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Title: Do evidence based interventions for chronic fatigue syndrome improve sleep? A systematic review and narrative synthesis

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Summary

Cognitive behavioural therapy (CBT) and graded exercise therapy (GET) are recommended evidence based treatments for chronic fatigue syndrome (CFS), with research supporting their effectiveness in reducing fatigue and functional impairment. However, little research has focussed on the effect of these treatments on sleep, despite high reported sleep disturbance in CFS. Using a narrative synthesis approach, we aimed to 1) Systematically identify and summarise the current evidence for the effectiveness of CBT and GET in improving sleep; 2) Consider factors influencing treatment effectiveness, including incorporation of sleep management techniques; and 3) Consider the appropriateness of sleep outcome measures used within evaluations. Studies evaluating CBT and/or GET for CFS, and including a sleep outcome were eligible for inclusion. Eight studies were identified. We found that that GET interventions can improve sleep but this effect is inconsistent across studies. For CBT the evidence is limited with only one of two evaluations demonstrating sleep-related improvements. We conclude from existing research that we know little about the effects of including sleep management components within CBT and GET interventions. We suggest that future research should explore the effectiveness of sleep components within interventions, and sleep specific interventions, using comprehensive outcome measures that fully capture the range of sleep difficulties experienced in CFS.

Keywords: Chronic fatigue syndrome; Sleep; Cognitive behavioural therapy; CBT; Graded exercise therapy; GET; Narrative synthesis

Abbreviations

APT	Adaptive pacing therapy
CBSM	Cognitive behavioural stress management
CBT	Cognitive behavioural therapy
CDC	Centers for Disease Control and Prevention
CFS	Chronic fatigue syndrome
CFIDS	Chronic fatigue and immune dysfunction syndrome
GET	Graded exercise therapy
MCT	Multi-convergent therapy
ME	Myalgic encephalomyelitis
PR	Pragmatic rehabilitation
PSQI	Pittsburgh sleep quality index
RCT	Randomised controlled trial
SMD	Standardized mean difference
UK	United Kingdom
US	United States

Introduction

Chronic fatigue syndrome (CFS) is a condition characterized by severe and persistent unexplained fatigue with a definite onset and a duration of longer than six months [1,2]. For a diagnosis to be made, the fatigue experienced has to substantially impact daily activities [1,2]. A high proportion of patients experience sleep difficulties, including poor sleep quality, difficulties initiating and maintaining sleep [3,4], and perceiving sleep to be unrefreshing [5,6].

Despite high levels of reported sleep disturbance in CFS, to our knowledge no study has evaluated the effectiveness of sleep-specific interventions in this group. This lack of focus on sleep is problematic because poor sleep is perceived by patients to exacerbate daytime symptoms [7] and models of CFS posit that sleep disturbance is involved in maintaining both biological and psychological symptoms associated with CFS [8]. Moreover, a recent empirical recent study found that poorer perceived sleep predicted increased following-day fatigue in CFS [9], suggesting that improving perceptions of sleep is likely to be beneficial as a target in CFS interventions.

Cognitive behavioural therapy (CBT) and graded exercise therapy (GET) are the recommended treatments for CFS [10, 11]. A recent large randomised controlled trial (RCT) supported their effectiveness in reducing fatigue and improving physical functioning [12]. CBT for CFS aims to formulate and modify unhelpful cognitive and behavioural responses to symptoms that may perpetuate the condition. This includes challenging unhelpful thoughts and beliefs, reducing symptom focus, and behavioural change [13]. GET aims to gradually increase physical activity without a specific focus on cognitive factors, and is based on the understanding that avoidance of activity and physical deconditioning may perpetuate CFS symptoms [13].

Although substantial research has evaluated the effectiveness of CBT and GET for improving fatigue and functioning, their effectiveness for improving sleep has been less studied. However, both CBT and GET are thought to positively impact sleep, and may do so through different mechanisms. For GET, a gradual increase in regular exercise may improve perceived sleep quality, as has been demonstrated in insomnia [14] and non-clinical samples [15]. It has also been suggested that exercise can improve sleep in CFS by reducing muscle tension and relieving stress [16]. For CBT, perceived sleep may improve via a number of different mechanisms including improved general mood and anxiety management strategies. Sleep-specific techniques, including sleep hygiene, can also be added to both GET and CBT in line with UK and US guidance for CFS [10,11]. When there is a focus on sleep, CBT can also modify unhelpful beliefs that increase preoccupation and worry about sleep, which itself can exacerbate sleep difficulties.

Although CBT and GET are understood to improve sleep, evaluation studies have not focused on improving sleep as a primary aim. A recent Cochrane review and meta-analysis [17] of GET for CFS included three RCTs that had examined sleep as a secondary outcome; it found that GET had a significant positive effect on sleep but that there was heterogeneity in the size of this effect [17]. It is likely that differences in the content or delivery of GET interventions, including the incorporation of sleep management approaches, and possibly different characteristics of the samples contributed to heterogeneity of findings. However there has not previously been an attempt to summarise how these factors might influence the effectiveness of GET on sleep. Additionally, the extent to which differences in the measurement of sleep outcomes contributed to variations in findings is also unclear. Moreover, the effect of CBT for CFS on sleep has not, to our knowledge, been evaluated systematically.

