Running head: CBT AND PHYSICAL EXERCISE

Cognitive Behavior Therapy combined with Exercise for Adults with Chronic Diseases: Systematic Review and Meta-Analysis

Bernard P [a,b*], Romain AJ [c], Caudroit J [d], Chevance G [e,f], Carayol M [e,g], Gourlan M [e,g], Dancause, KN [a], Moullec G [h,i]

[a] Université du Québec à Montréal, Montréal, Quebec , Canada

[b] Research Center, University Institute of Mental Health at Montreal, Montréal, Quebec, Canada

[c] Research Center, CHU de Montréal, Montréal, Canada

[d] Laboratoire sur la Vulnérabilité et L'innovation dans le Sport, University of Lyon 1, Lyon, France

[e] Laboratory Epsylon, Dynamics of Human Abilities and Health Behavior, University of Montpellier, Montpellier, France

[f] Les Cliniques du Souffle ®, Groupe 5 Santé, France

[g] Epidaure, Prevention Department of the Institut régional du Cancer de Montpellier, Montpellier, France

[h] Department of Social and Preventive Medicine, Public Health School, University of Montréal, Montréal, Quebec, Canada

[i] Research Center , CIUSSS Nord-de-l'Île-de-Montréal , Quebec , Canada

***Corresponding author: Paquito Bernard**

Université du Québec à Montréal, Montréal, Canada
Faculté des sciences
UQÀM, Complexe des Sciences
Pavillon des sciences biologiques (SB), Local: SB-4445
141, Avenue du Président Kennedy
Montréal, Québec, Canada, H2X 1Y4
bernard.paquito@uqam.ca

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Declaration of interest

All authors declare that they have no competing interests for this work.

Abstract

Objective. The present meta-analysis aimed to determine the overall effect of cognitive behavior therapy combined with physical exercise (CBTEx) interventions on depression, anxiety, fatigue, and pain in adults with chronic illness; to identify the potential moderators of efficacy; and to compare the efficacy of CBTEx versus each condition alone (CBT and physical exercise).

Methods. Relevant randomized clinical trials, published before July 2017, were identified through database searches in Pubmed, PsycArticles, CINAHL, SportDiscus and the Cochrane Central Register for Controlled Trials.

Results. A total of 30 studies were identified. CBTEx interventions yielded small-to-large effect sizes for depression (SMC = -0.34, 95% CI [-0.53; -0.14]), anxiety (SMC = -0.18, 95% CI [-0.34; -0.03]) and fatigue (SMC = -0.96, 95% CI [-1.43; -0.49]). Moderation analyses revealed that longer intervention was associated with greater effect sizes for depression and anxiety outcomes. Low methodological quality was also associated with increased CBTEx efficacy for depression. When compared directly, CBTEx interventions did not show greater efficacy than CBT alone or physical exercise alone for any of the outcomes.

Conclusion. The current literature suggests that CBTEx interventions are effective for decreasing depression, anxiety, and fatigue symptoms, but not pain. However, the findings do not support an additive effect of CBT and exercise on any of the four outcomes compared to each condition alone.

Keywords

Cognitive behavior therapy, physical activity, mental health, chronic disease

Introduction

In the article entitled 'No health without mental health', Prince et al. (2007) highlighted the need for mental health awareness to be integrated into health care, including chronic disease treatments (Prince et al., 2007). Indeed, comorbid psychological symptoms are highly prevalent among adults with physical chronic disease (Abrahams et al., 2016; Cruess et al., 2003; Matte et al., 2016; McCabe, 2010). Among the most prevalent comorbid psychological symptoms, four major psychological factors, namely depression, anxiety, fatigue, and pain, are related with a more rapid disease progression. These psychological symptoms are identified as risk factors for poor self-care, increased symptom burden, worsened physical functioning, more severe morbidity, and reduced quality of life among patients with various chronic diseases (such as chronic obstructive pulmonary disease (COPD) (Laurin, Moullec, Bacon, & Lavoie, 2011), diabetes (Deschênes et al., 2017), multiple sclerosis (Ensari et al., 2016), cancer (Trudel-Fitzgerald et al., 2014), and chronic fatigue syndrome (Wiltink et al., 2014).

Recently, a considerable literature has emerged about the prevention and treatment of psychological symptoms in patients with chronic diseases. Among available studies, using no pharmacological treatments to alleviate these symptoms, cognitive behavior therapy (CBT) and physical exercise interventions are empirically validated. The benefits of CBT and exercise are supported by meta-analyses of findings from multiple clinical trials for depression (Cuijpers, Cristea, Karyotaki, Reijnders, & Huibers, 2016; Schuch et al., 2016), anxiety (Cuijpers et al., 2016; Stonerock, Hoffman, Smith, & Blumenthal, 2015), fatigue (Larun, Brurberg, Odgaard-Jensen, & Price, 2016; Price, Mitchell, Tidy, & Hunot, 2008), and pain (Geneen et al., 2017; Williams, Eccleston, & Morley, 2012). CBT was also found to effectively decrease these psychological symptoms in adults with multiple sclerosis (Akker et al., 2016), chronic fatigue syndrome (Malouff, Thorsteinsson, Rooke, Bhullar, & Schutte, 2008), cancer (Sheard & Maguire, 1999), fibromyalgia (Bernardy, Klose, Busch, Choy, & Häuser, 2013), and coronary heart disease (Hackett, Anderson, House, & Xia, 2008). A review of meta-analyses concluded that CBT interventions are effective to manage psychological symptoms such as depression, anxiety, fatigue, and pain among adults with chronic illness (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012).

Other interventions such as exercise interventions were also found to improve psychological symptoms in adults with diabetes, cancer, chronic fatigue syndrome, and low back pain in many meta-analyses (Pedersen & Saltin, 2015). For example, two meta-analyses, including 40 and 90 randomized controlled trials (RCTs), concluded that exercise interventions reduce anxiety and depression symptoms in adults with chronic illness (Herring, O'Connor, & Dishman, 2010; Herring, Puetz, O'Connor, & Dishman, 2012). Moreover, physical exercise interventions were found to clinically reduce pain in patients with low back pain (Searle, Spink, Ho, & Chuter, 2015), and to decrease fatigue in cancer survivors (Brown et al., 2011). Hence, CBT and exercise have received considerable attention and represent effective interventions to deal with psychological comorbidities in patients suffering from chronic diseases.

Researchers have hypothesized an additive effect of CBT combined with physical exercise (CBTEx) when compared to each intervention alone. CBT directly addresses the cognitive distortions and emotional management that might improve self-care, while exercise facilitates behavioral activation and distraction (Piette et al., 2011). Several RCTs have examined these interactive effects on depression, anxiety, and fatigue in cancer survivors (Duijts et al., 2012), adults with COPD (Emery, Schein, Hauck, & MacIntyre, 1998), and chronic fatigue (Donta et al., 2003), with mixed results. Other studies have compared the effects of combined interventions to waitlist control group (Deale, Chalder, Marks, & Wessely, 1997), exercise alone (Gary, Dunbar, Higgins, Musselman, & Smith, 2010), CBT alone (Linton, Boersma, Jansson, Svard, & Botvalde, 2005), and CBT or exercise alone (McBeth et al., 2012) with inconclusive results. Furthermore, multi-arm RCTs did not facilitate a complete understanding of the effects of CBT, physical exercise or CBTEx effects. Two previous systematic reviews have described some of the available evidence (Kangas, Bovbjerg, & Montgomery, 2008; Wiles, Cafarella, & Williams, 2015). A significant reduction of depression and anxiety symptoms was found in interventions combining psychological components and exercise training for patients with COPD (Wiles et al., 2015). Kangas et al. (2008) found that both psychological and exercise interventions significantly decreased fatigue in adults with cancer but effects did not differ between the two interventions. However, these reviews assessed the effects of diverse psychological interventions (e.g., counselling, motivational interviewing) and included trials with mixed designs (i.e., single-group study,

controlled trial, RCT), thus limiting the conclusions that could be drawn. To the authors' knowledge, no previous study has systematically examined the additive effects of CBT combined with exercise on psychological symptoms in adults with chronic disease. Despite the evidence supporting the effects of both CBT and exercise interventions in the improvement of psychological symptoms among patients with chronic diseases, it is currently unclear if the combination of CBT and physical exercise results in greater improvements in psychological outcomes.

The purpose of this systematic review and meta-analysis was: (1) to summarize the literature on the effects of CBTEx for depression, anxiety, fatigue, and pain in adults with chronic disease; (2) to identify the potential moderators of efficacy; (3) to assess the efficacy of CBT versus exercise and the additive effects of CBT combined with exercise on outcomes of interest.

Method

Methods for collecting and summarizing data are in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). The study protocol was registered in PROSPERO (CRD42016048694).

Inclusion criteria

Studies were included in the systematic review if they met the following criteria, according to Participants, Intervention, Comparison, Outcomes, Study (PICOS).

1. Participants. Participants were adults with chronic disease as described by the World Health Organization (Alwan & Agis, 2011).

2. Interventions. Included trials examined the effects of CBTEx or CBT versus exercise. CBT is defined according to Cuijpers as "a therapy in which the therapist focuses on the impact that a patient's present dysfunctional thoughts affect current behaviour and functioning. CBT helps clients to evaluate, challenge, and modify their dysfunctional beliefs (cognitive restructuring), in part to promote behavioral change and improve their functioning. Therapists use a psychoeducational approach, and teach patients new ways to cope with stressful situations; however, CBT therapists emphasize homework assignments and outside-of-session activities, through the method of collaborative empiricism, to directly experience the value

of proposed changes within therapy sessions" (more details in Appendix 1) (Cuijpers, Berking, et al., 2013). Exercise interventions were defined as any physical interventions involving planned, structured, and repetitive movements. The nature of the exercise included, but was not limited to specific activities and included the following practices: walking programs, running, sports, and resistance training. Interventions could be home-based or supervised. No restriction was made regarding frequency, intensity, or duration of the program. Strictly relaxation interventions (e.g., deep breathing exercises) were excluded.

3. Controls. Included investigations compared CBTEx with usual care, wait-list, or an active comparison control condition.

4. Outcomes. Included trials measured at least one validated self-reported measure of depression, anxiety, fatigue, or pain as a primary or secondary endpoint at post-intervention time.

5. Studies. Only RCTs were included.

Exclusion criteria

Studies including healthy participants or those with severe mental illness, or interventions involving psychoeducation, counselling, physiotherapy, manual therapy, passive exercise, or lifestyle interventions were excluded.

Data sources and searches

Studies were identified by searching Pubmed, PsycArticles, CINAHL, SportDiscus and the Cochrane Central Register for Controlled Trials electronic databases until July 30th 2016 in English and French. An update was performed on July 14th 2017. The search strategy was adapted for each database using its specific vocabulary map. For instance, Mesh terms were used combined with filters for RCT, adult, and human studies. Additionally, relevant reviews were scanned. Details about research strategies are provided in Appendix 2. After duplicates were removed, titles and abstracts of all studies identified were examined independently (AJR, PB) to determine those meeting the selection criteria.

Data extraction

All relevant studies were scrutinized attentively to extract data on study participants and design, CBT and exercise components of interventions, and assessment tools. Risk of bias was assessed using four items

from the Cochrane collaboration assessment tool (Higgins et al., 2011). Methodological quality was assessed with six items from a scale validated for measuring quality of RCTs focusing on psychotherapy (Kocsis et al., 2010) and psychiatry settings (Moncrieff, Churchill, Drummond, & McGuire, 2001). Details are listed in Appendix 3. For each included study, data extraction and quality appraisal assessments were independently conducted by two of six researchers (AJ, PB, MC, JC, GC, MG). Any disagreements were resolved by discussion.

Statistical analysis

For each reported psychological outcome measure, the Standardized Mean Change score (SMC) using raw score standardization was calculated for both treatment and control groups. The difference between two standardized mean changes, after adjustment for estimation bias, served as the effect size for each study. Reported non-adjusted means and pretest standard deviations (SDpre) were used. If SDpre was not reported, it was estimated via the reported change score SD or pre-test range (Morris, 2008). For estimation of the SMC sampling variance, pre-test and post-test correlation was required. If this information was not reported, a correlation coefficient of 0.50 was used. Sensitivity analyses were carried out to ensure the robustness of results (0.30; 0.70; 0.90) (Higgins & Green, 2008).

For articles that reported insufficient information on outcomes, repeated attempts to contact corresponding authors were made to request more information. When the information was not provided, the effect size could not be calculated and these studies were therefore excluded from the meta-analysis. To estimate the overall effect of interventions and prevent a double counting of participants in a common arm, relevant groups from multi-arm RCTs were collapsed (Higgins & Green, 2011).

