What treatments work for anxiety and depression in children and adolescents with chronic fatigue syndrome? An updated systematic review

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ABSTRACT

Objectives Children with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) experience a higher prevalence of depression and anxiety compared with age-matched controls. Our previous systematic reviews in 2015/16 found little evidence for effective treatment for children with CFS/ME with comorbid depression and/or anxiety. This review updates these findings.

Design A systematic review. We searched Cochrane library, Medline, Embase and PsycINFO databases from 2015 to 2020. We combined the updated results with our previous reviews in a narrative synthesis.

Participants Inclusion criteria: <18 years old; diagnosed with CFS/ME (using Centers for Disease Control and Prevention, National Institute for Health and Care Excellence or Oxford criteria); validated measures of depression and/or anxiety.

Interventions Observational studies or randomised controlled trials.

Comparison Any or none.

Outcomes Studies with outcome measures of anxiety, depression or fatigue.

Results The updated review identified two studies. This brings the total number of paediatric CFS/ME studies with a measure of anxiety and/or depression since 1991 to 16. None of the studies specifically targeted depression, nor anxiety. One new study showed the Lightning Process (in addition to specialist care) was more effective at reducing depressive and anxiety symptoms compared with specialist care alone. Previous studies evaluated cognitive–behavioural therapy (CBT); pharmacological interventions and behavioural approaches. CBT-type interventions had most evidence for improving comorbid anxiety and/or depressive symptoms but varied in delivery and modality. Other interventions showed promise but studies were small and have not been replicated.

Conclusion Very few paediatric CFS/ME intervention studies have been conducted. This review update does not significantly add to what is known from previous reviews. The evidence is of poor quality and insufficient to conclude which interventions are effective at treating comorbid anxiety and/or depression in paediatric CFS/ME.

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INTRODUCTION

Chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) is a common but poorly understood condition causing disabling fatigue, malaise, myalgia, sleep difficulties and problems concentrating.1 In children and adolescents (henceforth referred to as children), prevalence is estimated at 0.55% (95% CI 0.22% to 1.35%) across community, primary care and hospital populations.2 CFS/ME has long-term impacts on children’s physical, cognitive, emotional and social functioning.3,4

Children with CFS/ME suffer from higher rates of both depression and anxiety than age-matched population samples. The prevalence estimates of comorbid depression and anxiety are 20%5 and 29%,6 respectively, compared with 2.1% and 7.2%7 in adolescents without CFS/ME. In those attending a specialist CFS/ME service, 61% who meet diagnostic criteria for depression also have an anxiety disorder.5

Having comorbid depression and/or anxiety is associated with less favourable outcomes and may impact on engaging with treatment.
Comorbid depression in paediatric CFS/ME is associated with greater functional disability, worse fatigue and more pain compared with those without depression. Low mood, anergia and anhedonia could be barriers to motivation to engage in behavioural treatment approaches and cognitive behavioural therapy for fatigue (CBT-f). Depressive symptoms are therefore likely to require tailored treatment. The impact of anxiety on outcomes is less clear. Given that most children with CFS/ME who have anxiety also have depression, it is important to explore treatments for both.

Despite the high prevalence of comorbid mental health problems, there is little evidence about the effectiveness of treatments. Our two previous systematic reviews looking at depression and anxiety outcomes in existing CFS/ME intervention studies found that no specifically adapted treatments had been trialled to target depression and anxiety in paediatric CFS/ME. Although CBT-f and a multicomponent inpatient programme showed promise in reducing depressive and anxiety symptoms, there was no consistent treatment approach for children with CFS/ME and comorbid depression or anxiety. Since conducting these reviews in 2015/2016, further intervention studies may have been published. It is important and timely to review the current evidence to provide an update on what treatments should be offered to this population. Further, it is important to consider anxiety and depression together given their overlap, whereas our previous reviews considered them separately.

We conducted an updated systematic review by synthesising the evidence regarding treatments for paediatric CFS/ME and comorbid depression and anxiety since 2015. We combined these findings with results from our previous systematic reviews (1991–2015) to give an overview of all interventions evaluated since 1991 (when CFS/ME was scientifically defined). Specifically, we aimed to address the following:

1. What treatment approaches are there for depression and anxiety in children with CFS/ME?
2. What is known about the treatment efficacy of these approaches for treating depression and anxiety in CFS/ME? Do different approaches have different outcomes?

### METHODS

#### Data sources and search strategy

We conducted searches on Medline, Embase, PsycINFO and Cochrane Library databases. Searches were designed with input from an information specialist to include the concepts: paediatric; CFS/ME; anxiety and depression (search strategies are in online supplemental material). We updated the searches from when they had last been run (February 2015 for depression search; July 2016 for anxiety search) up until September 2020. The two searches were carried out by different reviewer teams: anxiety search (PC and AR); depression search (KD and JB). Grey literature was not searched. Reference lists of articles for full-text screening were hand-searched.