It has been suggested that when there is inconsistency between findings of effectiveness studies, such as the effects of GET on sleep, a narrative synthesis approach can be used to understand

heterogeneity in outcomes [18]. This approach aims to systematically assess the strength of current evidence and the conclusions that can be drawn [19]. Therefore, in order to further understanding of the effects of GET and CBT on sleep, this review used a narrative synthesis approach to:

- Identify GET or CBT intervention studies including sleep as an outcome in order to summarise the current evidence for CBT and GET on sleep in CFS
- Consider factors influencing the effectiveness of these interventions, including whether sleep management strategies have been explicitly included
- Describe how sleep has been measured as an outcome within included studies
- Outline a research agenda to help advance understanding of sleep treatment in the management of CFS

Method

Search strategy

This study was approved by the University of Manchester ClinPsyD research committee and conducted in accordance with an approved protocol. To identify relevant studies, one researcher (C.R.) conducted searches in Medline (PubMed), PsychInfo (Ovid), Embase (Elselvier), Web of Science (Thomson Reuters) and CINAHL (Bbsco). All searches were completed in March 2015, and databases were searched up to and including March 2015. Two sets of search terms containing terms separated by "OR" were combined using "AND". The first set identified CFS literature by including "chronic fatigue syndrome" or "myalgic encephalomyelitis" or "CFS/ME" or "CFIDS" (chronic fatigue and immune dysfunction syndrome [20]) or "post-viral fatigue syndrome." The second set identified treatment or intervention studies and included "cognitive behavioural", "cognitive behavioral",

"cognitive behaviour", "cognitive behavior", "CBT", "graded exercise", "graded activity", "exercise therapy", "treatment", "intervention" or "trial".

Search results were exported to reference management software and merged to discard duplicates. Titles were reviewed and if the title indicated that the article was related to treatment evaluation in individuals with CFS, abstracts were reviewed. After reviewing abstracts, full texts of relevant articles were acquired and assessed against inclusion and exclusion criteria. The study selection process is shown in Figure 1.

Criteria for inclusion of research articles

Studies evaluating interventions based on the principles of CBT and/or GET were included if they incorporated at least one outcome relating to sleep (i.e. sleep questionnaire measures, sleep diaries and objective sleep parameters). As the literature is limited, we included all types of evaluation study designs including RCTs, uncontrolled trials and case studies. Only studies including adults (aged 18 or over) meeting the Oxford and/or CDC [1,2] diagnostic criteria for CFS were included. Only full text articles published in English were included.

Quality Assessment

To assess the methodological quality of included studies, the Downs and Black [21] checklist was used. This has been highlighted as one of the 'best' tools for evaluating both randomised and non-randomised intervention studies [22]. It includes 27 items assessing study reporting, external and internal validity, and has good inter-rater reliability [21]. Item 14, regarding participant blinding to intervention, was removed as this was not relevant to the current review. Item 27 relating to power was also omitted due to sleep being a secondary outcome within included studies, and therefore any

power calculations were not based on sleep outcomes. For the current review, quality assessment for each of the studies was assessed by two researchers independently. Agreement between researchers was good (Kappa = 0.872; p <0.001). Inconsistencies were then discussed and consensus was reached between researchers.

Extraction of sleep management components

Information regarding sleep components in interventions was extracted from published research articles and any published trial intervention manuals. The presence of sleep components based on extracted information was rated by consensus between two authors (C.R. & S.D.K) using the definitions shown in Table 1.

[Table 1]

Data Synthesis

Findings were combined and summarised in line with guidance for completing a narrative synthesis [19]. This included considering how CBT and GET interventions might influence sleep and presenting all available evidence. Differences in findings and how the methodology, delivery of the intervention, inclusion of sleep management strategies, and the sample used might influence effectiveness were considered and summarised. Conclusions that can be drawn based on the methodological quality of included studies were also evaluated [19]. As part of the synthesis, quantitative data regarding effect sizes, and the methodological quality of included studies was also provided in order to fully describe the current evidence. The standardized mean difference (SMD) was used as a measure of effect size and was calculated for studies providing appropriate post treatment and follow up data. The SMD expresses the size of the intervention effect and is calculated based on differences

between groups means for intervention and control groups at post treatment and follow up, relative to the variability observed in that study. SMD was calculated at both the post-intervention and follow-up time points, where data were available. Additional data were sought from authors where necessary.

Results

Study Selection

Searches of the databases and reference lists yielded 1390 titles and abstracts after duplicates were removed. 1134 articles were clearly irrelevant based on the title and/or abstract, so a total of 256 full text articles were reviewed for eligibility, and eight studies were eligible for inclusion. No studies were excluded due to differences between CFS diagnostic criteria .The study selection process is shown in Figure 1.

[Figure 1]

Description of studies included within the review

Characteristics of the eight included studies are shown in Table 2. There were four RCTs [11,23,24,25], one pilot study with randomisation [26], one non-randomised trial [27], and one case study [28]. The remaining study was an uncontrolled follow up of an included RCT [29].

Studies varied in quality, scoring 8 to 25 out of a possible 26 (mean score = 18). The two large RCTs [11,25] scored highly, indicating high methodological quality, and more highly than the non-randomised and pilot studies [2,27]. The case study [28] scored poorly, as although it provided a detailed description of the participants and methods, the nature of this design allowed for a high risk of bias. Full quality ratings for each of the included studies are shown in web appendix 1 (link).

[Table 2]

Description of Interventions

Included studies differed considerably in their treatment approaches. Two RCTs evaluated GET interventions over 12 weeks [23], and 24 weeks [11] respectively.

Two studies evaluated interventions derived from a CBT approach [11, 26]. One study evaluated formal individual CBT sessions over 24 weeks [11], and one piloted a 12 week cognitive behavioural stress management group [26]. We did not find any studies evaluating sleep focused CBT interventions.

Four studies combined aspects of GET and CBT within a pragmatic rehabilitation (PR) intervention [24,25,28,29]. PR includes education to encourage graded increases in activity based on an understanding of CFS encompassing physiological dysregulation maintained by behavioural and cognitive factors. The first PR study [28] was a case study of two patients completed over a two year period. The Powell et al. [24] study and its two year follow up [29], evaluated PR delivered in different doses, namely in two face-to-face sessions with or without telephone support, or the same intervention delivered over seven face-to-face sessions. The final study evaluated the effectiveness of 10 sessions (5 face-to-face, 5 telephone) of individual nurse-led PR sessions [25].

The remaining, non-randomised, study evaluated 'multi-convergent therapy', described as combining aspects of CBT, GET and adaptive pacing therapy [27].