Random-effects models were performed due to the expected heterogeneity of studies. The standardized SMC value can be interpreted as 0.20, 0.50, and 0.80, representing small, medium, and large effect sizes, respectively (Cohen, 1977). Signs of effect sizes were set so that negative effect sizes for depression, anxiety, fatigue, and pain indicated improvements in favor of intervention. Heterogeneity was quantified with the I^2 statistic ranging from 0% to 100% (small: < 25%; moderate: 25 to 50%; large: ≥ 50%) (Higgins &

Green, 2008). Publication bias was evaluated by examining funnel plots. Regression residuals were screened to identify potential multivariate outliers using residual Cook distances.

Moderator analysis

According to clinical experience and literature background, the following set of factors were selected: (i) population-related characteristics: age, proportion of women; (ii) intervention-related characteristics: length, frequency, number of sessions, group versus individual delivery modes (two categories), and exercise nature (aerobic, resistance, combined, graded intervention; each category vs. all others); (iii) total methodological quality score. A set of bivariate random-effects meta-regression models were performed to identify potential moderators. Analyses were run after the exclusion of possible multivariate outliers (Higgins & Green, 2011). All continuous variables were zero-centered based on their means. Beta values (β) quantify the amount of variability in SMDs associated with one-unit increase of each moderator of interest. All analyses were carried out in R 3.3 using the *metafor* package (Viechtbauer, 2010).

Results

Search Results

The initial electronic searches identified 717 references, of which 105 were duplicates. After a review of titles and abstracts, 422 were excluded because they did not meet all inclusion criteria. Assessment of full-text articles was performed for 233 references. Thirty RCTs met the inclusion criteria, including 8 multi-arm RCTs. The number of studies included for each outcome of interest is detailed in the flow diagram (see Appendix 4). References of included trials are available in Appendix 4.

Characteristics of included studies

Participants

Sample sizes of included studies varied from 30 to 555 patients, with a mean age of 47.4 (SD = 9.0). The samples were mixed-sex in a majority of interventions (mean rate of women of 66% in samples). Adults with chronic fatigue were the most represented in included studies (9 RCTs, 30%) (Deale et al., 1997; Janse, Wiborg, Bleijenberg, Tummers, & Knoop, 2016; Jason et al., 2007; O'Dowd, Gladwell, Rogers, Hollinghurst, & Gregory, 2006; Prins et al., 2001; Ridsdale, Darbishire, & Seed, 2004; Sharpe et al., 1996; Zedlitz,

Rietveld, Geurts, & Fasotti, 2012). Participants with low back pain or COPD were found in 4 (13%) (Khan, Akhter, Soomro, & Ali, 2014; Linton et al., 2005; Smeets et al., 2006; Tummers, Knoop, van Dam, & Bleijenberg, 2012) and 3 RCTs (10%) (de Godoy & de Godoy, 2003,2005; Emery et al., 1998), respectively. Two RCTs included participants with current or history of depressive disorders (Gary et al., 2010; Piette et al., 2011) and five included adults with chronic fatigue syndrome (Deale et al., 1997; Janse et al., 2016; Jason et al., 2007; Prins et al., 2001; Sharpe et al., 1996). Appendix 5 provides details about country, diseases, age, and psychotropic medications (Bernard & Carayol, 2015).

Intervention and outcome characteristics

The CBT interventions mainly targeted fatigue (10 RCTs, 33%) and pain (4 RCTs, 13%) symptom management and decrease of depression and/or anxiety symptoms (5 RCTs, 17%). The group format was preferred in 16 RCTs (53%). Most CBT interventions were provided by psychologists or CBT therapists.

Supervised sessions of physical exercise were reported in 19 (63%) interventions. Principles of graded exercise therapy were applied in 10 studies (33%) (Fulcher & White, 1998). Aerobic and resistance exercise were combined in 8 RCTs (27%). Exercise interventions were mainly supervised by physiotherapists or physical fitness instructors. All CBTEx interventions were simultaneously delivered.

Outcomes measures were all self-reported scales. The Hospital Anxiety Depression Scale (Herrmann, 1997) was the most commonly used measure of depression. The fatigue subscale of the Checklist Individual Strength (Beurskens et al., 2000) and a visual analog scale were used to assess fatigue and pain, respectively. All measures are detailed in forest plots. Table 1 summarizes the interventions' characteristics.

Risk of bias and methodological quality

Detailed assessment of the risk of bias and methodological quality for each trial is presented in Appendix 5. Risks of bias assessment of studies with a CBTEx arm are summarized in a figure in Appendix 5. The mean methodological quality score was 5.97 (SD = 3.05). The highest score was 12, but 5 studies received a score ≤2.

Effects of CBT combined with physical exercise interventions

Meta-analyses were carried out on depression, anxiety, fatigue, and pain outcomes with 16, 11, 9, and 4 RCTs, respectively (see table 2 for details on studies' outcomes). Controlled comparisons of pre- and post-intervention indicated that CBTEx significantly reduced depression (SMC = -0.34; 95% CI [-0.53, -0.14]), anxiety (SMC = -0.18; 95% CI [-0.34, -0.03]), and fatigue (SMC = -0.96; 95% CI [-1.43, -0.49]), but not pain (SMC = -0.18; 95% CI [-0.55, 0.19]). Forest plots are presented in Figure 1. Heterogeneity among studies was moderate to large. The funnel plots appeared to be relatively asymmetrical (presented in Appendix 6). Cook's distance analyses identified two multivariate outliers that were also excluded from the final analysis concerning anxiety outcome.

Based on available data, CBTEx interventions were also compared to usual care/wait list arms. A significant effect size was observed for depression (SMC = -0.46; 95% CI [-0.68, -0.24]), anxiety (SMC = -0.36; 95% CI [-0.54, -0.18]), fatigue (SMC = -1.22; 95% CI [-1.70, -0.75]), and pain (SMC = -0.19; 95% CI [-0.37, 0.02]), with small to large effects. Detailed information is presented in Appendix 7.

Moderating variables

Population, intervention, and methodological characteristics were examined in univariate analysis. For depression, longer intervention (β = -0.19; 95% CI [−0.34, −0.04]; p = .01; I^2 = 53%) and poorer methodological quality (β = 0.23; 95% CI [0.03, 0.42]; p = .02; I^2 = 64%) were associated with greater effect size. Longer intervention (β = -0.42; 95% CI [-0.83, -0.01]; p = .04; I^2 = 0%) was also associated with greater effect size in anxiety scores. A larger effect on fatigue was observed in samples with more women (β = -0.62; 95% CI [-1.17, -0.08]; p = .03; I^2 = 87%). Figure 2 presents the scatterplots of these significant univariate moderators.

Efficacy of CBT combined with physical exercise versus CBT and exercise alone

For CBTEX versus CBT, the set of analyses was performed on depression, anxiety, and pain outcomes with 9, 6, and 3 RCTs, respectively. No data were available for fatigue. For CBTEx versus exercise, analyses were carried out on depression, anxiety, fatigue and pain outcomes with 6, 4, 2 and 3 RCTs. Direct comparison of combined CBT and exercise with either CBT or exercise alone showed no significant differences for any outcome. Details are presented in Table 2 and forest plots in Appendix 7.

Discussion

This systematic review summarizes the available empirical evidence on the effects of CBTEx interventions on psychological outcomes in adults with chronic diseases. To the best of our knowledge, this is the first systematic review to address this specific question.

The findings highlighted that CBTEx significantly decreased depression and anxiety with small effect sizes, and fatigue with a large effect size, across a wide spectrum of adults with chronic illness. However, no significant effects were observed for pain, except in comparison with wait list or usual care arms. Although the two largest RCTs were not included in the pooled effect size, they did not individually demonstrate significant effects on pain (Donta et al., 2003; McBeth et al., 2012). Regarding depression and fatigue, larger effect sizes were found when CBTEx was compared to usual care or waitlist, as previously reported (Barth et al., 2013; Cuijpers et al., 2014).

The effect sizes found for depression, anxiety, and fatigue were of similar magnitude as findings of previous meta-analyses investigating effects of exercise in samples with mixed or specific chronic illness. Summary effects sizes (*d*) were 0.30 for depression and 0.29 for anxiety (Herring et al., 2010, 2012) and -0.68 for chronic fatigue (Larun et al., 2015). In previous meta-analyses examining CBT efficacy, the pooled effect sizes were also comparable (Hofmann et al., 2012) for depression, anxiety, and fatigue (Malouff et al., 2008). These findings indirectly suggest that efficacy of CBTEx interventions is not superior to exercise or CBT interventions alone for decreasing depression, anxiety, and fatigue symptoms.

Regarding CBTEx moderators, longer interventions were related to greater reduction of depression and anxiety symptoms at the end of intervention. For fatigue, women participants had more benefits from CBTEx interventions. Moreover, a poor methodological quality of included trials was also associated with a larger effect size for depression. This result provides some evidence that the efficacy of CBTEx on depression could be overestimated due to methodological weaknesses of RCTs. This finding is consistent with previous meta-analyses examining the efficacy of psychotherapy (Cuijpers, van Straten, Bohlmeijer, Hollon, & Andersson, 2010), health behavior change (Bernard et al., 2017), and physical exercise (Carayol,

Delpierre, Bernard, & Ninot, 2015), which highlighted that low methodological quality was associated with larger effect sizes.

Regarding trials that directly compared CBTEx with CBT or exercise, no significant effect sizes were consistently observed. Despite the small number of comparative trials for some of the analyses, data suggest that CBTEx was not more effective than CBT or exercise interventions alone in direct comparisons. Additionally, the exploratory analyses did not find significant differences between CBT and exercise interventions on selected outcomes. Taken together, these results suggest an absence of superiority of CBTEx and CBT or exercise alone on depression, anxiety, fatigue, and pain at the end of intervention. Indeed, CBT and exercise interventions, combined or individually, may produce equivalent psychological benefits that could be attributed in part to 'common factors' embodied in these two treatments. Although factors such as support (e.g., therapeutic alliance), learning (e.g., changing expectations), and actions (e.g., success experience) are initially proposed to explain the equivalent outcomes between psychotherapies (Huibers & Cuijpers, 2014), they can also be applied in exercise. Furthermore, experimental investigations found that leadership, style of intervention, or group leadership in exercise professionals are associated with higher affective benefits (Turner, Rejeski, & Brawley, 1997), physical activity expectations (McAuley, Talbot, & Martinez, 1999), and motivation (Puente & Anshel, 2010; Waters, Reeves, Fjeldsoe, & Eakin, 2012).

Based on the direct comparison between CBT and exercise, no superiority was found which suggests that these two interventions can be equally recommended in adults with chronic disease. However, exercise may have supplementary benefits to CBT on other health outcomes. Exercise not only improves chronic disease specific symptoms (e.g., dysnpea for COPD patients) (Pedersen & Saltin, 2015), but also decreases the risk of metabolic or cardiovascular disease that are highly prevalent in adults with chronic illness and psychological distress (Vancampfort et al., 2015).

The conclusions drawn from this meta-analysis, however, should be tempered by a number of methodological issues. The absence of effect of CBTEx versus CBT or exercise alone might reflect a contamination effect (a well-known methodological limit of exercise trials) of CBT groups (i.e., CBT participants deliberately increase their physical activity levels after randomization). Thus, researchers could

compare CBTEx versus 'partial' CBTEx participants. This contamination effect has been recently identified in 11 of 30 exercise-oncology RCTs, with rates from 22 to 52% (Bisschop et al., 2015). Second, the effects of CBTEx could have been overestimated due to methodological weaknesses associated with larger effect sizes (for depression), high level of heterogeneity (for depression and fatigue), and a systematic publication bias identified for all outcomes. Furthermore, the meta-analysis was limited to the examination of the short-term efficacy of CBTEx, whereas CBTEx participants can maintain their benefits over time (Cuijpers, Hollon, et al., 2013). Third, psychotropic medications could confound the effects of CBT or exercise, particularly in adults with chronic illness (Bernard & Carayol, 2015). Indeed, populations with chronic illness are known to report higher use of psychotropic medications compared to the general population (Azzone, Frank, Pakes, Earle, & Hassett, 2009). However, only eight of the reviewed trials provided details about these medications. Finally, the direct comparison between CBTEx and CBT or exercise alone were performed with RCTs that were not large enough (particularly for fatigue and pain outcomes), thus limiting the generalizability of findings.

In conclusion, this meta-analysis provides evidence that CBTEx interventions are effective to improve depression, anxiety, and fatigue, compared to controls. However, the findings do not support an additive effect of CBT with exercise on any of the four outcomes compared to each intervention alone. Further research is needed to assess the long-term efficacy of CBTEx interventions. Future research is required to identify the respective mechanisms of CBT and exercise interventions, to improve the tailoring of combined interventions. Finally, noninferiority trials are needed in order to directly compare CBTEx, CBT, and physical exercise interventions.