#### Inclusion and exclusion criteria

Studies were included if they met inclusion criteria (table 1).

#### Study selection

Articles returned from database searches were inputted into Endnote and duplicates removed. Each reviewer (PC, AR, KD, JB) conducted title and abstract screening independently. Full texts of potentially eligible articles were screened against specifically created eligibility checklists. The final articles for inclusion were cross-checked between all four reviewers and any conflicts discussed and resolved with input from the senior author (ML) if necessary. Where information from the paper was insufficient to determine eligibility, authors were contacted by email for additional information. If authors did not reply after two follow-up emails, the study was excluded. Figure 1 presents the PRISMA flow chart.

#### Data extraction

For all included articles, data were extracted independently by two reviewers (PC and AR) using a purpose-designed data extraction form to collect information about: study design; setting; recruitment; participant characteristics; CFS/ME definition used for diagnosis; assessment of depression and anxiety; other outcomes; treatment and interventions provided; definition of response and treatment/intervention outcomes.

### Table 1 Inclusion criteria

<table>
<thead>
<tr>
<th>Anxiety review</th>
<th>Depression review</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td></td>
</tr>
<tr>
<td>1. Children &lt;18 years of age</td>
<td>1. Diagnosed with CFS/ME defined using one of these criteria:</td>
</tr>
<tr>
<td>2. Diagnosed with CFS/ME defined using one of these criteria:</td>
<td></td>
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<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Observational cohort studies</td>
<td>Any study with intervention—for example, observational clinical cohorts, clinical trials.</td>
</tr>
<tr>
<td><strong>Baseline measure</strong></td>
<td></td>
</tr>
<tr>
<td>Validated measure of anxiety</td>
<td>Validated assessment of depression</td>
</tr>
<tr>
<td><strong>Outcome measure</strong></td>
<td></td>
</tr>
<tr>
<td>Either an anxiety and/or fatigue measure on psychometrically validated assessments or validated diagnostic interviews.</td>
<td>Either a depression and/or fatigue measure on psychometrically validated assessments or validated diagnostic interviews.</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td></td>
</tr>
<tr>
<td>Non-English language papers were considered for inclusion.</td>
<td></td>
</tr>
</tbody>
</table>

CDC, Centers for Disease Control and Prevention; CFS/ME, chronic fatigue syndrome/myalgic encephalomyelitis; NICE, National Institute for Health and Care Excellence.
Quality assessment
PC and AR used Risk of Bias (ROB) assessment tools\textsuperscript{13,14} to assess methodological quality of the included studies.

Data synthesis
We combined results from the included studies identified in the updated search with findings from the two previous systematic reviews\textsuperscript{10,11} to conduct a narrative synthesis,\textsuperscript{15} providing an overview of all longitudinal studies that have been evaluated in this clinical cohort since 1991 (when CFS/ME was scientifically defined). There was insufficient comparable data to conduct a meta-analysis as interventions were heterogeneous and a range of outcome measures were reported. For each of the new studies, the effects of interventions on outcomes using mean differences were compared.

Patient and public involvement
No patients were involved.

RESULTS

Studies included
In the updated search (2015–2020), a total of 625 and 415 references were found by database searching for the depression and anxiety searches, respectively. After full-text screening, both searches returned the same two eligible studies.\textsuperscript{16,17} One was a randomised controlled trial (RCT),\textsuperscript{17} one was a retrospective observational cohort study.\textsuperscript{16} The PRISMA\textsuperscript{12} flow chart is in Figure 1.

The previous systematic reviews for depression\textsuperscript{10} (search conducted in 2015) and anxiety\textsuperscript{11} (search conducted in 2016) found 362 and 1274 references, respectively. After full-text screening, the depression search returned nine eligible studies (one RCT,\textsuperscript{18} and eight observational studies\textsuperscript{18–20}), and the anxiety search returned nine eligible papers from eight studies (three RCTs,\textsuperscript{27–30} six observational studies\textsuperscript{19,21,22,25,31,32}). Four of the studies from these two searches were the same.

Therefore, in total, 16 eligible studies were included in this narrative synthesis review. Figure 2 shows a flow chart combining studies from this updated search with studies identified from previous reviews.