Description of control and comparative conditions

Three studies had more than one comparator delivered over the same duration. One RCT evaluated CBT, GET, and an adaptive pacing intervention, each in addition to specialist medical care [11]. During analyses, CBT and GET were compared against adaptive pacing therapy and against specialist medical care alone [11]. In another RCT a PR intervention, in addition to GP treatment as usual, was compared against nurse led supportive listening with equivalent contact (in addition to GP treatment as usual), and with GP treatment as usual alone [25]. The remaining, non-randomised, study compared an intervention combining aspects of CBT, GET and adaptive pacing therapy with controls receiving relaxation sessions or no intervention [27].

Among studies with one control group only, one RCT compared GET against flexibility sessions [23]. One RCT evaluated a PR intervention (in different doses) against standardised medical care [24]. A pilot study compared a 12 week cognitive behavioural stress management programme with a half day seminar on the same approach [26]. The case study did not include a control condition [28].

Description of participants

A total of 1249 participants meeting the Oxford or Fukuda criteria for CFS participated in the eight included studies. The mean age of participants across studies was 39.6 (SD= 9.1), and the mean proportion of females across studies was 77.7% (SD=10.4). For six of the studies, interventions were provided on an outpatient basis requiring mobility to attend sessions [11,23,24,26,27,29]. Two studies evaluated interventions delivered by home visit and telephone contact [25,28] and in one of these studies 11% of participants were non ambulatory and would have had difficulty attending outpatient appointments [25]. Within the case study the two individuals who participated were described as severely affected and requiring the use of wheelchairs prior to intervention [28].

Five of the studies had no sleep related participant exclusion criteria [11,25,26,27,28]. One study offered treatment to patients who had had 'symptomatic insomnia' prior to participation, and included participants only if that insomnia had been treated successfully and they still met the criteria for CFS [23]. One study (and its follow up) excluded patients who were 'taking other treatments including antidepressants' which although not specified would presumably exclude patients taking medications for sleep [24,29].

Sleep Management Components within Interventions

Information regarding sleep components was extracted from each article, and for two studies from published trial intervention manuals [11,25]. Studies varied substantially in the extent to which they reported sleep management approaches within interventions. Table 3 shows sleep components extracted from interventions.

[Table 3]

Description of sleep related outcome measures

Five studies used the Jenkins et al. [30] sleep scale as an outcome measure [11,24,25,28,29]. This contains four items relating to initiating and maintaining sleep, and unrefreshing sleep, rated on the frequency of each difficulty during the past month, with higher scores indicating increased frequency. One study [23] used the Pittsburgh sleep quality index (PSQI) [31], a comprehensive measure of sleep problems including difficulties initiating and maintaining sleep, poor sleep quality, use of medication and the impact of sleep problems on daytime functioning. One study [26] used the Centre for Disease Control symptom checklist for CFS [32], which contains four items measuring the frequency and severity of unrefreshing sleep and 'sleeping problems' using Likert style responses. The remaining study [27] used the Smith et al. [33] sleep questionnaire which classifies sleep

abnormality based on reported average sleep duration and difficulties initiating and maintaining sleep. No studies used sleep diaries or objectively measured sleep parameters as outcomes.

Effect Sizes for Sleep Outcomes

Where appropriate data were available, the standardised mean difference (SMD) between treatment and control groups at follow up was calculated as a measure of effect size. For two studies without control conditions [28,29], SMD could not be calculated. For one study, insufficient data were provided and authors could not be contacted for clarification [27]. For another, the nature of the outcome measure meant that interquartile range was reported rather than standard deviation [23] and therefore SMD could not be calculated. For two studies [11,26] additional data were obtained from authors.

Effect sizes (SMD) were calculated and presented for both post intervention and follow up time points where these data were available. For Lopez et al. [26] study, SMD was calculated for the frequency of unrefreshing sleep. In the Powell et al [24] study, the PR intervention was delivered at 3 doses, and for the purpose of this review the SMD was calculated for the maximum intervention (7 sessions) only. For the two studies where there was more than one control group [11,25], specialist medical care or GP treatment as usual was used to calculate SMD due to these being more similar and comparable to control groups used in other included studies.

For four studies (evaluating five interventions) post treatment data were provided and used to calculate SMD as Figure 2. Three studies (evaluating four interventions) provided follow up data which is presented in Figure 3. Data used to calculate SMD are provided in Web Appendix 2 (link). For measures used within all studies presented, lower scores indicate improvements in sleep.

[Figure 2]

[Figure 3]

Narrative Synthesis

Current Evidence for the Effect of CBT and GET on sleep

Of the two studies evaluating GET interventions, one found that GET can significantly improve sleep [11] and the other reported no effect [23]. However, the latter study excluded participants experiencing insomnia symptoms unless these could be successfully treated prior to participation. This may explain the intervention having no effect on sleep given that the sample were not experiencing sleep difficulties prior to intervention, which may also be unrepresentative of CFS patients more generally.

Four included studies [24,25,28,29] evaluated a PR intervention encouraging graded exercise based on an understanding of CFS that included cognitive and behavioural factors. PR includes education around sleep rhythms and sleep hygiene advice. Two high quality RCTs evaluated PR on sleep. One showed that PR can be more effective at improving sleep than standardised medical care at post treatment, and at follow up, with participants' sleep continuing to improve between in the 12 months post treatment [24]. In contrast, the other RCT found that PR did not significantly improve sleep at 70 week follow up. A significant improvement in sleep in the intervention group was reported by authors at post treatment (20 weeks), but in our SMD calculations, based only on post treatment data without the consideration of baseline scores, differences between treatment and control groups were not significant [25]. There are several possible explanations for PR not improving sleep in this evaluation, including that the intervention was delivered via home visit, allowing the inclusion of more severely affected participants who may be less responsive to intervention [25]. Moreover, the intervention was delivered by trained non-specialist nurses, and

not by experienced therapists [25]. In contrast, in the earlier PR trial [24] and case study [28] where sleep improvements were observed, the intervention was delivered by an experienced therapist who had developed this treatment approach.