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Table 1

Description of intervention contents

		Arms				Exercise									CBT				
Author	Year	CBTEx	Ex	CBT	Ex/CBT		Aero	Resi	Comb	Grad	Gp	Ind	Sup	NoSup	Pro		Gp	Ind	Face	Home	Pro
Deale	1997	●	○	○	○	PA planned, graded, manageable portions spread across the day; daily targets covering a range of activities during 3 CBT sessions	○	○	○	●	○	●	○	●	Therapist	CBT aim was to show patients that activity could be increased steadily and safely without exacerbating symptoms. Patients identified distressing thoughts including fear about symptoms, perfectionism, self-criticism	○	●	●	○	Therapist
deGodoy	2003	○	●	○	○	Physical exercise sessions included aerobic conditioning with a treadmill, and flexibility training	●	○	○	○	●	○	●	○	-	CBT for anxiety and depression. CT and logotherapy techniques (12 sessions) focused on social, marital, work, health, and interpersonal philosophy and habits	●	○	●	○	-
deGodoy	2005	○	●	●	○	Treadmill sessions ; 75-85 % maximum HR	●	○	○	○	●	○	●	○	Physical education instructor	CBT addressed the psychological needs of the patients, including difficulties in daily life and maintenance of anxiety control	○	●	●	○	Psychologist
Donta	2003	●	●	●	○	Participants were asked to exercise independently 2-3 times per week during the 12-week and throughout the follow-up period. (Helped to develop the ability to set the intensity based on their symptoms)	●	○	○	○	●	○	●	●	Physical therapists , masters-level exercise physiologi sts	CBT was designed to target physical function, with 2 goals: teaching behavioral skills to help participants experience a safe and gradual improvement in physical functioning without exacerbation of symptoms and teaching cognitive strategies to help participants learn systematic ways of analyzing and producing solutions to problems that serve as barriers to functioning	●	○	●	○	Trained in CBT psychologists
Duijts	2012	●	●	●	○	Individually tailored, home-based, self-directed exercise program	●	○	○	○	○	●	○	●	Physiothe rapist	CBT for flashes and night sweats, other symptoms (e.g, vaginal dryness) and problem areas (body image, sexuality, and mood disturbance)	○	-	●	○	Psychologist + trained social worker
Emery	1998	●	○	●	○	4h daily during 5 weeks, then 5-week less intensive regimen. Daily sessions: aerobic exercise, strength training with equipment	○	●	○	○	-	-	●	○	-	Stress management groups with a cognitive-behavioral format. Participants were taught progressive muscle relaxation, strategies to increase awareness of cognitive distortions associated with physical limitations, and the negative emotional consequences of cognitive distortions	●	○	●	○	-
Fossati	2004	●	○	●	○	PA recommendations: to increase the number of daily activities and plan 3 sessions	●	○	○	○	●	○	○	●	Psycholo gists	CBT to reorganize eating behavior, reintroduce eating schedules, modify contents of the meals, develop cognitive restructuring, and identify the psychological	●	○	●	○	Psychologist s

			of 30 min of exercise			patterns that caused cognitive distortions		
Gary	2010	● ● ● ○	Exercise prescription at home (walking with graded intensity and duration)	● ○ ○ ○ ○ ● ○ ●	Trained nurse	CBT for depression	○ ● ● ○	Trained nurse
Janse	2016	● ○ ○ ○	CBT self-help booklet : gradual increase of PA; explanation of different PA patterns ; gradually increase of PA by walking or riding; beliefs that PA exacerbate symptoms	○ ○ ○ ● ○ ● ○ ●	Trained/ experienced CBT therapists	CBT for CFS (booklet with 13 modules). Fatigue related cognitions were challenged and patients encouraged to develop sense of control over their symptoms	○ ● ○ ●	Tained /experienced CBT therapists
Jason	2007	● ● ● ○	Schedule of planned, graded PA. Activity and rest were pre-planned and time-contingent rather than symptom-driven.	○ ○ ○ ● ○ ● ○ ●	Trained and experienced nurses	CBT for CFS. Participants were asked to evaluate the effects of gradual and consistent increases in activity and use strategies other than avoidance	○ ● ● ○	Trained and experienced nurses
Johnson	2007	● ○ ○ ○	Exercise	- - - - ● ○ ● ○	Trained physiotherapist	CBT for pain management ; control back pain through the use of PA and psychological help techniques; problem solving ; relaxation	● ○ ● ○	Trained physiotherapist
Jonsbu	2011	● ○ ○ ○	Treadmill session exposition (>75% max HR) for 12min with repeated measures of perceived exertion. Patients were encouraged to engage in PA between sessions	● ○ ○ ○ ○ ● ● ○	Psychiatrist trained in CBT	CBT for fear of bodily sensations. 3 CBT sessions (interpretation of physical symptoms; exposition to PA; identification of avoidance behaviors)	○ ● ● ○	Psychiatrist trained in CBT
Khan	2014	● ● ○ ○	Cycling + treadmill for 10min ; resistance exercise with 20 repetitions	○ ○ ● ○ ● ○ ● ●	Physical therapists	CBT consisted of operant behavioral graded activity and problem solving training and modify dysfunctional beliefs	● ○ ● ○	Physical therapit trained for CBT
Koopamn	2015	○ ○ ○ ●	Exercise was designed specifically to enhance patients' physical capacity. The supervised group-training program consisted of individually tailored muscle strengthening and functional exercises	○ ○ ● ○ ● ○ ● ●	Trained physiotherapists	CBT for perpetuating factors of fatigue. These involve dysfunctional cognitions, pain, or fatigue; dysfunctional attention to pain and fatigue symptoms; deregulation of sleep; deregulation of physical, social, and/or mental activities; and low social support. For each factor a standardized module was available as part of the intervention	○ ● ● ○	Trained CBT therapists
Linton	2005	● ○ ● ○	Physical training tailored according to patient characteristics	- - - - - - ● ○	Physical therapist	CBT for pain management aimed at preventing future problems in 3 parts: to provide relevant facts, problem solving where pairs of participants solve problems from a case study, training about coping skills +	● ○ ● ○	Experienced/ trained in CBT therapists

																						homework assignments	
May	2008	○	●	○	○	Individual aerobic training; muscle strength training; progressive resistance muscle training ; group sports (e.g., curling).	○	○	●	○	●	○	●	○	Experienced psychologist, social worker	CBT to solve problems associated with psychosocial and physical consequences of cancer. CBT aimed at finding effective and adaptive solutions to stressful problems, and changing dysfunctional cognition and behaviors.	●	○	●	○	Experienced psychologist, social worker
McBeth	2012	●	●	●	●	Leisure-facility– and gym-based exercise program for improving cardiorespiratory fitness ; (40% - 85% of HR reserve) ; non–gym days to engage in “everyday” activities	-	-	-	○	○	●	●	○	Experienced fitness instructors	Telephone-delivered CBT. Therapists developed a shared understanding and formulation of the current problem, and identified patient-defined goals. CBT techniques included : behavioral activation, cognitive restructuring and lifestyle changes.	○	●	○	●	Therapists accredited by the BABBCP
O’Dowd	2006	●	○	○	○	Structured incremental exercise program. Instructions were given about pacing up by small increments	○	○	○	●	●	○	●	○	Experienced physiotherapist	CBT to modify thoughts and beliefs about symptoms and illness, and behavioral responses to symptoms. The ultimate goal was to increase adaptive coping strategies	●	○	●	○	Experienced psychologist
Pendlton	2002	●	○	●	○	Subjects were provided memberships to a Rehabilitation Center. They were encouraged to gradually increase their levels of aerobic exercise + 1 home-base session of brisk walking	●	○	○	○	●	○	●	●	-	CBT treatment for BED. The first half of each session dealt with eliminating binge eating by establishing regular healthy eating patterns. Weight concerns were put on hold until binges were under control. The second half included efforts to enhance social influence processes and to develop problem-solving skills	●	○	●	○	Experienced/ trained in CBT dietitians
Piette	2011	●	○	○	○	Pedometer-based walking program with walking homework	●	○	○	○	○	●	○	●	Experienced CBT nurses	CBT (12 weekly sessions + 9 monthly booster sessions) presented concepts related to a walking program, and the links among depression, PA, and diabetes outcomes	○	●	○	●	Experienced CBT nurses
Prins	2001	●	○	○	○	Patients were encouraged to attain a base level of PA. A structured PA program was started. After a gradual PA increase, a plan for work rehabilitation was carried out	○	○	○	●	●	○	○	●	Trained in CBT psychologist, psychiatrist	The model of perpetuating factors was explained during the first sessions. Fatigue-related cognitions were challenged to diminish somatic attributions, improve sense of control over symptoms, facilitate behavior change, and deal with relapse prevention	●	○	●	○	Trained for CBT psychologist, psychiatrist
Redondo	2004	○	○	○	●	Each week:1 session of exercises in a warm-water pool, 2 sessions of flexibility and endurance exercises, 2 sessions of cardiovascular fitness	○	○	●	○	●	○	●	○	Physiotherapists	CBT was mainly designed for reducing distorted pain dimensions, to cope with chronic pain, increase self efficacy, and to use techniques for the management of chronic pain	●	○	●	○	-

Sharpe	1996	● ○ ○ ○	Patients were encouraged to evaluate the effects of gradual and consistent increases in PA and to try strategies other than avoidance	○ ○ ○ ● ○ ● ○ ●	Cognitive therapists	Patients were encouraged to question a simple disease explanation of the illness, to consider the role of psychological and social factors. CBT included strategies to reduce excessive perfectionism and self-criticism, and to increase active problem solving	○ ● ● ○	Cognitive therapists
Smeets	2006	● ● ● ○	The PA treatment consisted of aerobic training (65-80% of the max HR, and 3 dynamic static strengthening exercises (70% of 1-RM)	○ ○ ● ○ ● ○ ● ○	Physiotherapists with training for LBC	CBT was aimed to help patients to reach their individual daily life goals, to increase their PA level and to modify dysfunctional beliefs. Patients received a course book with additional information, a summary of each session and homeworks	● ● ● ○	Clinical psychologists, experienced social workers
Tummers	2012	● ○ ○ ○	3 chapters from CBT booklet self-help guide: explanation of different PA patterns; gradual increase of PA by walking or riding; beliefs that PA exacerbate symptoms	○ ○ ○ ● ○ ● ○ ●	Trained psychiatric nurses	CBT for CFS: fatigue-related cognitions were challenged; patients were encouraged to develop a sense of control over their symptoms and reduce the focus on fatigue	○ ● ○ ●	Trained psychiatric nurses
VanKoulila	2010	● ○ ○ ○	Exercise training aimed at increasing the level of physical fitness and flexibility. Each exercise session included relaxation training, aerobic and anaerobic exercises	○ ○ ● ● ● ○ ● ○	Trained physiotherapists	CBT aimed at diminishing the daily perceived cognitive, behavioral, emotional, and social consequences of pain. Pain-avoidance treatment aimed at increasing the patient's level of PA and diminishing pain-avoidance behaviors by stimulating them to gradually and systematically increase their daily activities and exposure to fear-related situations	● ○ ● ○	Experienced and trained psychotherapist + social worker
Zedlitz	2012	● ○ ● ○	Walking on a treadmill, strength training, home-work assignments. Intensity was slowly increased	○ ○ ● ● ● ○ ● ○	Experienced physiotherapist	The aims of CBT were to foster behavioral change, to decrease fatigue-related anxiety and to help to accept and manage existing fatigue symptoms.	● ○ ● ○	Experienced neuropsychologist
RCTs with direct comparison of CBT versus physical exercise								
Huang	2015	○ ○ ○ ●	Participants were encouraged to engage in 150 min/week of exercise by completing 3 50-min sessions in groups of 2–4 participants	○ ○ ● ○ ● ○ ● ○	Experienced trained physical fitness instructor	CBT intervention with 3 phases: behavioral activation (participants learn to monitor their daily activities and experiences); cognitive assessment and restructuring; participants work on altering core beliefs and analysis of dysfunctional coping mechanisms	● ○ ● ○	Geriatric nurse
Risdale	2004	○ ○ ○ ●	Home exercise. Initial sessions lasting between 5 and 15 min at an intensity of 50% max HR. Gradual and progressive increase in aerobic activities, walking	● ○ ○ ● ○ ● ● ●	Physiotherapist	CBT for CFS. It involved activity planning, homework, establishing a sleep routine. The CBT ensures levels of activity and rest are both consistent and realistic given the patients' responsibilities. Relapse prevention was addressed in the last two sessions	○ ● ● ○	CBT therapist
Voet	2014	○ ○ ○ ●	Home training twice a week and supervised exercise.	● ○ ○ ○ ○ ● ● ●	Physical therapist	CBT comprised 6 modules based on known fatigue-perpetuating factors. The therapist helps the	○ ● ● ○	CBT therapist

Every 4 weeks, the level was increased by 5% from 50% to 65% of the HR reserve	participant formulate his or her thoughts regarding fear of progression. These thoughts are then challenged against reality, thereby reducing daily unhelpful thoughts regarding disease progression