Quality assessment
Of the total 16 studies in this review, 10 were observational and six were RCTs. Of the observational studies, five had an overall ROB as ‘unclear’, and five had ‘high’ ROB (as defined by the Cochrane ROB scale, ROBINS-I (Risk of Bias In Non-Randomised Studies)\textsuperscript{13}). Of the RCTs, all six had an overall rating of ‘low’ ROB (as defined by the Cochrane ROB-2 scale).\textsuperscript{14} See online supplemental material for the quality assessment table. For detailed reporting on the quality assessment of studies from the previous searches, please refer to our previous two reviews.\textsuperscript{10,11}

In this paper, we report in detail on the quality assessment of the two new studies found in the updated search. The RCT\textsuperscript{17} was conducted by members of our CFS/ME research team (EC). The study has a low ROB from the concealed allocation randomisation process, minimal deviation from how interventions were intended to be delivered, and appropriate intention-to-treat analysis. Outcome measurement is biased because of self-reported...
measures, but this is standard for behavioural treatments. It is also biased due to loss to follow-up. In the control arm at 3 months, 13 of 49 (27%) were lost to follow-up and at the primary outcome of 6 months, 12 of 49 (24%) were not included in analysis. In the intervention arm 8 of 51 (16%) were lost to follow-up at 3 months and 7 of 51 (14%) were not included in primary analysis at 6 months. Although baseline characteristics between those who did and did not provide primary outcome data were similar, it is possible that missingness was related to the outcome.

The retrospective observational study16 is also biased due to poor follow-up rates at any one time point (making comparison difficult), and no pre-published analysis plan. In the cohort, there are two samples; one with baseline data for anxiety and depression and one without. Follow-up questionnaires were mailed to all participants on a number of occasions between January 2008 and June 2011. This produced a range of follow-up time points (1–21 years) after illness onset, meaning some patients would not have had contact with the clinic for a long time when they were sent the questionnaire, so it is likely that both disease status and time since illness influenced outcome data. Of the 489 patients who were sent baseline questionnaires, 74% returned a follow-up questionnaire on at least one occasion (range 1–7). For the sample of 366 without baseline data for anxiety and depression, 76% returned a follow-up questionnaire on one occasion, while only 8% returned a questionnaire on more than one occasion. Outcome measures were also self-reported, and many participants did not complete all measures.

Participant and study characteristics

The two studies identified in the updated search were: an RCT evaluating the ‘Lightning Process’ intervention alongside ‘specialist medical care’ compared with ‘specialist medical care’ alone17; and an observational cohort study assessing ‘routine specialist care’ over a 20-year period.16 Studies from the previous reviews included the following. Four RCTs evaluating: inpatient programmes with predominantly behavioural approaches, an online CBT programme and intravenous gammaglobulin; eight observational cohort studies evaluating: CBT, an antiviral treatment and an inpatient programme; and two prospective observational community studies that did not assess a specified intervention.21 22 Follow-up times varied from immediately post-treatment to 21 years. Total number of participants included across all studies was 965. Most sample sizes were small but ranged between one and 418. Participant ages ranged between 11 and 18. Most studies were conducted across Europe (UK, Netherlands, Spain) and Australia. One was in Japan, one in the USA (table 2).

None of the studies identified were specifically aimed at treating anxiety or depression in children with CFS/ME (all primary outcomes were measures of fatigue or recovery). Anxiety and/or depression were measured as secondary outcomes using a variety of self-report questionnaires including the Hospital Anxiety and Depression Scale (HADS), Spence Children’s Anxiety Scale (SCAS), the State-Trait Anxiety Inventory for Children, the Multidimensional Anxiety Scale for Children, Spielberger State Trait Anxiety Questionnaire, Beck Depression Inventory, and Children’s Depression

![Flow chart of studies combined from updated review and previous reviews.](https://bmjopen.bmj.com/)