Within the remaining study that included GET, CBT and adaptive pacing therapy in combination, it was reported that the intervention improved ratings of sleep [27]. However, it was not clear how ratings of sleep had been calculated making it difficult to draw conclusions based on this finding, particularly given that this was a small non-randomised trial with a risk of bias.

Interestingly, all four interventions including GET (alone or in combination) that report significant improvements in sleep, also report including sleep hygiene advice within their interventions [11,24,27,28]. This suggests that GET interventions including sleep hygiene advice can be effective at improving sleep. However, because of the limited research in this area, it is unclear how much the addition of sleep hygiene advice to GET interventions enhances their effectiveness on sleep or whether other aspects of GET aid sleep. The latter may be more likely given that there is limited evidence for the effectiveness of sleep hygiene advice for those experiencing sleep problems [34].

In terms of the current evidence regarding the effect of CBT on sleep, we found only one high quality RCT that evaluated CBT and GET separately, and examined sleep as an outcome [11]. The individual CBT sessions delivered over 24 sessions in this study incorporated comprehensive sleep management approaches. At post treatment and one year follow up, significant improvements in sleep were observed compared to controls receiving specialist medical care [11]. This suggests that providing a comprehensive sleep management approach within CBT for CFS may improve sleep. However, in this study it appeared that the treatment effect size for GET was larger than the effect size for CBT, particularly at follow up, suggesting that GET may have a greater effect on sleep over a

one year period. However, CBT and GET were not compared directly to one another in the analyses, making it difficult to draw conclusions about their relative effectiveness.

In a different study, CBT focusing on stress management did not have a significant effect on sleep [26]. In this study, sleep was measured as part of a broad CFS symptom measure, with the frequency and severity of 'sleep difficulties' rated on single four point Likert scales. Consequently these ratings may not have been a sensitive measure of change in sleep difficulties following intervention. Moreover, this was a small pilot study with a high risk of bias, limiting conclusions that can be drawn.

Measurement of sleep outcomes

All included studies used self-report measures of sleep difficulties. Most used the Jenkins et al. [30] Sleep Scale on which difficulties with initiating and maintaining sleep, and unrefreshing sleep are rated based on their frequency within the past month. The measure does not assess the severity of these difficulties, their duration beyond one month, or whether they are problematic or distressing, and consequently may not provide a sufficiently comprehensive indicator of change. One study used Likert style ratings of the frequency and severity of sleeping problems and unrefreshing sleep within a CFS symptom checklist [32]. Although such ratings provide a useful general assessment of symptoms, as was intended in this study, they are not likely to form a sufficiently comprehensive measure of sleep difficulties, particularly given that a number of difficulties were rated within one 'sleep problems' item. Only one study [23] used a more detailed and comprehensive measure of sleep difficulties, the PSQI [31]. This instrument has good psychometric properties and has been recommended for assessing sleep disturbance as an outcome in intervention studies [35]. Unfortunately however, the sleep related exclusion criterion used in this study limits the conclusions that can be made about the effect of the intervention on sleep problems.

Discussion

Only eight studies have evaluated the effects of CBT and GET on sleep, and these studies varied markedly in their methodological quality. Only three studies provided high quality evidence from which robust conclusions could be drawn and only one of these studies evaluated CBT. We found that no studies had examined the effects of interventions on sleep as a primary outcome. This lack of focus on sleep is problematic given the high levels of reported sleep disturbance in CFS and because sleep problems are hypothesised as being involved in the maintenance of the condition [8].

The current evidence for the effect of GET and CBT on sleep

In our review, GET interventions differed in their effect on sleep with the two included studies showing opposing findings, although this may reflect sample limitations in one of these studies [23]. The other high quality trial did however clearly show that GET can have a significant impact on sleep at post treatment and one year follow up [11].

Our review also showed that a PR intervention which combines elements of GET and of CBT can have a significant effect on sleep, but that the size and durability of the effect appears to depend on the delivery of the intervention and characteristics of participants. In one study, PR delivered in secondary care over seven outpatient sessions by an experienced therapist significantly improved sleep and that these treatment gains were maintained to one year follow up [24].

Taken together, the findings of the GET and PR interventions show that interventions based on GET principles can be effective at improving sleep in CFS but in line with what was reported in the a recent Cochrane review [17], this positive effect is not consistent across studies. We have highlighted that improvement in sleep outcomes may depend on factors such as the characteristics of the sample, inclusion criteria, and the content and delivery of the intervention itself.

Evidence examining the effectiveness of CBT on sleep is limited with only two studies evaluating CBT interventions. The large high quality RCT, demonstrated that CBT had a positive impact on sleep which perhaps reflects that the intervention included a fairly comprehensive sleep management component [11].

The White et al. [11] trial was also the only study which evaluated the effects of CBT and GET on sleep separately and it was found that both these treatments significantly improved ratings of sleep at post treatment and follow up. In this trial, CBT and GET were delivered over 24 sessions which may not to be representative of the current provision for CFS which within the UK has been described as "patchy at best" [36]. Even in areas where a specialist CFS service is available, it is unlikely that all patients could be offered this level of service input due to practical and financial service constraints.

Our review highlighted that differences in sample inclusion criteria may contribute to variation in the effectiveness of interventions on sleep outcomes. This may be particularly pertinent for the CFS population given that the symptom profile can overlap considerably with other conditions, including insomnia, and patients often present with comorbidities [37]. This presents a challenge for adequately evaluating intervention effectiveness in this group and underscores the importance of full description and justification of inclusion/exclusion criteria in prospective treatment studies.

Inclusion of sleep management approaches within interventions

Although sleep management techniques are recommended in symptom management guidance in both the US and the UK [10,16], this review highlighted that the inclusion of sleep management approaches within interventions varied. Due to this variation and because of the small number of

studies available, it is unclear whether incorporating sleep management components within CBT and GET enhances their effectiveness. This is an area requiring further research.