Note. BED = Binge Eating Disorder, CFS = Chronic Fatigue Syndrome, CBTEx = Cognitive Behavioral Therapy combined with physical exercise, CBT = Cognitive Behavioral Therapy, CBT/Ex = direct comparison of CBT versus physical exercise, Aero = Aerobic, Resi = Resistance, Comb = Aerobic and resistance exercise combined, Gp = group, Ind = individual, NoSup = No supervised exercise, Pro = Professional providing treatment, Face = Face to face intervention, Home = Home-based intervention, HR = Heart rate, PA = Physical activity, BABCP = British Association for Behavior and Cognitive Psychotherapies, LBC = Low back pain, ○ = No, ● = Yes, - = not applicable

Table 2

Results of meta-analyses

	Depression							Anxiety						
	K/Tot	K_{sm}/K	Ne	Nc	SMD [95 %CI]	I^2	Pub bias	*K/Tot*	K_{sm}/K	Ne	Nc	SMD [95 %CI]	I^2	Pub bias
CBTEx vs. All	16/17	10/17	814	1265	-0.34 [-0.53; -0.14]	70 %	●	9/12*	4/11	459	792	-0.18 [-0.34; -0.03]	30 %	●
CBTEx vs. UCWL	8/8	3/8	519	515	-0.46 [-0.68; -0.24]	55 %	●	5/5	2/5	268	285	-0.36 [-0.54; -0.18]	5%	●
CBTEx vs. Ex	6/7	4/7	288	277	-0.26 [-0.74; 0.23]	80%	-	4/5	3/5	205	201	-0.36 [-0.92; 0.19]	80%	-
CBTEx vs. CBT	9/10	5/10	399	388	-0.08 [-0.24; 0.07]	0%	-	6/7	4/7	272	272	-0.31 [-0.84; 0.23]	86%	-
Ex vs. CBT	7/8	5/8	246	259	0.17 [-0.19 ; 0.48]	50%	-	4/5	2/5	189	204	-0.19 [-0.28; 0.66]	54%	-
	Fatigue							**Pain**						
	K/Tot	K_{sm}/K	Ne	Nc	SMD [95 %CI]	I^2	Pub bias	*K/Tot*	K_{sm}/K	Ne	Nc	SMD [95 %CI]	I^2	Pub bias
CBTEx vs. All	9/11	4/11	492	728	-0.96 [-1.434; -0.49]	87 %	●	4/7	0/4	352	924	-0.18 [-0.55; 0.19]	86%	-
CBTEx vs. UCWL	5/6	1/5	319	339	-1.22 [-1.70; -0.75]	80 %	●	3/4	0/3	283	268	-0.19 [-0.37; -0.02]	0 %	○
CBTEx vs. Ex	2/4	0/4	188	184	-0.12 [-0.36; 0.12]	0%	-	3/6	1/6	194	182	-0.38[-1.03; 0.27]	77%	-
CBTEx vs. CBT	-	-	-	-	-	-	-	3/6	1/6	236	205	-0.03 [-0.33; 0.28]	51%	-
Ex vs. CBT	3/5	2/5	166	147	-0.23 [-0.47; 0.02]	0%	-	4/7	2/4	144	134	-0.16 [-0.14; 0.46]	32%	-

Notes. K/Tot number of interventions with available data for statistical analysis,K_{sm}/ number of interventions with <35 participants per arm, Ne = Number of participants in experimental arm, Nc = Number of participants in control arm(s), SMC = Standardized Mean Change, CI = confidence interval, Pub bias = Publication biais, ○ = No, ● = Yes, - = not applicable, CBTEx = Cognitive Behavioral Therapy combined with physical exercise, CBT = Cognitive Behavioral Therapy, CBT/Ex = direct comparison of CBT versus physical exercise, UCWL = Usual care or wait list arm

Ne and Nc include only arms with available data to pool size effects.

* Two multivariate outliers excluded (Emery et al., 1998; Fossati et al., 2004)

Figure 1

Forest plots for overall effect of CBT combined with physical exercise on depression, anxiety, and fatigue.

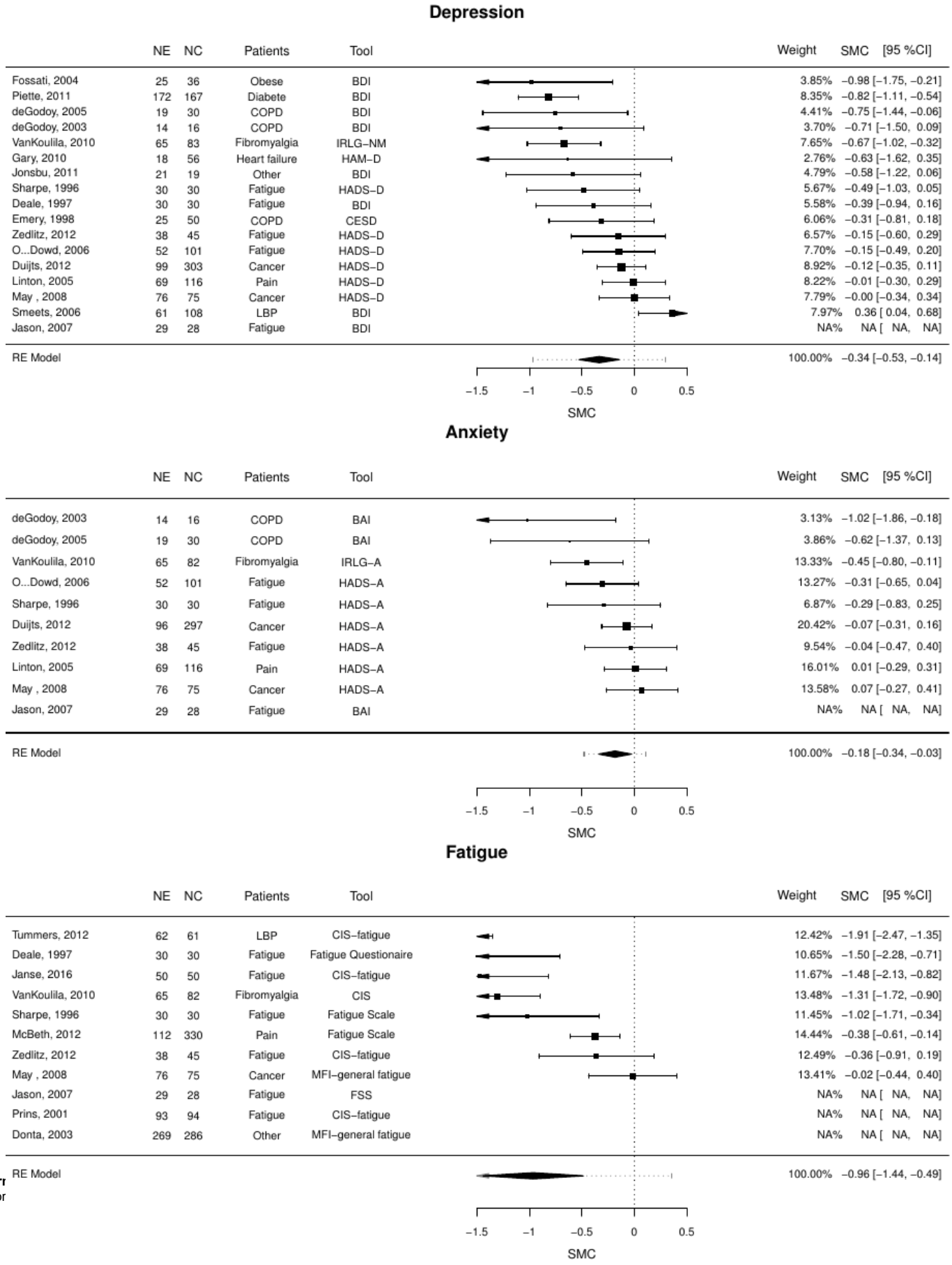

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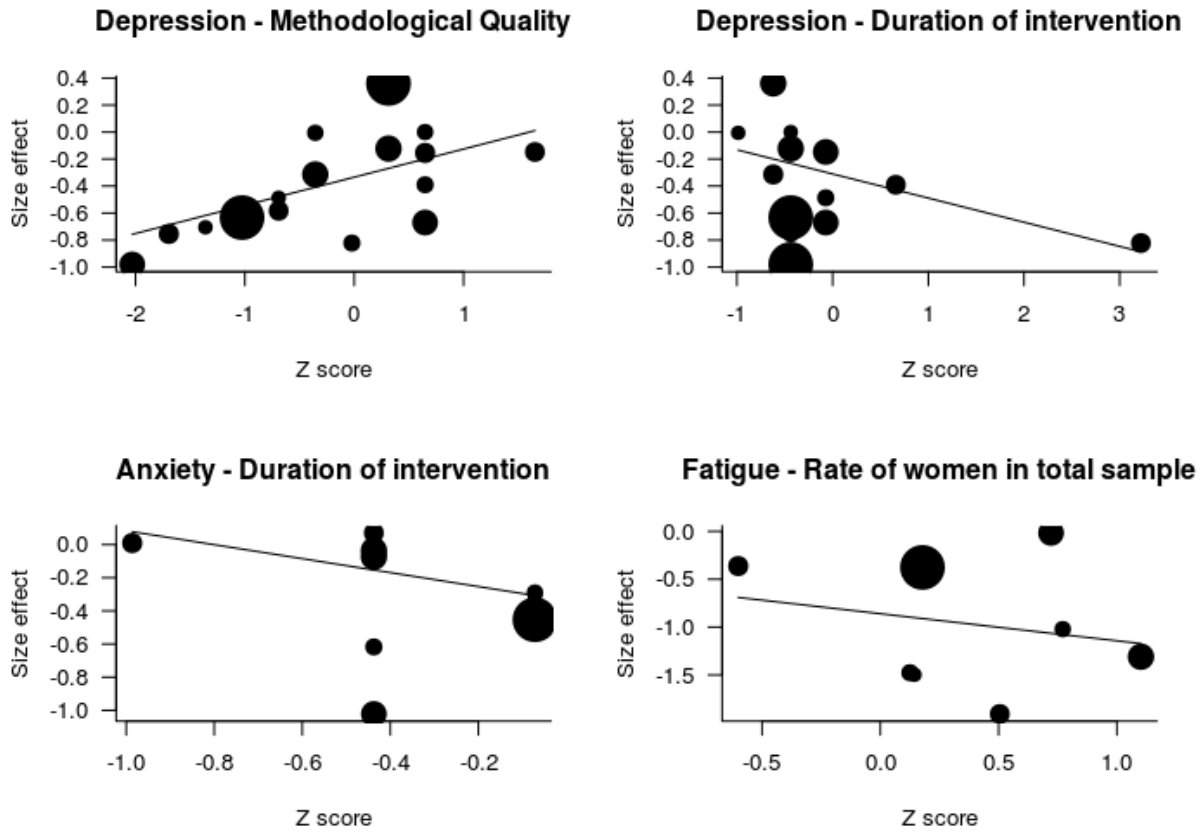
Figure 2

Scatterplots of univariate moderators for depression, anxiety, and fatigue



Appendix

Appendix 1 CBT definition from Cuijpers et al. 2013

"*a therapy in which the therapist focuses on the impact that a patient's present dysfunctional thoughts affect current behavior and functioning. CBT helps clients to evaluate, challenge, and modify their dysfunctional beliefs (cognitive restructuring), in part to promote behavioural change and improve their functioning. Therapists use a psychoeducational approach, and teach patients new ways to cope with stressful situations; however, CBT therapists emphasize homework assignments and outside-of-session activities, through the method of collaborative empiricism, to directly experience the value of proposed changes within therapy sessions. We distinguished 2 main types of CBT:*

1. CBT in which cognitive restructuring is the core element of the treatment.

2. CBT in which cognitive restructuring is an important component, but in which at least 2 other components (such as behavioural activation (BA), social skills training, relaxation, or coping skills) also have a prominent place. One example of this latter approach is the Coping with Depression course.

Within the first subtype, we distinguished 2 variants:

a. The manual developed by Beck et al1 is the most widely used manual for CBT (which includes a module on BA; see below).

b. In several studies, cognitive restructuring is used as a treatment (with or without a module on BA), but no explicit reference is made to Beck et al's manual, or where major adaptations were made to this manual.13 Therapies that could be considered to be part of a broader family of CBT, such as PST, BA, or social skills training, were not considered to be CBT if they did not include a module specifically focused on cognitive restructuring."

Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., & Dobson, K. S. (2013). A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie*, *58*(7), 376–385. https://doi.org/10.1177/070674371305800702

Appendix 2. Research equation strategy

For each databases, we performed a first paper selection after abstract screening, then we checked the presence of all inclusion criteria in full-text form. This method respects the PRISMA recommendations (Liberati et al., 2009).