**Figure 2** Flow chart of studies combined from updated review and previous reviews.

<table>
<thead>
<tr>
<th>Author (year), country</th>
<th>Sample size</th>
<th>Length of follow-up</th>
<th>Setting</th>
<th>Study design</th>
<th>Intervention</th>
<th>Control</th>
<th>Intervention</th>
<th>Primary outcome</th>
<th>Measure of anxiety/depression</th>
<th>Treatment specifically targeted to anxiety or depression</th>
<th>Outcomes stratified by those with anxiety/depression?</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowe (2018), Australia</td>
<td>N/A</td>
<td>Mean: 8 years; range 1–21 years</td>
<td>Outpatient secondary care</td>
<td>Observational retrospective</td>
<td>N/A</td>
<td>418 (789 recruited but 366 did not have baseline questionnaire)</td>
<td>N/A</td>
<td>14.8</td>
<td>CDC/Fukuda et al</td>
<td>Reported recovery and duration of illness</td>
<td>No</td>
<td>No</td>
<td>Routine specialist medical care provided in the outpatient clinic. Designed as a person-centred goal-oriented holistic programme which targets educational, physical, social and emotional aspects of life.</td>
</tr>
<tr>
<td>Crawley (2018), UK</td>
<td>49</td>
<td>N/A</td>
<td>Outpatient secondary care</td>
<td>RCT</td>
<td>51</td>
<td>14.5</td>
<td>14.7</td>
<td>78%</td>
<td>NICE</td>
<td>SF-36 PFS at 6 months</td>
<td>SCAS, HAIDS</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Henderson (2014), USA</td>
<td>N/A</td>
<td>Varied post-treatment</td>
<td>Outpatient secondary care</td>
<td>Observational, retrospective, case-control</td>
<td>N/A</td>
<td>15 (14 at follow-up)</td>
<td>N/A</td>
<td>15.46</td>
<td>CDC/Fukuda et al</td>
<td>Fatigue self-assessment scores (CFS, PSS, FSS, MFS)</td>
<td>CDI</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rimes (2014), UK</td>
<td>36 healthy controls</td>
<td>N/A</td>
<td>Outpatient secondary care</td>
<td>Observational case-control</td>
<td>49 (34 at follow-up)</td>
<td>15</td>
<td>14.9</td>
<td>63%</td>
<td>CDC/Fukuda et al</td>
<td>School attendance</td>
<td>SCAS</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Nijhof (2012, 2013, Netherlands)</td>
<td>67 (63 at follow-up)</td>
<td>N/A</td>
<td>Outpatient secondary care</td>
<td>Both RCTs</td>
<td>68 (64 at follow-up)</td>
<td>15.8</td>
<td>15.9</td>
<td>85%</td>
<td>CDC/Fukuda et al</td>
<td>School attendance, absence of severe fatigue and normal physical functioning</td>
<td>STAI</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Lloyd (2012), UK</td>
<td>N/A</td>
<td>N/A</td>
<td>Outpatient secondary care</td>
<td>Observational</td>
<td>63 (52 at follow-up)</td>
<td>N/A</td>
<td>Median 15</td>
<td>N/A</td>
<td>Oxford Sharp et al</td>
<td>Fatigue (Chalder Fatigue Questionnaire Total) and school attendance</td>
<td>STAI</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Kawatani (2011), Japan</td>
<td>19</td>
<td>N/A</td>
<td>Outpatient secondary care</td>
<td>Observational</td>
<td>N/A</td>
<td>13.6</td>
<td>N/A</td>
<td>63%</td>
<td>Jazon et al</td>
<td>Chalder’s Fatigue Scale</td>
<td>Zung self rating depression scale</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Author (year), country</td>
<td>Anxiety, depression or both?</td>
<td>Study design</td>
<td>Setting</td>
<td>Sample size</td>
<td>Mean age, years</td>
<td>Gender, female %</td>
<td>CFS/ME diagnostic criteria</td>
<td>Primary outcome</td>
<td>Measure of anxiety/ depression</td>
<td>Treatment specifically targeted to anxiety or depression?</td>
<td>Intervention/control</td>
<td>Length of follow-up</td>
<td></td>
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<td>------------------------</td>
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<td></td>
</tr>
<tr>
<td>Gordon (2010), Australia</td>
<td>Depression</td>
<td>RCT</td>
<td>Inpatient secondary care</td>
<td>16</td>
<td>15</td>
<td>50%</td>
<td>CDC/Fukuda et al</td>
<td>Global rating</td>
<td>Physical and physiological measures for example, aerobic capacity (VO2 peak), time to fatigue, physical component score of SF-36</td>