Our review also found that to date, there has not been a published evaluation of sleep focused interventions, such as CBT for insomnia within CFS. As a consequence, we do not currently know the effects of targeting sleep specifically in this patient group. Future research could aim to establish whether such interventions may be useful in this group given the high levels of reported sleep disturbance, and the perceived importance of sleep in the maintenance of the condition.

Measurement of sleep outcomes

Reflecting the fact that sleep was a secondary outcome, four studies employed a brief sleep measure [30] which does not sample the full range of sleep problems. Only one study [23] used a comprehensive self-report measure of sleep in the form of the PSQI [35], a measure which has previously been recommended for use in CFS [38]. However it has been suggested that using an abbreviated version of the PSQI without the item of daytime dysfunction would better assess subjective sleep quality, as demonstrated by three-factor analysis of the questionnaires [39]. Any future sleep focused interventions in CFS should aim to use comprehensive measures, such as the PSQI to assess the effects of interventions on different aspects of sleep. The PSQI could be supplemented by specific measures of difficulties associated with CFS, such as unrefreshing sleep, which is reported by up to 95% of CFS patients [6,40]. These measures would however require validation within the CFS population.

White et al [11] demonstrated that both CBT and GET can improve sleep, however it is likely that these interventions improve sleep through different mechanisms. For GET, this may include improving perceived sleep quality [14,15], reducing muscle tension and relieving stress [16]. CBT

may improve general anxiety management and modify unhelpful beliefs that may exacerbate anxiety related to sleep. It is possible that CBT and GET can also impact different aspects of sleep but because the sleep outcome measure used in this trial produces a global score of sleep difficulties, it is not possible to determine whether this is the case. Further research using more detailed measures could provide further information about the aspects of sleep that can be improved by CBT and GET for CFS.

Our review did not identify any studies that used sleep diaries to provide self-reports of sleep as outcome variables. Sleep diaries have been recommended as a useful way of prospectively assessing treatment effects within insomnia research [35, 41] and provide reliable data due to being less susceptible to memory bias than retrospective reports over a longer duration. Furthermore, it has been found recently that perceptions of sleep, measured by sleep diaries, can predict following day fatigue in CFS [9], whereas objective sleep was not a significant predictor. Therefore, because of the association with fatigue, perceptions of sleep are likely to be a useful target for intervention and sleep diaries are an effective way of capturing this.

We did not find any CFS intervention studies which used objective recordings of sleep, such as polysomnography or actigraphy, to measure sleep-related outcomes possibly due to the fact that substantial research investigating sleep in CFS has found little evidence for objective sleep disturbance [42, 43].

CFS is a condition with a wide range of symptoms, and consequently the measurement of treatment response is complex. Most studies focus on fatigue and functioning as primary outcomes, but there is a debate within the field about the appropriateness of condition specific, domain specific and generic measures [44]. While that debate is beyond the scope of this review, it is clear that the

inclusion of sleep outcomes, using detailed and comprehensive measures, is necessary to further examine the effects of CBT and GET on sleep.

This review has a number of limitations. First, an aim was to gain information on the effectiveness of including sleep management techniques within interventions; however, this depended on information being reported accurately and in sufficient detail. Overall, most studies in the present review did not provide sufficient details of interventional ingredients in relation to sleep. Recent guidance has suggested that intervention studies should improve completeness of their reporting in order to allow accurate replication of interventions [45]. Implementing this guidance could potentially increase the robustness of reviews of intervention effectiveness.

Secondly, the inclusion criteria used were broad and allowed inclusion of a range of methodological designs including randomised controlled trials, non-randomised studies, an uncontrolled follow up and a case study. However, the inclusion of studies with low methodological quality meant that although these studies could be described, robust conclusions could not be drawn based on their findings. Therefore their inclusion could be viewed as having little utility, and may be a limitation of the inclusion criteria used. However, their inclusion was in line with the aim of identifying and summarising all of the available evidence in an area of very limited research.

A meta-analysis was not considered appropriate for the current review because initial scoping searches had revealed that only a small number of studies were available (particularly for CBT) and because of the heterogeneity in study methodology, including sleep components within interventions, and in outcomes. A narrative synthesis approach was instead used, which aimed to consider factors that may have contributed to heterogeneity in outcomes. However, because of the small number of studies, and because studies differed substantially both in design, sample inclusion criteria and outcomes, it was not possible to make strong conclusions based on our synthesis.

Narrative synthesis reviews have also been criticised for having less transparency and rigour than other methods of combining information [46]. As a result our findings should be viewed with these limitations in mind.

In conclusion, in spite of a limited number of high quality studies and some methodological limitations, the current evidence suggests that CBT and GET can improve sleep in CFS under certain conditions. Given the limited research in this area, this review highlights a number of important areas in need of further research. First, further research should establish whether the addition of sleep management components to CBT and GET approaches may enhance their effectiveness on sleep. The likelihood of establishing this will be improved by studies providing explicit descriptions of intervention content, including sleep components, within trial manuals [47]. Second, the effectiveness of sleep specific interventions in this patient group should also be evaluated using prospective RCTs aiming to evaluate the effect of interventions on sleep as a primary outcome. Including sufficiently comprehensive measures of sleep designed to capture commonly reported sleep difficulties in CFS in such research could also establish the types of difficulties that can be treated using CBT and GET. A third issue to be addressed in future research is whether improved sleep may be one mechanism by which CBT and GET impact on symptoms and daytime functioning. An analysis of mechanisms of change in the White et al. [11] trial showed that the most important mediator of improvement in fatigue and physical functioning after both CBT and GET was a reduction in fear avoidance. However, improved sleep did also partially mediate the impact of CBT and GET on those primary outcomes [48]. Moreover, given recent findings that subjective sleep predicts following day fatigue in CFS [9], the role of sleep as a potential mediator of the effects of CBT and GET on fatigue in CFS should be explored further.