PUBMED MESH
"Behavior Therapy"[Mesh] AND "Exercise"[Mesh] AND ("Depression"[Mesh] OR "Anxiety"[Mesh] OR "Pain"[Mesh] OR "Fatigue"[Mesh]) AND (Randomized Controlled Trial[ptyp] AND "humans"[MeSH Terms] AND "adult"[MeSH Terms])

EMBASE
#2 'cognitive behavior therapy'/exp OR 'cbt (cognitive behavioral therapy)' OR 'cbt (cognitive behavioural therapy)' OR 'cognitive behavior therapy' OR 'cognitive behavior treatment' OR 'cognitive behavioral therapy' OR 'cognitive behavioral treatment' OR 'cognitive behaviour therapy' OR 'cognitive behaviour treatment' OR 'cognitive behavioural therapy' OR 'cognitive behavioural treatment' OR 'cognitive therapy' AND 'exercise'/exp AND ('depression'/exp OR 'central depression' OR 'clinical depression' OR 'depression' OR 'depressive disease' OR 'depressive disorder' OR 'depressive episode' OR 'depressive illness' OR 'depressive personality disorder' OR 'depressive state' OR 'depressive symptom' OR 'depressive syndrome' OR 'mental depression' OR 'parental depression' OR 'anxiety'/exp OR 'pain'/exp OR 'acute pain' OR 'cheiragra' OR 'chiragra' OR 'deep pain' OR 'lightning pain' OR 'nocturnal pain' OR 'pain' OR 'pain response' OR 'pain syndrome' OR 'treatment related pain' OR 'fatigue'/exp OR 'fatigue' OR 'tiredness') AND ('randomised controlled trial'/exp OR 'controlled trial, randomized' OR 'pragmatic clinical trial' OR 'pragmatic clinical trials' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled')
#1 AND ('randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de) AND ('article'/it OR 'article in press'/it)

CINAHL
((MH “cognitive behaviour therapy”) OR MH (“cognitive therapy”) OR MH (“cognitive behavior therapy”)) AND ((MH "Exercise+") OR (MH “physical activity”)) AND TX depress* OR anxi* OR pain OR fatigue

PSY ARTICLES
results for Index Terms : { Cognitive Behavior Therapy} OR { Cognitive Therapy} *AND* Index Terms : { Exercise} *AND* Age Group : Adulthood (18 yrs & older) *AND* Methodology : Treatment Outcome/Randomized Clinical Trial *AND* Peer-Reviewed Journals only

Cochrane library
#1 MeSH descriptor: [Behavior Therapy] explode all trees
#2 MeSH descriptor: [Exercise] explode all trees

Sportdiscus
“cognitive behaviour therapy” OR "cognitive therapy" OR "behavior therapy" AND exercise
Randomized Controlled trials peer reviewed

Screened Reviews

Bernardy, K., Klose, P., Busch, A. J., Choy, E. H. S., & Häuser, W. (2013). Cognitive behavioural therapies for fibromyalgia. The Cochrane Database of Systematic Reviews, (9), CD009796. https://doi.org/10.1002/14651858.CD009796.pub2

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Wiles, L., Cafarella, P., & Williams, M. T. (2015). Exercise training combined with psychological interventions for people with chronic obstructive pulmonary disease. Respirology (Carlton, Vic.), 20(1), 46–55. https://doi.org/10.1111/resp.12419

Appendix 3. Items assessing risk of bias and methodological quality

Cochrane Collaboration's tool

Domain	Support for judgement	Review authors' judgement
SELECTION BIAS		
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
DETECTION BIAS		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
ATTRITION BIAS		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons why attrition/exclusions were reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
REPORTING BIAS		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.

Methodological quality

Items from Kocsis et al. (2010) A new scale for assessing the quality of randomized clinical trials of psychotherapy

Item 5. Treatment(s) (including control/comparison groups) are sufficiently described or referenced to allow for replication
0 = poor or no treatment description or references
1 = brief treatment description or references (also if full description of one group and poor description of another)
2 = full treatment description or references (manual not required)

Item 6. Method to demonstrate that treatment being studied is treatment being delivered (only satisfied by supervision if transcripts or tapes are explicitly reviewed)
0 = poor or no adherence reporting
1 = brief adherence reporting with standardized measure or full adherence reporting with nonstandardized measure (eg, nonindependent rater)
2 = full adherence reporting with standardized measure (must be quantitative and completed by an independent rater)

Item 15. Intent-to-treat method for data analysis involving primary outcome measure
0 = no description or no intent-to-treat analysis with primary outcome measure
1 = partial intent-to-treat analysis with primary outcome measure
2 = full intent-to-treat analysis with primary outcome measure

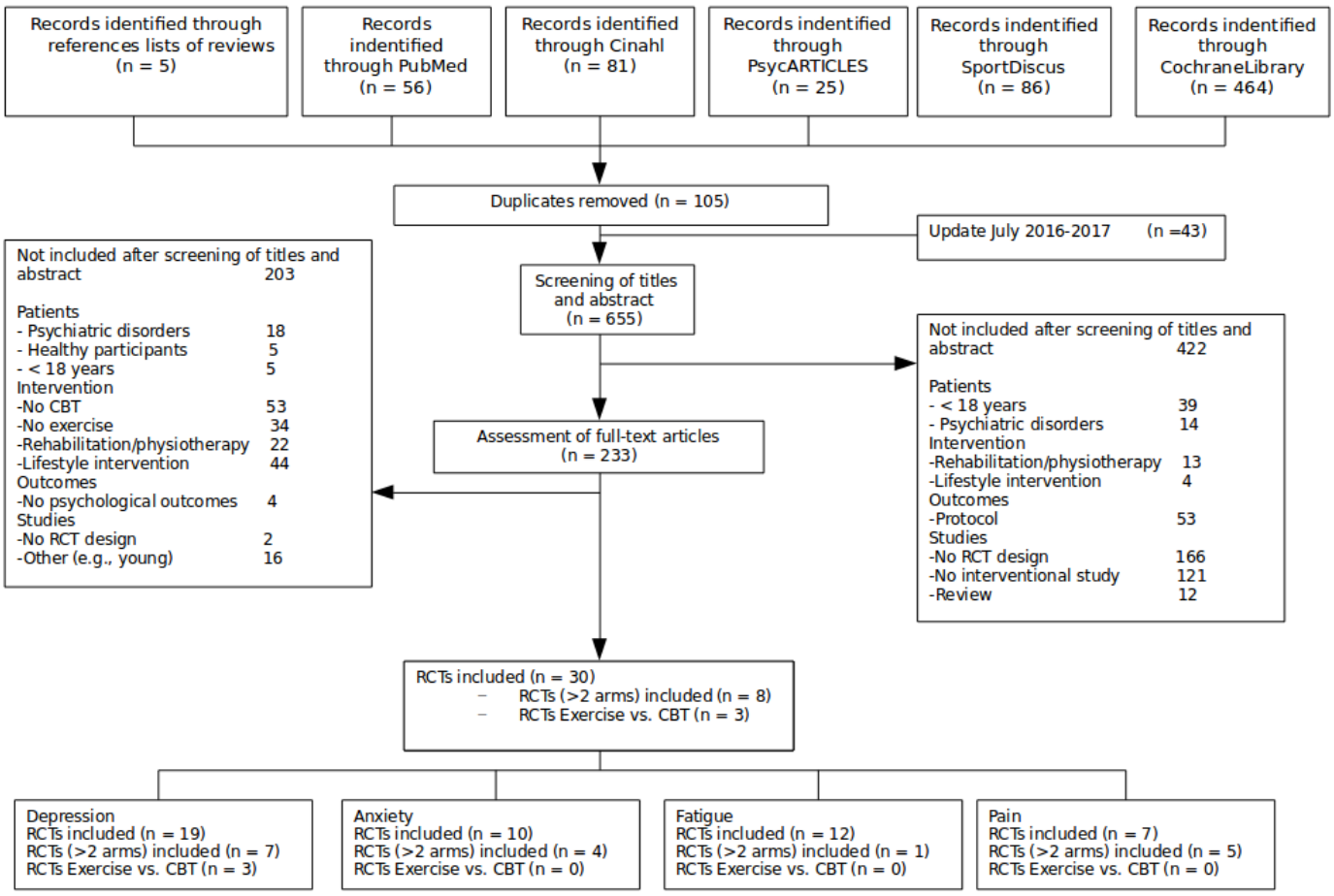
Item 16. Description of dropouts and withdrawals
0 = poor or no description of dropouts and withdrawals
1 = brief description of dropouts and withdrawals
2 = full description of dropouts and withdrawals (must be explicitly stated
and include reasons for dropouts and withdrawals)

Items from
Moncrieff, J., Churchill, R., Drummond, D.C., & McGuire, H. (2001). Development of a quality assessment instrument for trials of treatments for depression and neurosis. *International Journal of Methods in Psychiatric Research*, 10(3), 126–133

Power calculation
0 = not reported
1 = mentioned without details
2 = details of calculations provided

Assessment of adherence with experimental treatments
0 = not assessed
1 = assessed for some experimental treatments
2 = assessed for all experimental treatments

Appendix 4 Flow diagram



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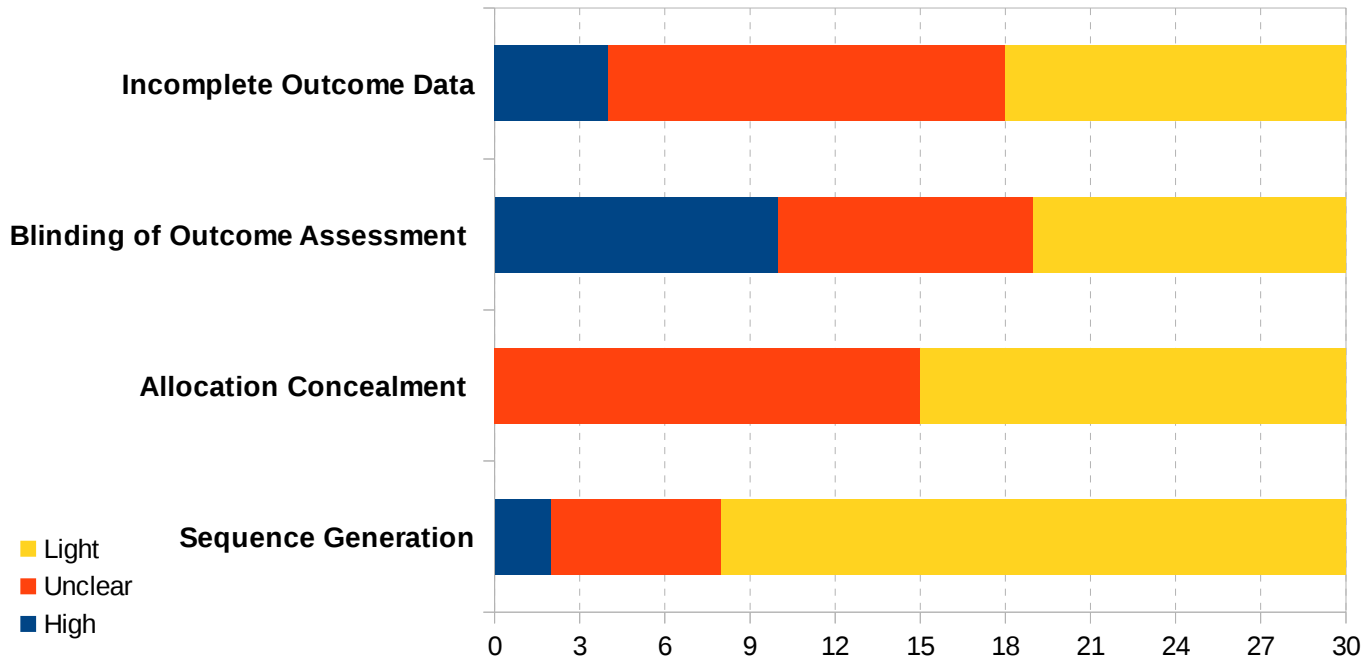
Appendix 5. Graphical representation of risk of bias