<td>No</td>
<td>BDI</td>
<td>No</td>
<td>4 week inpatient programme including graded exercise therapy, psychological/psychiatric support, attendance at school. Patients randomised to either graded aerobic exercise training or progressive resistance training programme for 5 days/week for 4 weeks. The graded aerobic training consisted of 20–40 min of stationary cycling and treadmill exercise. The progressive resistance training involved 16 exercises performed with single set, moderate load and high repetitions.</td>
</tr>
<tr>
<td>Gordon (2009), Australia</td>
<td>Depression</td>
<td>Observational</td>
<td>Inpatient secondary care</td>
<td>N/A</td>
<td>16</td>
<td>N/A</td>
<td>CDC/Fukuda et al</td>
<td>Global rating</td>
<td>Fatigue</td>
<td>SSTAQ, CDS</td>
<td>No</td>
<td>4–6 months</td>
<td></td>
</tr>
<tr>
<td>Diaz Caniña (2007), Spain</td>
<td>Anxiety</td>
<td>Observational case study</td>
<td>Outpatient secondary care</td>
<td>N/A</td>
<td>15</td>
<td>100%</td>
<td>Oxford/Sharpe et al</td>
<td>Global rating</td>
<td>Self-reported fatigue, pain symptoms</td>
<td>MA10C</td>
<td>No</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>Frieses (2007), UK</td>
<td>Anxiety</td>
<td>Observational prospective</td>
<td>Community</td>
<td>1 case of CFS at time 1-4 cases of CFS at time 2</td>
<td>13</td>
<td>Not reported</td>
<td>CDC/Fukuda et al</td>
<td>Global rating</td>
<td>Incidence and prevalence of fatigue, chronic fatigue and CFS</td>
<td>DAWBA</td>
<td>No</td>
<td>None specifically stated or evaluated</td>
<td></td>
</tr>
<tr>
<td>Van de Putte (2007), Netherlands</td>
<td>Depression</td>
<td>Observational prospective</td>
<td>Community</td>
<td>40 at baseline, 36 at follow-up</td>
<td>16</td>
<td>N/A</td>
<td>78%</td>
<td>CDC/Fukuda et al</td>
<td>Global rating</td>
<td>Fatigue</td>
<td>SSTAQ, CDS</td>
<td>No</td>
<td>18 months</td>
</tr>
<tr>
<td>Weight (2005), UK</td>
<td>Anxiety</td>
<td>RCT</td>
<td>Outpatient secondary care</td>
<td>6 (6 at follow-up)</td>
<td>12.9</td>
<td>66%</td>
<td>Oxford/Sharpe et al</td>
<td>Global rating</td>
<td>Global Health on Child Health Questionnaire</td>
<td>HA10S</td>
<td>No</td>
<td>STAIRway to Health intervention is a structured rehabilitation programme including conceptualising CFS as having both physical and psychological components, formulating and addressing various cycles around activity, sleep, social isolation, physical deconditioning, and developing adaptive coping strategies while challenging negative and unhelpful attributions about illness and the future.</td>
<td>1 year</td>
</tr>
<tr>
<td>Denborough (2003), Australia</td>
<td>Anxiety</td>
<td>Observational</td>
<td>Inpatient secondary care</td>
<td>39 (19 at follow-up)</td>
<td>16.2</td>
<td>N/A</td>
<td>CDC/Fukuda et al</td>
<td>Global rating</td>
<td>Functional score including school attendance, schoolwork, social activity and physical activity</td>
<td>HA10S</td>
<td>No</td>
<td>CBT based rehabilitation programme. Up to 15 sessions, 1 hour duration.</td>
<td>6 months</td>
</tr>
<tr>
<td>Chalder (2002), UK</td>
<td>Anxiety</td>
<td>Observational</td>
<td>Inpatient secondary care</td>
<td>23</td>
<td>N/A</td>
<td>87%</td>
<td>Oxford/Sharpe et al</td>
<td>Global rating</td>
<td>The fatigue questionnaire, school attendance</td>
<td>HA10S</td>
<td>No</td>
<td>CBT based rehabilitation programme. Up to 15 sessions, 1 hour duration.</td>
<td>6 months</td>
</tr>
<tr>
<td>Rowan (1997), Australia</td>
<td>Anxiety</td>
<td>RCT</td>
<td>Outpatient secondary care</td>
<td>15</td>
<td>15.6</td>
<td>75%</td>
<td>CDC/Fukuda et al</td>
<td>Global rating</td>
<td>Functional score including school attendance, schoolwork, social activity and physical activity</td>
<td>SSTAQ</td>
<td>No</td>
<td>3 monthly infusions of gammaglobulin</td>
<td>3 and 6 months</td>
</tr>
</tbody>
</table>
Treatment approaches and their efficacy treating anxiety and/or depression in paediatric CFS/ME