This work was carried out in partial fulfilment of the requirements for the degree of ClinPsyD awarded at the University of Manchester.

Practice Points

- While sleep management components are recommended for use within CBT and GET interventions for CFS, inclusion of these techniques in research to date varies markedly.
- Limited current evidence suggests that GET interventions, incorporating sleep hygiene advice, can improve sleep, although only if the intervention is delivered by experienced therapists to CFS patients experiencing sleep difficulties.
- The limited evidence suggests that CBT delivered individually over 24 sessions incorporating comprehensive sleep management components can improve sleep. However whether sleep improvements could be seen in fewer sessions or in group settings is unclear.
- Sleep outcome measurement in the CFS field has not been sufficiently comprehensive to fully capture changes in the sleep difficulties experienced by this group, or the aspects of sleep that may improve following intervention.

Further research should aim to:

- Establish whether the inclusion of sleep specific components within CBT and GET enhances their effectiveness on sleep
- Evaluate whether sleep specific interventions, such as CBT for insomnia, may be beneficial in this group
- Use comprehensive sleep outcome measures that reflect sleep difficulties experienced by CFS patients
- Explore the role of perceived sleep as a potential mediator of the effects of CBT and GET on fatigue in CFS

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Table 1: Definitions of Sleep Components within Interventions used for Data Extraction

Sleep Component	**Definition**
Sleep hygiene	Instructional advice to sleep management including keeping consistent bedtime and wake times, avoiding napping, avoiding caffeine, alcohol and stimulating activities prior to sleep, and ensuring a comfortable sleeping environment.
Education regarding circadian desynchronisation	Educational information about circadian rhythms, factors that can disrupt rhythms, and resulting symptoms.
Stimulus Control	Instructional advice to maintain associations between the bedroom and sleep, using the bed only for sleep and leaving the bedroom when unable to sleep.
Relaxation techniques	Teaching specific techniques such as 'progressive muscle relaxation' aimed at increasing skills in relaxation prior to sleep. General advice regarding increasing 'relaxation time' or 'relaxing activities' was not included.
Managing worry prior to sleep	Cognitive strategies including problem solving and thought challenging.
Cognitive restructuring	Modifying unhelpful beliefs about sleep using cognitive strategies and behavioural experiments.
Sleep restriction advice	Instructional advice to restrict the amount of time spent in bed in order to improve sleep efficiency.
Dealing with oversleeping	Instructional advice to reduce total sleep time in those with hypersomnia.

Table 2: Characteristics of studies included within the review

Author (year)	Design	Description and duration of intervention (number of participants)	Control condition/ Comparator (number of participants)	Mean age, % female	Length of follow up	Sleep outcomes	Summary of sleep outcomes at follow up	Quality rating
Fulcher & White (1997)[23]	RCT	12 weeks of individual graded exercise sessions (29)	12 weeks of individual flexibility sessions (30)	37.2, 74%	Post treatment/ 12 weeks after baseline	Pittsburgh Sleep Quality Index (PSQI)	No significant difference in ratings of sleep difficulties following treatment, compared to controls	19/26
Lopez et al. (2011)[26]	Pilot study (with random allocation)	12 week group cognitive behavioural stress management programme(CBSM;44)	Half day psycho-education seminar on CBSM (25)	45.9, 88.4%	Post treatment/ 12 weeks after baseline	CDC Symptom Inventory for CFS self-report ratings of sleep problems and unrefreshing sleep	Ratings of the frequency, but not the severity of unrefreshing sleep reduced significantly in the CBSM group compared to controls.	18/26
Powell et al. (1999)[28]	Case Study	Pragmatic rehabilitation (PR) sessions incorporating elements of CBT & GET 2 participants 55-60 essions over 27 months	None	20.5, 100%	30 & 33 months after baseline	Jenkins at al. sleep scale	Ratings of sleep problems decreased from near the maximum possible score (18 & 19/20) to 0 following treatment for both participants.	8/26
Powell et al. (2001)[24]	RCT	Individual patient education to encourage graded exercise (PR). Three treatment levels: Minimum– 2 sessions (37) Telephone– 2 sessions plus telephone contact (39) Maximum– 7 sessions(38)	Standardised medical care (34)	Min 34, 76% Tel 32, 85% Max 33, 82% SMC 34, 71%	3, 6 & 12 months after baseline,	Jenkins at al. sleep scale	Intervention groups showed significant improvements in ratings of sleep difficulties, compared to standardised medical care at 3, 6 and 12 months.	20/26

Table 2 *(continued)*

Author (year)	Design	Description and duration of intervention (number of participants)	Control condition/ Comparator (number of participants)	Mean age, % female	Length of follow up	Sleep outcomes	Summary of sleep outcomes at follow up	Quality rating
Powell et al (2004)[29]	Uncontrolled follow up	As above	None – control participants from earlier RCT were offered PR intervention	As above	2 years after baseline	Jenkins at al. sleep scale	Sleep improvements appeared to be maintained at follow up although statistical analysis for sleep outcome was not reported.	18/26
Thomas et al. (2006)[27]	Non-random-ised trial	10 sessions of individualised multi-convergent therapy (MCT) combining elements of CBT, GET and adaptive pacing therapy (12)	10 sessions of relaxation therapy (14), No intervention controls (9)	MCT 46.7, 67% Relaxation 45.7, 71.4% Control 46.2, 67%	10 weeks and 6 months after baseline	Smith at al. Sleep questionnaire	There were a significantly greater number of participants whose sleep was rated as improved in the MCT group, compared to the relaxation and control groups.	11/26
Wearden et al. (2010)[25]	RCT	10 sessions of individual nurse led pragmatic rehabilitation sessions including elements of CBT & GET (95)	10 sessions of nurse led supportive listening (101), General practitioner treatment as usual (100)	44.6, 78%	20 weeks & 70 weeks after baseline	Jenkins at al. sleep scale	PR group showed significant improvement in ratings of sleep difficulties at 20 weeks, but not at 70 weeks compared to control conditions	25/26
White et al. (2011)[11]	RCT	24 weeks of individual CBT sessions (161), or individual GET sessions (160) each in combination with standardised specialist medical care	Up to 15 sessions of standardised specialist medical care (160), alone or in combination with 24 weeks of individual adaptive pacing therapy APT(159)	38, 77%	12, 24 and 52 weeks after baseline	Jenkins at al. sleep scale	CBT and GET groups showed significantly improved ratings of sleep difficulties, compared to APT and specialist medical care groups.	25/26