Detailled results about assessment of risk of bias and methodological quality

		Risk of bias					Methodological Quality					
Author	**Year**	**Sequence Generation**	**Allocation Concealment**	**Blinding of outcome Assessment**	**Incomplete Outcome data**	**Treatment(s) are Sufficiently Described/referenced**	**Method to demonstrate that treatment being studied is treatment Being delivered**	**ITT analyses**	**Description of dropouts & Withdrawals**	**Power Calculation**	**Assessment Of adherence**	**Total**
Deale	1997	U	L	L	L	1	1	2	2	2	0	8
deGodoy	2003	H	U	H	U	1	0	0	1	0	0	2
deGodoy	2005	H	U	H	U	1	0	0	0	0	0	1
Donta	2003	L	L	U	L	2	1	2	1	1	2	9
Duijts	2012	L	U	U	H	1	0	2	1	1	2	7
Janse	2016	L	L	U	L	1	2	2	1	2	2	10
Emery	1998	L	L	H	U	1	0	0	2	0	2	5
Fossati	2004	U	U	H	U	0	0	0	0	0	0	0
Gary	2010	U	U	L	U	1	2	0	0	0	0	3
Huang	2015	L	U	L	H	1	0	0	0	2	2	5
Jason	2007	L	U	U	U	2	2	0	0	0	1	5
Tummers	2012	L	L	H	L	2	0	2	2	2	1	9
VanKoulila	2010	U	U	H	U	2	0	2	2	0	2	8
Voet	2014	U	U	L	U	2	0	2	2	2	2	10
Zedlitz	2012	L	L	L	L	1	1	1	1	2	2	8
O'Dowd	2006	L	L	L	L	2	1	2	2	2	2	11
Linton	2005	L	L	H	L	2	0	1	1	0	1	5
May	2008	L	U	U	L	2	0	2	2	1	1	8
McBeth	2012	L	U	L	L	2	1	2	2	2	2	11
Pendlton	2002	U	U	H	H	1	0	0	1	0	0	2
Johnson	2007	L	L	U	U	2	2	2	2	2	2	12
Jonsbu	2011	L	L	U	L	2	0	0	1	0	1	4
Khan	2014	U	U	U	U	0	0	0	0	1	0	1
Koopman	2015	L	U	L	L	2	0	2	0	2	1	7
Piette	2011	L	L	U	U	1	0	2	0	1	2	6
Prins	2001	L	L	H	U	2	0	2	1	1	1	7
Redondo	2004	L	U	L	U	1	0	2	1	0	2	6
Sharpe	1996	L	L	L	L	1	0	1	1	0	1	4
Smeets	2006	L	L	L	L	2	0	2	1	0	2	7
Risdale	2004	L	L	H	L	1	0	2	2	2	2	9

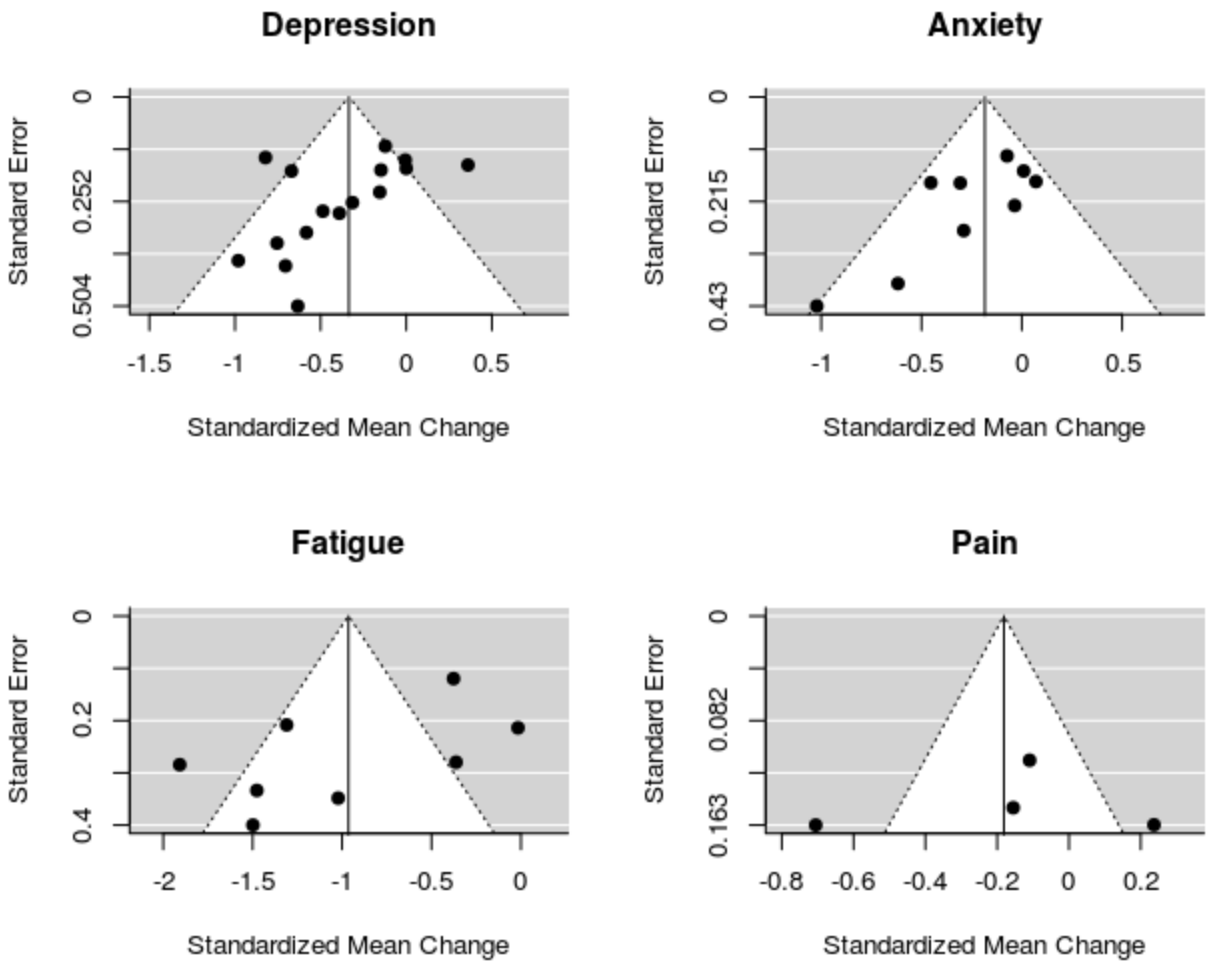
Appendix 6 Table 1 Participant characteristics

Author	Year	Country	Participants	Age	AD	AX	Pain
Deale	1997	UK	Adults with chronic fatigue syndrome	34,5	20	-	-
deGodoy	2003	Brazil	COPD	60,2	3	-	-
deGodoy	2005	Brazil	COPD	-	10	8	-
Donta	2003	USA	Gulf war veterans reporting at last 2 of 3 symptom types (pain, fatigue, cognitive symptoms)	40,8	-	-	-
Duijts	2012	Nederland	Breast Cancer	48,2	10,3	-	8,7
Emery	1998	USA	COPD	66,6	-	-	-
Fossati	2004	Switzerland	Obese adults with binge eating disorder	41,8	-	-	-
Gary	2010	USA	Heart failure with depressive disorders	65,8	29,7	12,2	-
Janse	2016	Nederland	Adults with idiopathic chronic fatigue	33,5	-	-	-
Jason	2007	USA	Chronic fatigue syndrome	43,8	-	-	-
Johnson	2007	UK	Chronic LBP	47,7	-	-	-
Jonsbu	2011	Norway	Adults with persistent complaints 6 months after a negative evaluation at a cardiological outpatient clinic	52	-	-	-
Khan	2014	Pakistan	Adults with chronic low back pain	39,6	-	-	-
Koopamn	2015	Nederland	Adults in post-polio syndrome	60,1	-	-	-
Linton	2005	Sweden	Employed with less than 4 months of sick leave the past year for spinal pain	48.2	-	-	-
May	2008	Nederland	Cancer survivors	48,8	-	-	-
McBeth	2012	International	Chronic Widespread Pain	56,2	-	-	-
O'Dowd	2006	UK	Adults in primary care with chronic fatigue syndrome/myalgic encephalopathy (CFS/ME)	41,1	32,5	7,6	58
Pendlton	2002	USA	Obese women with binge eating disorder	45	-	-	-
Piette	2011	USA	Depressed diabetes adults	56,2	57	-	-
Prins	2001	Nederland	Adults with chronic fatigue syndrome	36,5	-	-	-
Redondo	2004	Spain	Women with fibromyalgia	-	-	-	-
Sharpe	1996	UK	Adults with chronic fatigue syndrome	36	13	-	-
Smeets	2006	Nederland	Adults with chronic low back pain	41,9	-	-	-
Tummers	2012	Nederland	Adults with chronic low back pain in a mental health centre	36,3	-	-	-
VanKoulila	2010	Nederland	High-risk adults with Fibromyalgia	41,7	-	-	-
Zedlitz	2012	Nederland	Stroke patients with severe fatigue	41,5	-	-	-
			RCTs assessed CBT versus physical exercise				
Huang	2015	Taiwan	Community-dwelling elderly adults with depressive symptoms	76,5	0	-	-
Risdale	2004	UK	Adults with complaints of fatigue as a main or important problem (>3 months)	40	-	-	-
Voet	2014	Nederland	Adults with facioscapulohumeral muscular dystrophy		-	-	-

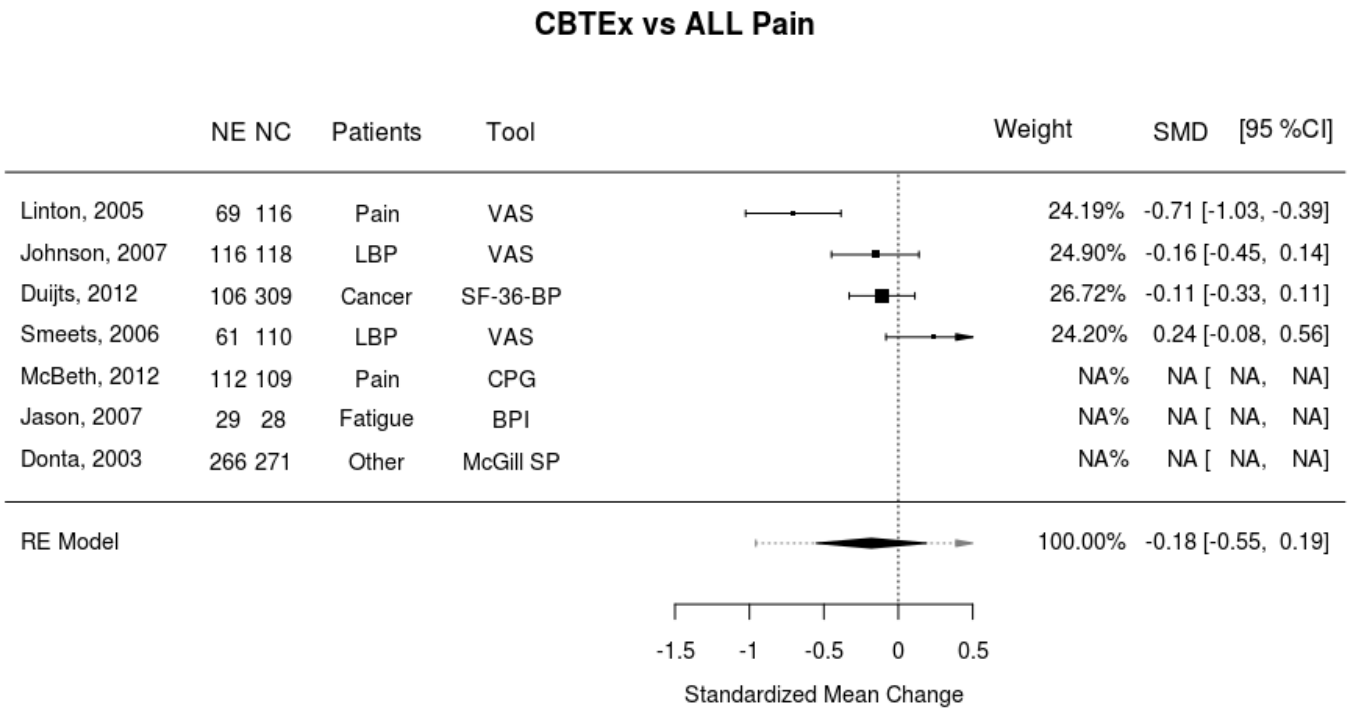
Notes. AD = antidepressant, AX = anxiolitic, Pain = pain medication.