Of the 16 studies: one study evaluated routine specialist outpatient care; one evaluated the Lightening Process outpatient intervention; one evaluated the ‘STAIRway to health’ outpatient intervention; six evaluated various outpatient CBT programmes; two evaluated outpatient pharmacological interventions (antiviral and gammaglobulins); three evaluated inpatient programmes focused on graded exercise therapy; and two were epidemiological observational studies so were uninformative about interventions.

There were common cognitive and behavioural elements across the behavioural and CBT programmes, including: behavioural strategies for a goal-oriented graded approach to increasing activity, often with the goal to return to full-time education or to commit to a regular activity; cognitive strategies to address the psychological implications of CFS/ME, illness-related beliefs and negative thoughts; and psychoeducation about the consequence of the illness and tools to navigate this. They varied in their intensity (eg, inpatient treatment, consecutive daily 4-hour outpatient sessions, and fortnightly 30 min phone calls), duration of treatment (days to years), and modality (eg, face to face, telephone and online). The antiviral and gammaglobulin studies did not include these elements and were distinct from the other studies in their approach.

Table 3 summarises outcomes of depression and/or anxiety and other relevant findings for each included study from (1) the updated review and (2) previous reviews. Below, we discuss the efficacy of the treatment approaches in the 14 studies which evaluated an intervention, by whether they were (1) an outpatient or (2) an inpatient programme.

Outpatient programmes

The two new studies from this updated review evaluated two outpatient programmes. Crawley et al compared adding the Lightening Process intervention (https://lightningprocess.com) to specialist care (recommended by National Institute for Health and Care Excellence (NICE)), to specialist medical care alone. The Lightning Process is developed from osteopathy, life coaching and neurolinguistic programming and more than 250 children use it for their CFS/ME each year in the UK. It is delivered in intensive three, 4-hour sessions on consecutive days in small groups, with theory elements on the stress response, how the mind and body interact and how thought processes and language can be either helpful or negative, followed by practical sessions where participants identify an activity goal and are given cognitive strategies to attempt it. The study showed a significant reduction in adjusted difference in mean depressive and anxiety symptoms at 12 months (−1.8, p=0.04 for depression; −14.5, p<0.001 for anxiety) among participants allocated to the Lightening Process intervention (in addition to specialist medical care) arm than those allocated to the specialist medical care-only control. The Lightening Process was more effective than specialist medical care at reducing anxiety symptoms compared with depression (at both 6 and 12 months follow-up). Outcomes in this study were not stratified by those with depression or anxiety, so we cannot comment on other CFS/ME outcomes (such as fatigue or recovery) in context of comorbid depression or anxiety.

The other study identified in this updated review evaluated routine specialist care delivered at the authors’ CFS/ME outpatient clinic in Australia. Routine specialist care offers a ‘person-centred goal-oriented holistic programme’ to ‘target educational, physical, social and emotional aspects of life’. This includes symptom management (eg, sleep, migraine, dizziness, nausea, orthostatic intolerance, concentration difficulties) and focussing on increasing activity and a commitment to something enjoyable outside the home on a regular basis. This study measured depressive and anxiety symptoms at baseline but not post-treatment, so we cannot comment on the effectiveness of the intervention at reducing depression or anxiety. Instead, the study compared mean baseline depression and anxiety scores between those who had self-reported ‘recovery’, defined as answering ‘yes’ to the question ‘Do you feel you are no longer suffering from CFS?’ measured at a mean length of follow-up of 8 years (range 1–21). There was no difference in depression or anxiety at baseline between those who reported that they had recovered and those who had not that is, depression nor anxiety were found to be associated with recovery.