Table 3: Sleep components within included interventions

Author (year)	Intervention	Sleep hygiene	Education re: circadian desynchronisation	Stimulus control	Relaxation techniques	Managing worry prior to sleep	Cognitive restructuring	Sleep restriction	Dealing with oversleeping
Fulcher & White (1997)[23]	GET								
Lopez et al. (2011)[26]	CBT				✓				
Powell et al. (1999)[29]	PR	✓	✓						
Powell et al. (2001,2004) [24,29]	PR	✓	✓						
Thomas et al. (2006)[27]	Combined	✓							
Wearden et al. (2010)[25]	PR	✓	✓						
White et al. (2011)[11]	CBT	✓		✓		✓	✓	✓	✓
White et al. (2011)[11]	GET	✓			✓				

Figure 1. Flow diagram of the study selection process

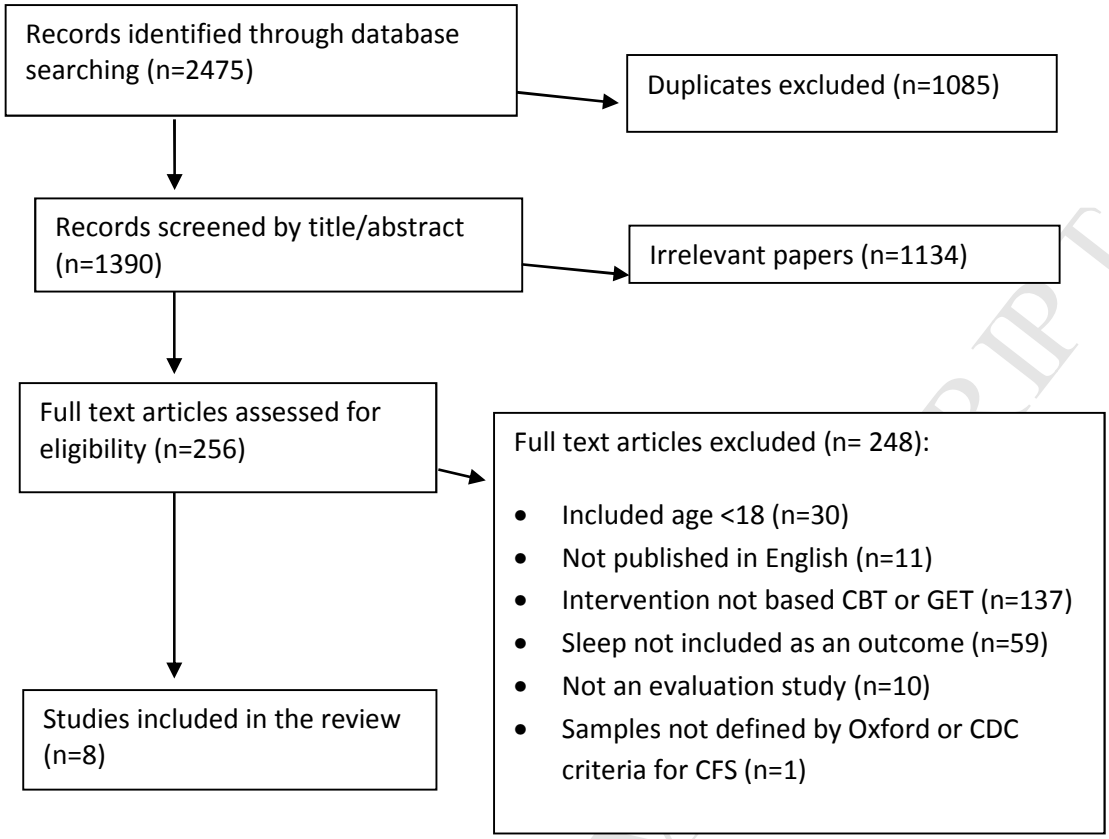


Figure 2: Comparison of sleep outcomes for CBT, GET and PR versus standardised/specialist medical care, GP treatment as usual or a half day psycho-education seminar (post treatment)