Appendix 7 Funnel and forest plots

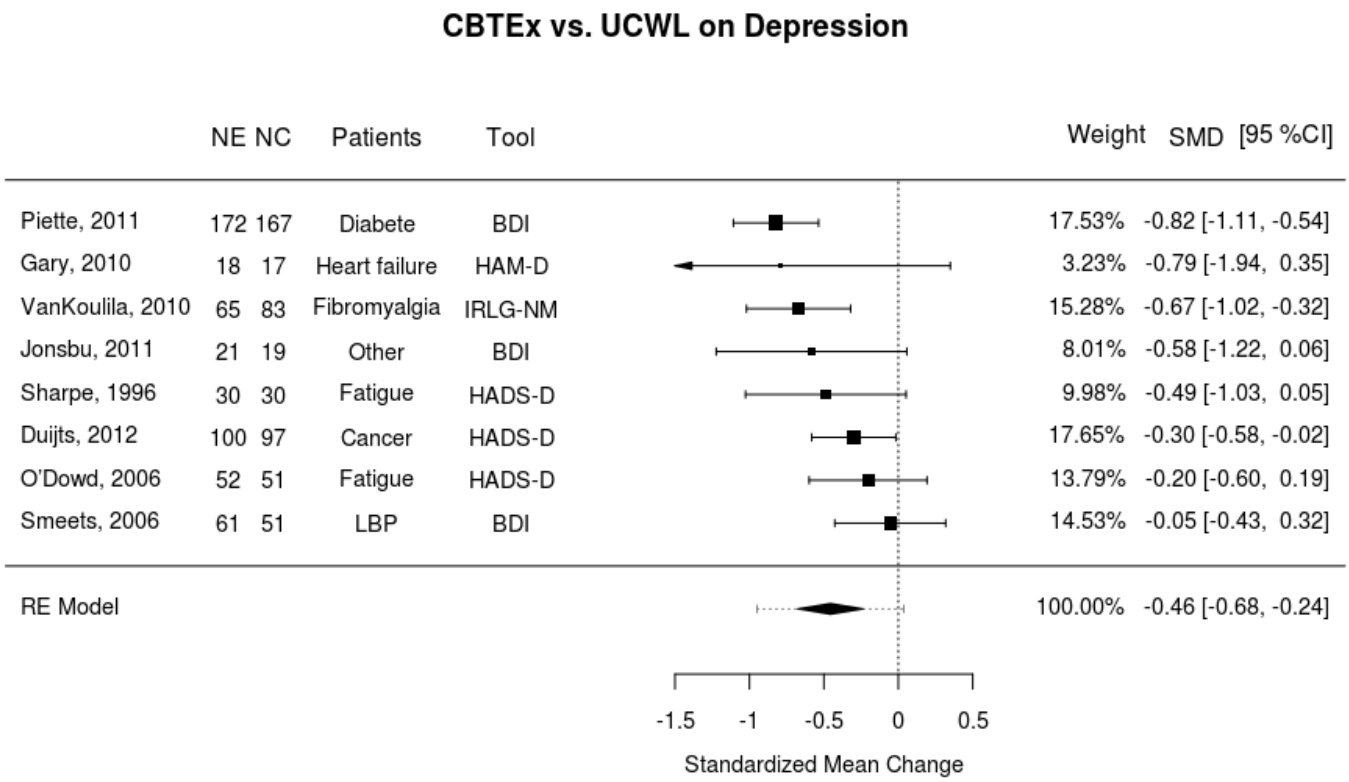
Funnel plots for overall efficacy of CBTEx



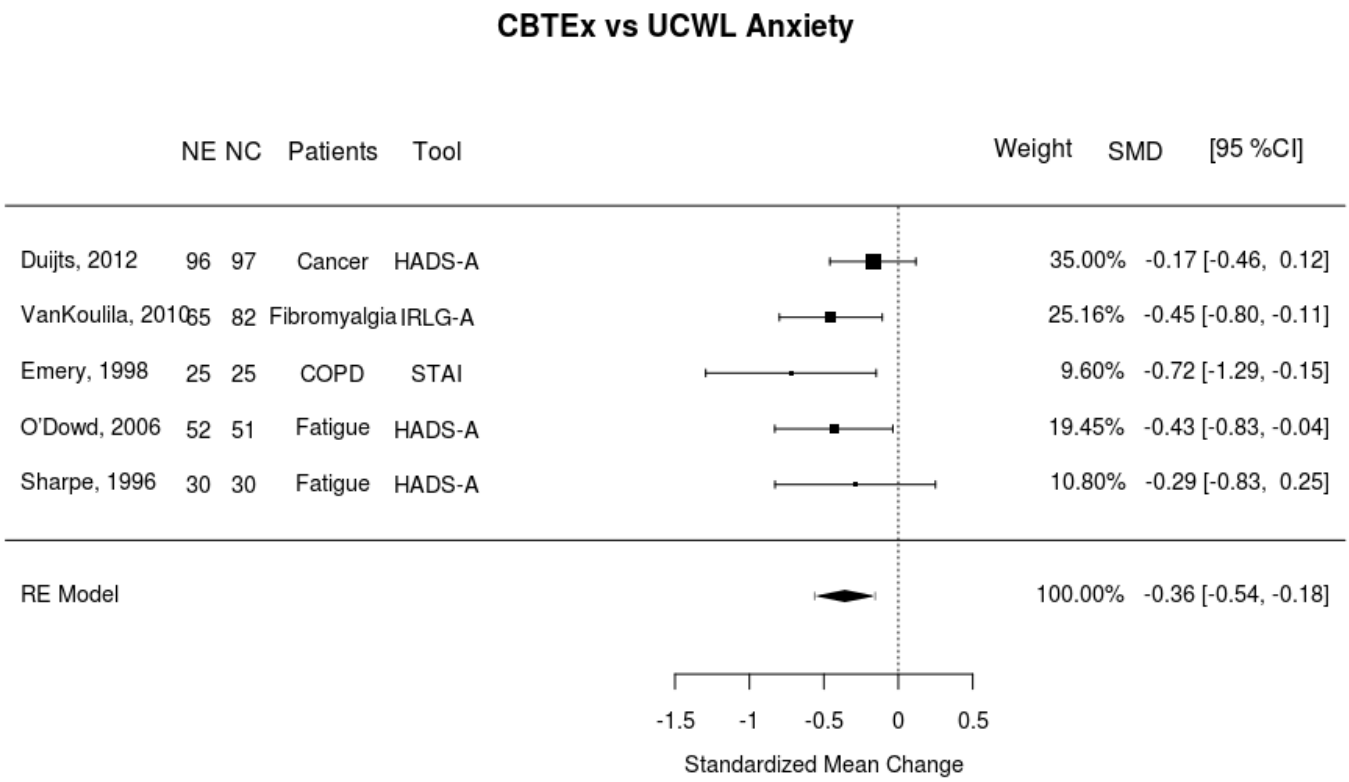
Forest plot for overall efficacy of CBTEx on pain



Forest plot CBTEX versus usual care or waitlist arms on depression



Forest plot CBTEX versus usual care or waitlist arms on anxiety



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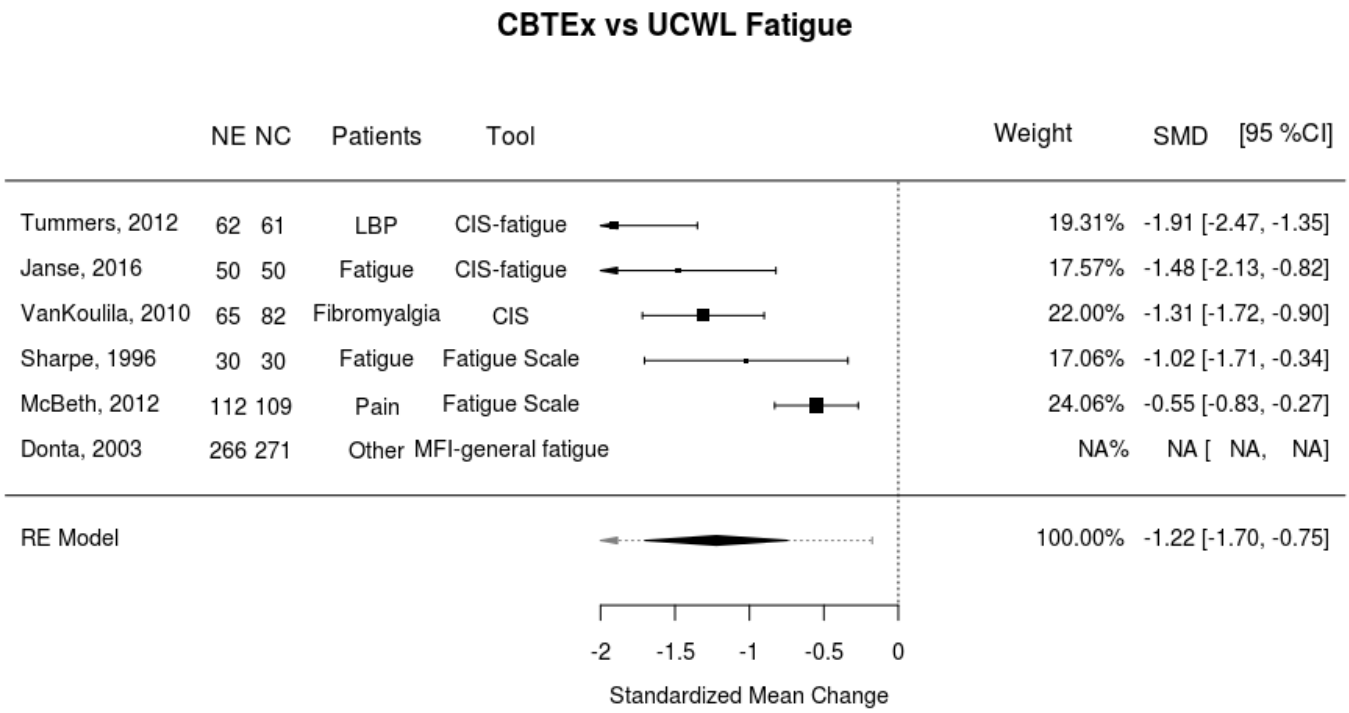
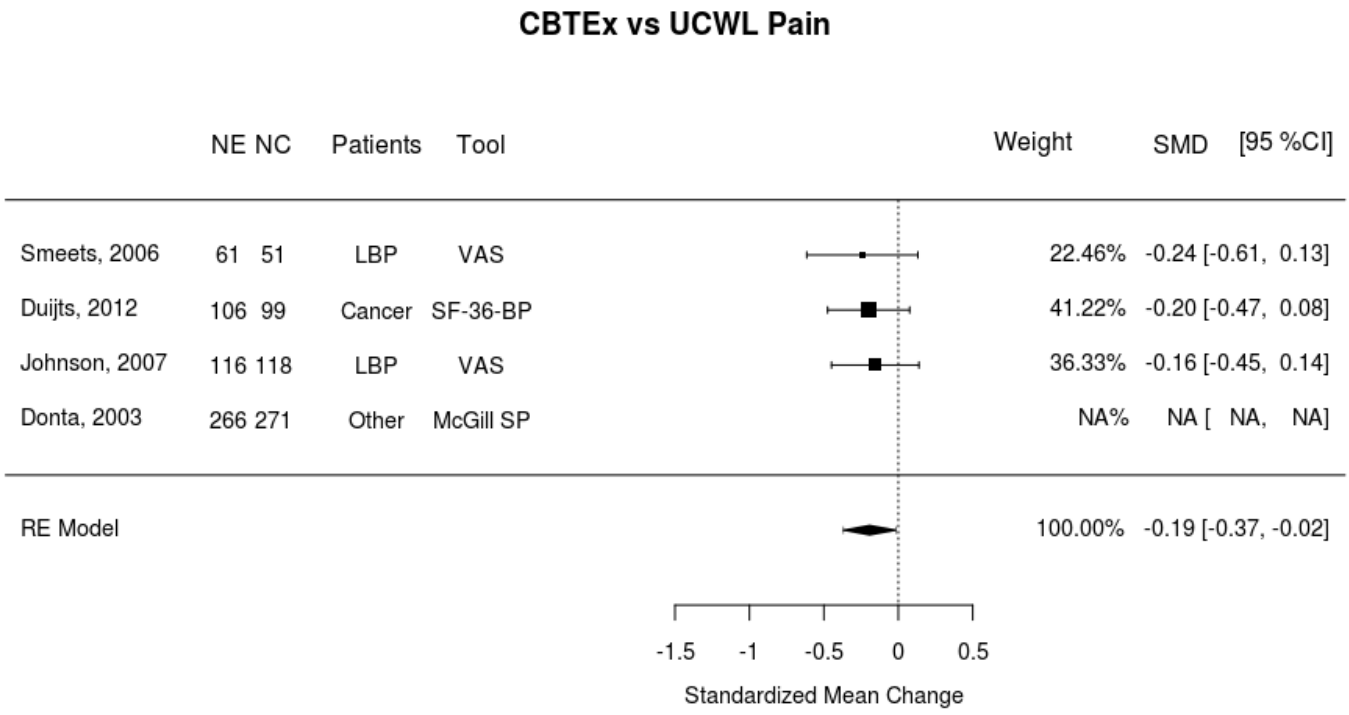
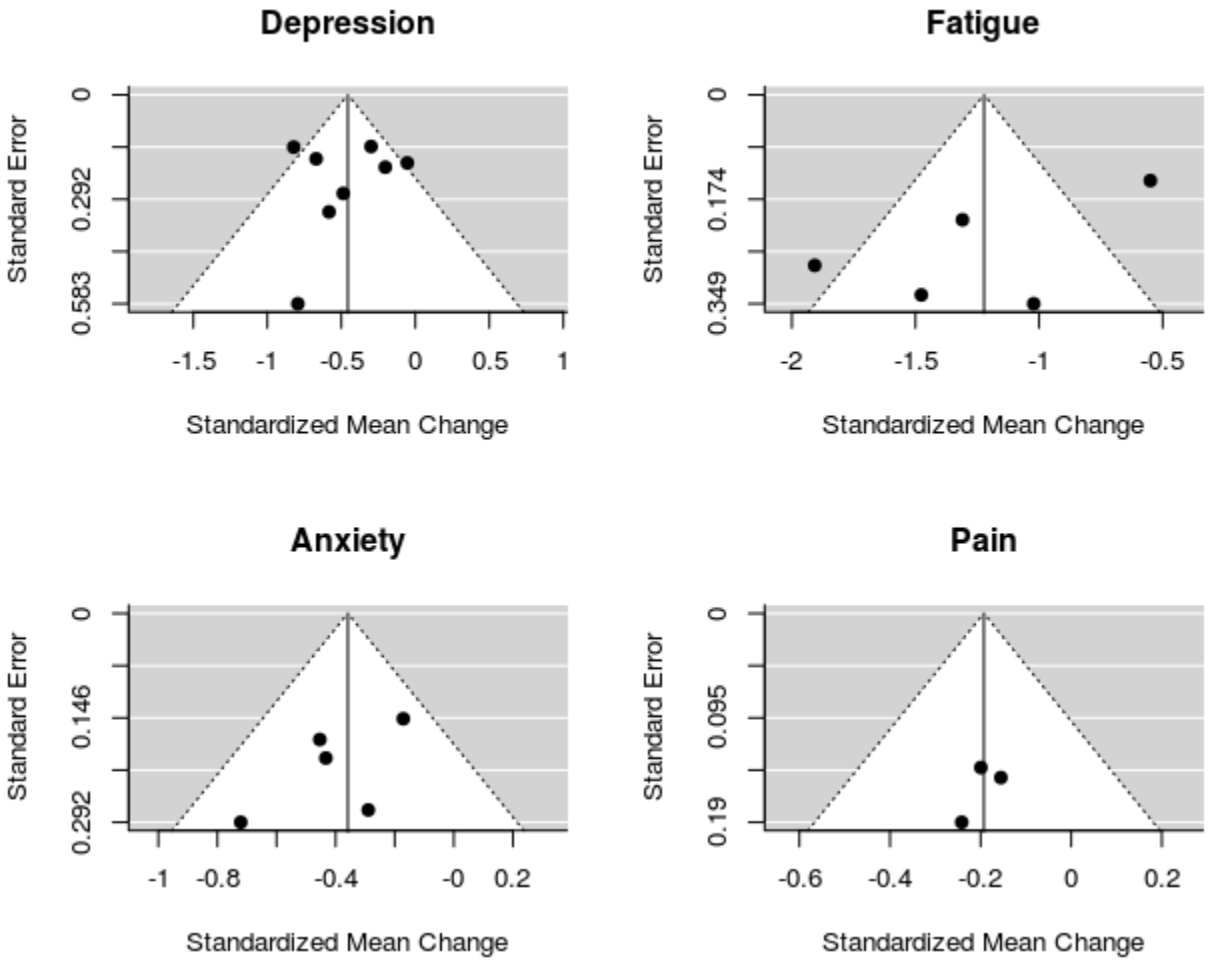


