention description provided in the articles. In many cases these descriptions were limited, and e.g. did not present enough information regarding the behavior change techniques used. As we did not contact the authors to retrieve this information, we were not able to explore the moderating effect of behavior change techniques (e.g. use of self-regulation strategies such as goal setting). The same accounts for the description of the content of manuals that were used in different interventions. Future studies should give a sufficiently detailed account of the content of the intervention/self-help manual offered to patients (e.g. trial protocol).

Fifth, although we compared our results to the results of previous meta-analyses, this comparison is hampered by a number of differences related to the focus of the meta-analysis as well as the statistical procedures that were followed. More in particular, this meta-analysis (1) included recently published studies that were not included in previous meta-analyses, (2) did not include studies targeting children/youth with chronic fatigue, (3) was conducted separately for each outcome at post-treatment and follow-up, (4) compared activity based interventions to interventions with an additional psychological component, which was not limited to CBT, and (5) as Castell et al. (2011) different procedures for calculating effect sizes may have been adopted based on the information provided in the original trials included in this meta-analysis.

Sixth, although most outcomes were assessed using validated self-report scales, the way scores were calculated was not always clear. Future randomized controlled trials should pay more attention to the way statistical data are presented, making an effort to present effect sizes and raw data (means and standard deviations) for all outcomes, trial arms and assessment periods.

Seventh, the number of studies included in this meta-analysis that presented follow-up data (without crossovers) was limited and only available for a maximum period of 17 months. Hence, although these interventions seem to lead to sustainable beneficial effects on chronic fatigue management (Malouff et al., 2008), more research is needed to understand long-term effects as well as the potential mechanisms contributing to the maintenance of self-management behaviors.

Finally, future studies should also examine the effect of interventions on additional outcomes (e.g. recovery rate), and compare different treatment formats (telephone, web-based, face to face).

5. Conclusion

This meta-analysis of behavioral and psychological interventions targeting graded activity suggests that these interventions have sustained beneficial effects on chronic fatigue management, in particular on fatigue severity reduction for which a medium effect was found. The finding that minimal contact interventions have similar and in some cases higher effects on fatigue severity and depression compared to more intensive interventions is important as these interventions can be more easily implemented in standard health care, can be useful for patients presenting difficulties in regularly attending health care facilities (Burgess et al., 2012), and can be suitable for patients who do not need more intensive forms of treatment (Tummers et al., 2012). All trials included in this meta-analysis had an initial face to face contact with patients, which may have led to increased motivation of patients to engage in a behavior change process (Burgess et al., 2012). Most of these minimal interventions also included patient (self-help) manuals and

allowed flexible physical activity/exercise levels that take into consideration the patients' own resources, which can add to chronic fatigue management. Notwithstanding the beneficial effects of the behavioral and psychological interventions included in this meta-analysis and the valuable indications about targets and format of future interventions, more research is needed to identify optimal features of interventions for chronic fatigue management.

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All authors declare that they have no conflicts of interest.

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