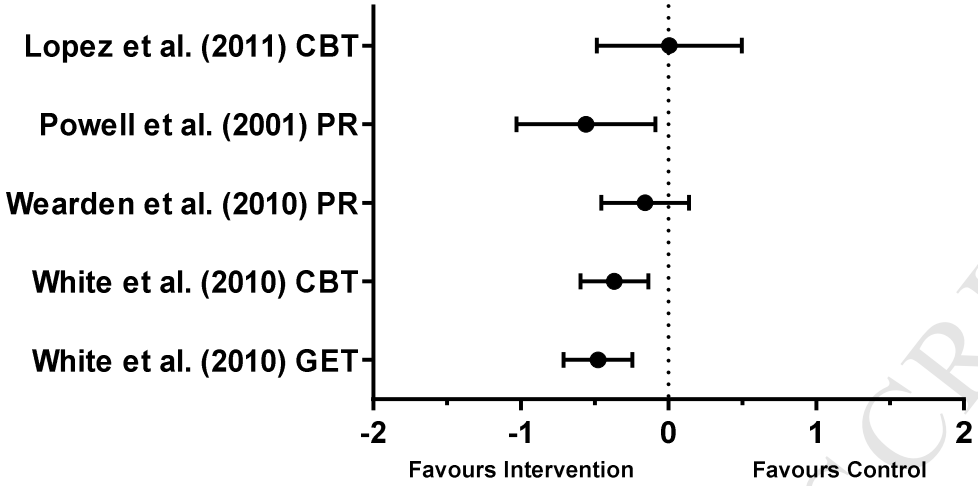
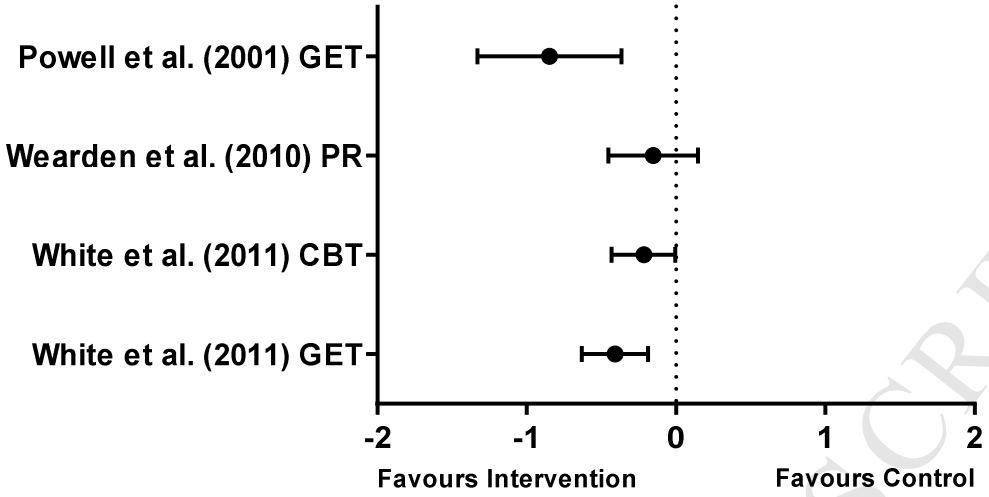


Figure 3: Comparison of sleep outcomes for CBT, GET and PR versus standardised/specialist medical care or GP treatment as usual (follow up)



Web Appendix 1 : Full Quality Ratings for Included Studies

Criteria	Fulcher & White [23]	Lopez et al. [18]	Powell et al. [28]	Powell et al. [24]	Powell et al [29]	Thomas et al. [11]	Weardenet al. [25]	White et al. [11]
1.Hypothesis/aim clear?	1	1	0	1	1	1	1	1
2. Main outcomes clearly described?	1	1	1	1	1	1	1	1
3. Participants clearly described?	1	1	1	1	1	1	1	1
4. Interventions clearly described?	1	1	1	1	1	0	1	1
5. Distribution of principal confounders clearly described? Age, severity (0,1,2)	0	1	1	2	2	2	2	2
6. Main findings clearly described?	1	1	1	1	1	0	1	1
7. Estimates of random variability provided?	1	1	0	1	1	0	1	1
8. Adverse events reported?	0	0	1	0	0	0	0	1
9. Characteristics of participants lost to follow up reported?	0	0	0	0	0	0	1	1
10. Actual probability values reported?	1	1	0	0	1	0	1	1
11. Sample approached representative?	0	0	0	1	1	0	1	1
12. Participants representative?	0	1	0	1	1	1	1	1
13. Treatments representative?	1	1	0	1	1	0	1	1
14. Attempted blinding – participants?								
15. Attempted blinding – assessors?	0	0	0	0	0	0	1	0
16. Unplanned analyses?	1	1	1	1	1	0	1	1
17. Time period same for cases and	1	0	0	1	0	1	1	1

controls?								
18. Statistical tests appropriate?	1	1	0	1	0	0	1	1
19. Was compliance with the intervention reliable?	1	1	0	0	0	0	1	1
20. Main outcomes valid & reliable?	1	1	1	1	1	0	1	1
21. Intervention and control from same population?	1	1	0	1	1	1	1	1
22. Recruited over same time period?	1	1	0	1	1	1	1	1
23. Randomisation?	1	1	0	1	1	1	1	1
24. Randomisation concealed?	1	0	0	0	0	1	1	1
25. Adequate adjustment for confounding?	1	0	0	1	1	0	1	1
26. Numbers lost to follow up accounted for?	1	1	0	1	0	0	1	1
27. Sufficient power?								
Total Score	19	18	8	20	18	11	25	25

Web appendix 2

Table 4: Post intervention data used to calculate SMD

Author	Intervention	Assessment point	Intervention Group			Control Group			SMD (95% CI)
			N	Mean	SD	N	Mean	SD	
Lopez et al. (2011)[26]	CBT	12 weeks	44	3.05	1.61	25	3.04	1.59	0.006 (-.485, 0.497)
Powell et al. (2001)[24]	PR	3 months	38	8.7	4.9	34	11.6	5.5	-0.559 (-1.030, -0.09)
Wearden et al.(2010)[25]	PR	20 weeks	83	11.31	5.27	92	12.17	5.59	-0.158 (-0.455, 0.139)
White et al. (2011)[11]	CBT	24 weeks	147	9.63	4.945	148	11.42	4.795	-0.368 (-0.598, -0.137)
White et al. (2011)[11]	GET	24 weeks	145	9.21	4.452	148	11.42	4.795	-0.478 (-0.645, -0.183)

Table 5: Follow up data used to calculate SMD

Author	Intervention	Follow up (weeks)	Intervention Group			Control Group			SMD (95% CI)
			N	Mean	SD	N	Mean	SD	
Powell et al. (2001)[24]	PR	52	38	7.1	4.9	34	11.5	5.5	-0.848 (-1.331,-0.365)
Wearden et al.(2010)[25]	PR	70	81	12.32	5.61	90	13.18	5.71	-0.152 (-0.453, 0.149)
White et al. (2011)[11]	CBT	52	143	9.92	5.331	151	11.04	5.034	-0.216 (-0.446,-0.013)
White et al. (2011)[11]	GET	52	144	9.01	4.759	151	11.04	5.034	-0.414 (-0.645, 0.183)