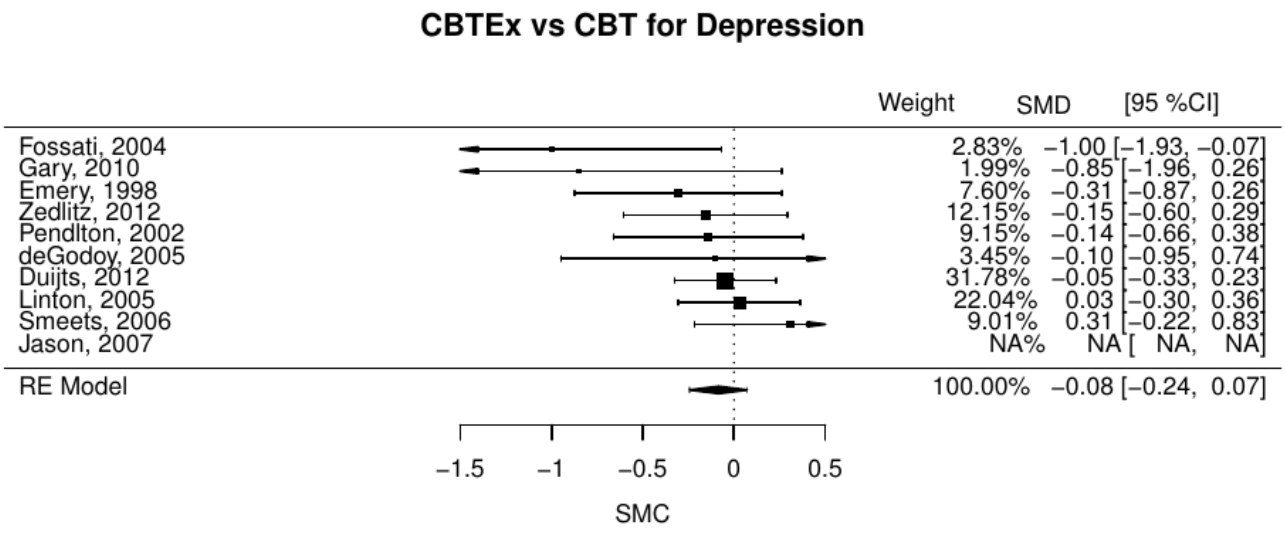
Forest plot CBTEX versus usual care or waitlist arms on pain

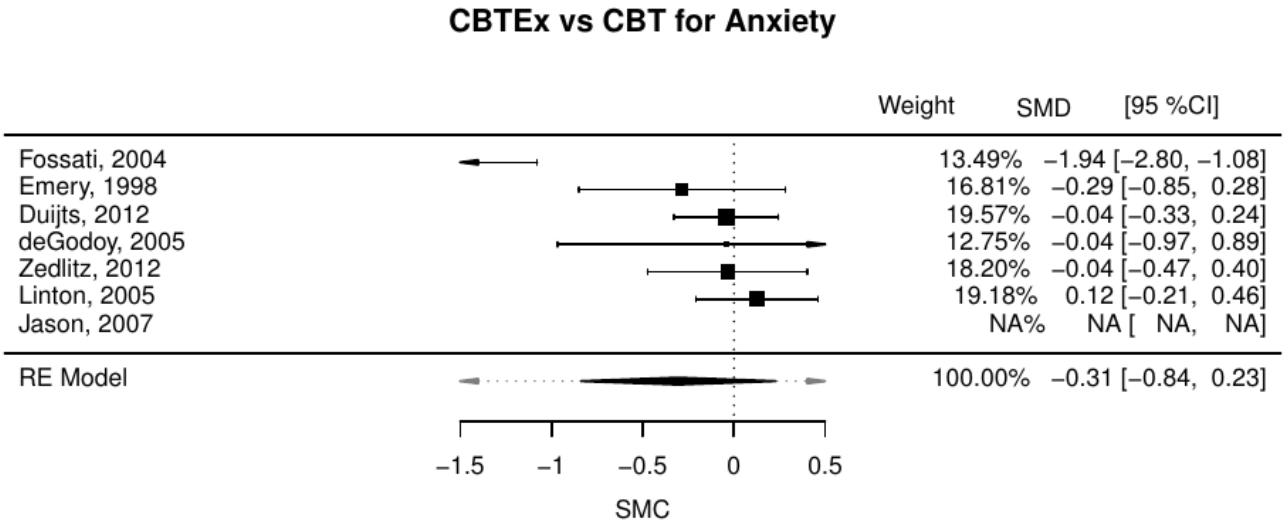


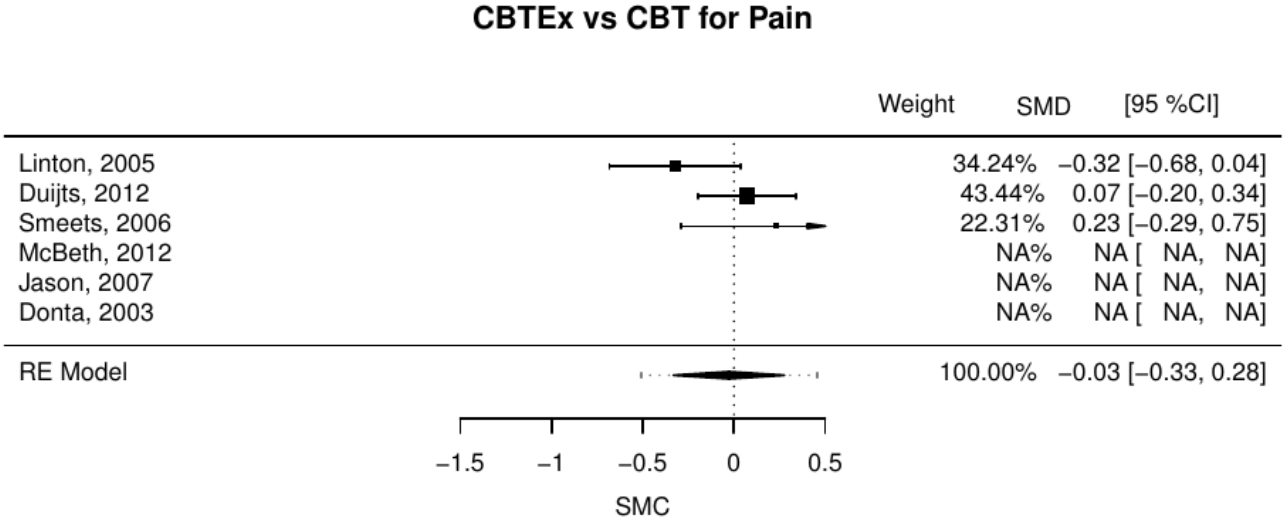
Funnel plots CBTEX versus usual care or waitlist arms on depression, anxiety, fatigue, and pain



Forest plots CBTEx versus CBT on depression, anxiety, fatigue, and pain

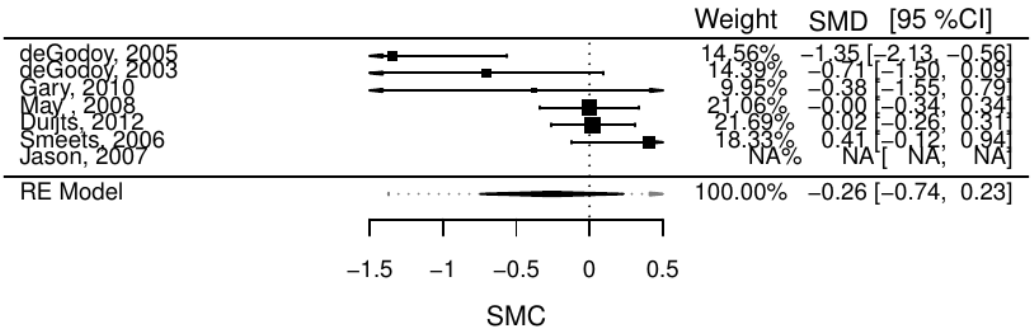




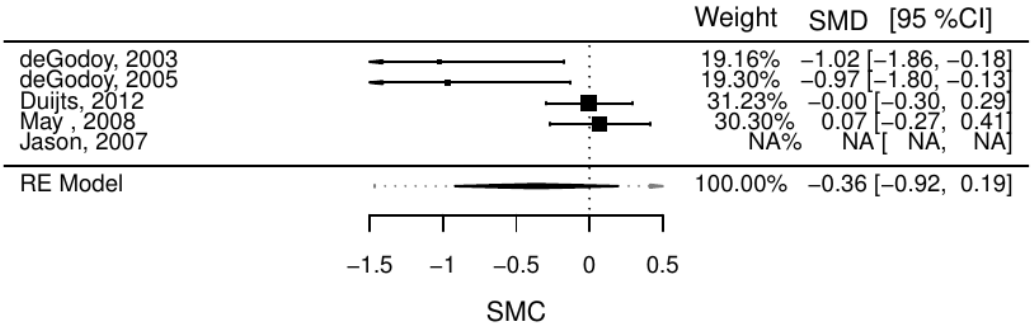


Forest plots CBTEx versus Exercise on depression, anxiety, fatigue, and pain

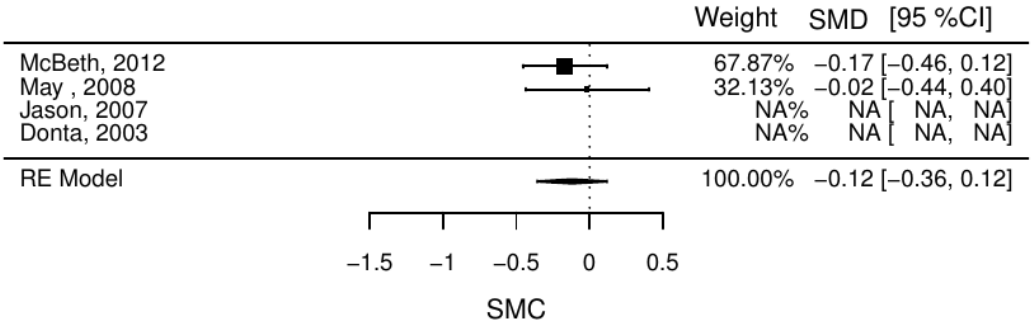
CBTEx vs. Ex for Depression



CBTEx vs Ex for Anxiety



CBTEx vs Ex for Fatigue



CBTEx vs Ex for Pain