As per our previous reviews, several studies have evaluated other outpatient programmes. Outpatient CBT interventions demonstrated inconsistent efficacy and varied in terms of delivery modality (family-focused; face to face; telephone or internet-delivered modules with therapist e-consults), intensity (15 weekly, hourly therapist-led sessions; six fortnightly 30 min telephone calls), duration of treatment (12 weeks to 1 year), and whether pharmacotherapy was offered alongside CBT (antidepressants and antihypotensives). Three observational studies showed that face-to-face and telephone CBT resulted in improved depression, anxiety, functioning and social adjustment. An RCT showed that participants who received internet-based CBT demonstrated improvement in fatigue and school attendance at 6 months follow-up, compared with participants who received usual care. However, the study did not measure anxiety at follow-up. Two studies that evaluated CBT alongside pharmacotherapy were uninformative as they either did not reassess mood at follow-up or reported on only a single case-study. In terms of behavioural approaches,
### Table 3
Summary of outcomes for symptoms of depression and anxiety and other relevant findings for included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Measure of depression and anxiety</th>
<th>Pre treatment: depression, mean (SD)</th>
<th>Pre treatment: anxiety, mean (SD)</th>
<th>Post treatment: depression, mean (SD)</th>
<th>Post treatment: anxiety, mean (SD)</th>
<th>Statistical analysis of change in depression/anxiety symptomatology</th>
<th>Summary of other relevant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intervention /case</td>
<td>Intervention /case</td>
<td>Intervention /case</td>
<td>Intervention /case</td>
<td>Depression</td>
<td>Anxiety</td>
</tr>
<tr>
<td>A) Studies identified in updated review</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rowe (2019)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(depression scale), STAI*(anxiety scale)</td>
<td>13.8 (8.9)</td>
<td>N/A</td>
<td>88.9 (2.49)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Crawley et al (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(depression and anxiety scales), SCAS* (anxiety scale)</td>
<td>7.5 (3.1)</td>
<td>8.1 (4.4)</td>
<td>4.2 12 months: 2.8</td>
<td>6 months: 5.9 12 months: 4.6</td>
<td>HADS 6 months: 6.1 12 months: 5.3 SCAS 6 months: 24.7 12 months: 19.6</td>
<td>Adjusted difference in means† (95% CI, p value): 6 months: −1.5 (−3.5 to 0.5, 0.1) 12 months: −1.8 (−3.4 to −0.1, 0.04)</td>
<td>Adjusted difference in means† (95% CI, p value): HADS at 6 months: −3.5 (−5.6 to −1.5, 0.001) SCAS at 6 months: −10.0 (−18.5 to −1.5, 0.02) HADS at 12 months: −2.6 (−4.7 to −0.4, 0.019); SCAS at 12 months: 14.5 (−22.4 to −6.7, &lt;0.001)</td>
</tr>
<tr>
<td>(B) Studies identified in previous reviews</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henderson (2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDI</td>
<td>14 (2.8)</td>
<td>N/A</td>
<td>N/A</td>
<td>Not reported</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Rimes et al (2014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCAS</td>
<td>N/A</td>
<td>N/A</td>
<td>Cases: 22 (17) Median 16.0 (IQR 9.0–34.0)</td>
<td>Controls: Median 16.5 (IQR 8.0–22.8)</td>
<td>N/A</td>
<td>N/A</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Study</th>
<th>Measure of depression and anxiety</th>
<th>Pre treatment: depression, mean (SD)</th>
<th>Post treatment: depression, mean (SD)</th>
<th>Statistical analysis of change in depression/anxiety symptomatology</th>
<th>Summary of other relevant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nijhof et al (2012, 2013)</td>
<td>STWIC</td>
<td>N/A</td>
<td>32.1 (8.1)</td>
<td>N/A</td>
<td>Intervention (FITNET) was significantly more effective than the control (usual care) at 6 months—full school attendance (50 (75%) vs 10 (16%); relative risk 4.8, 95% CI 2.7–8.9; p&lt;0.0001), absence of severe fatigue (57 (85%) vs 17 (27%); 3.2, 2.1–4.9; p&lt;0.0001), and normal physical functioning (52 (78%) vs 13 (20%); 3.8, 2.3–6.3; p&lt;0.0001). The short-term effectiveness of FITNET was maintained at 2.5 years follow-up. At 2.5 years follow-up, usual care led to similar recovery rates, although progress had taken longer to make. At 6 months additional analyses of main findings with adjustments for anxiety, depression and primary outcomes, had no effects on the results. When looking at factors related to recovery at 2.5 years, anxiety OR 1.01 (95% CI 0.96 to 1.06), p=0.66.</td>
</tr>
<tr>
<td>Lloyd et al (2012)</td>
<td>BiReson Depression Scale; SCAS</td>
<td>Baseline mean 13.38 (4.76)</td>
<td>Pre-treatment mean 12.91 (5.57)</td>
<td>Multi-level modelling and Wald tests Treatment effect estimate at 6 months: 3.69 (95% CI 2.5–5.17), significance (two-tailed) &gt;0.001, effect size 0.78.</td>
<td></td>
</tr>
<tr>
<td>Kawatani et al (2011)</td>
<td>Zung Self-Rating Depression Scale</td>
<td>53.3 (6.7)</td>
<td>N/A</td>
<td>Multi-level modelling and Wald tests Treatment effect estimate at 6 months: 0.49, significance (two-tailed) 0.003, effect size 0.16</td>
<td></td>
</tr>
<tr>
<td>Gordon et al (2010)</td>
<td>BDI</td>
<td>Resistance arm: 20.9 (11.3)</td>
<td>Aerobic arm: 16.4 (4.3)</td>
<td>There was no control group. Significant improvement in BDI scores in both arms.</td>
<td></td>
</tr>
<tr>
<td>Gordon and Lubitz (2009)</td>
<td>BDI</td>
<td>19.88 (8.62)</td>
<td>N/A</td>
<td>Paired t-test p value 0.001, sig 0.008</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Continued
<table>
<thead>
<tr>
<th>Study</th>
<th>Measure of depression and anxiety</th>
<th>Pre treatment: depression, mean (SD)</th>
<th>Post treatment: depression, mean (SD)</th>
<th>Statistical analysis of change in depression/anxiety symptomatology</th>
<th>Summary of other relevant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaz-Caneja et al. (2007)</td>
<td>MASC</td>
<td>N/A</td>
<td>N/A</td>
<td>Not stated although it is reported that anxiety improved</td>
<td>N/A</td>
</tr>
<tr>
<td>Rimes et al. (2007)</td>
<td>DAWBA</td>
<td>Only states ‘3 of 4 had at least one psychiatric diagnosis at baseline’</td>
<td>N/A</td>
<td>N/A</td>
<td>Not reported</td>
</tr>
<tr>
<td>Van de Putte et al. (2007)</td>
<td>CDI at baseline only; HADS (anxiety)</td>
<td>11.7 (6.1)</td>
<td>36.9 (7.8)</td>
<td>Not stated</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wright et al. (2005)</td>
<td>HADS (anxiety)</td>
<td>N/A</td>
<td>10.17 (3.71)</td>
<td>Post-treatment: 6.00 (4.73)</td>
<td>Activity (child and clinician rated) and school attendance improved markedly in the intervention (STARway) arm compared with little improvement in activity scores in the control (Pacing) arm, and a deterioration in school attendance. Global health (child and clinician rated) improved in both arms although more in the STARway arm than the pacing arm.</td>
</tr>
<tr>
<td>Denborough et al. (2009)</td>
<td>BDI</td>
<td>21</td>
<td>N/A</td>
<td>Improvement p=0.001 Maintained at 6 month follow-up (p=0.038)</td>
<td>On discharge, mean depression score significantly better than on admission. Also significant improvement in Chronic Fatigue Illness Disability score and significant decrease in FSS score (maintained at 6 months follow-up). Achenbach Youth Self-Report scores improved significantly by discharge, but returned to above admission levels at 6 months.</td>
</tr>
</tbody>
</table>

Report of a moderate response to treatment with the young person tolerating more activity. She had resumed contact with her friends, and although she still complained of tiredness and pain, she was attending classes daily.

Of the four participants who developed CFS/ME over the follow-up period, 3 of 4 had at least one psychiatric diagnosis at baseline. 3 had reported being ‘much more tired and worn out than usual over the last month’ at time 1, 2 participants had frequent headaches at time 1, 1 also had sleep problems and post-exertional malaise at time 1.

47% of adolescents ‘fully recovered’ (below score that is mean plus 2 SD of subjective fatigue distribution in health adolescents).
<table>
<thead>
<tr>
<th>Study</th>
<th>Measure of depression and anxiety</th>
<th>Pre treatment: depression, mean (SD)</th>
<th>Post treatment: depression, mean (SD)</th>
<th>Statistic analysis of change in depression/anxiety symptomatology</th>
<th>Summary of other relevant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chalder et al.</td>
<td>HADS</td>
<td>8.4 (IQR 5.7–11)</td>
<td>N/A</td>
<td>Wilcoxon signed ranks test −3.33 (two-tailed significance 0.00)</td>
<td>Depression: The 20 participants who completed treatment had all returned to school at 6 months follow-up, with 19 of 20 attending full time. Depression significantly improved, as did social adjustment. Anxiety: All 20 treatment completers returned to school at 6 months follow-up, with 95% attending full time. Depression significantly improved, as did social adjustment.</td>
</tr>
<tr>
<td>Rowe (1997)</td>
<td>SSTAQ</td>
<td>N/A</td>
<td>N/A</td>
<td>T value (df) 2.63 (6), Sig p value 0.01</td>
<td>Significant mean functional improvement in both groups.</td>
</tr>
</tbody>
</table>

*Higher score = more symptoms, poorer function.†Adjusted for age, gender, baseline outcome, SCAS and Visual Analogue Scale.

Reported recovery was based on the question “Do you feel you are no longer suffering from CFS?” (yes/no).

BDI, Beck’s Depression Inventory; CDI, Children’s Depression Inventory; CFS/ME, chronic fatigue syndrome/myalgic encephalomyelitis; DAWBA, Development and Well-Being Assessment; FSS, Fatigue Symptom Inventory; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; LP, lightning process; MASC, Multidimensional Anxiety Scale for Children; MF-SII, Multidimensional Fatigue Symptom Inventory-Short Form; N/A, not available; SCAS, Spence Children’s Anxiety Scale; SMAC, Specialist Medical Care; SSTAQ, Spielberger State-Trait Anxiety Questionnaire; STAI(C), State-Trait Anxiety Inventory (for children).
the STAIRway to Health—an incremental rehabilitation intervention—showed greater improvement in anxiety levels, when compared with a ‘pacing’ intervention in an RCT. Pharmacological studies showed insufficient evidence for improving anxiety or depressive symptoms with intravenous gammaglobulin infusions or valacyclovir respectively.

**Inpatient programmes**
As per our previous review, three studies including one RCT, evidenced an improvement in mood post-treatment with a 4-week inpatient behavioural programme focused on graded exercise (including physiotherapy, aerobic exercise and resistance training), which were maintained at 6 month follow-up in one study. However, they did not measure anxiety symptoms; internalising problems at 6 months returned to preadmission levels; two studies did not have follow-up data; all studies had small sample sizes; and the multicomponent intervention also included psychological therapy (with no further specified details about this). Therefore, these studies are uninformative for drawing conclusions about the efficacy of this behavioural intervention, or about what the key effective components of the approach may have been.

**DISCUSSION**
Our updated review of interventions for comorbid depression and/or anxiety in children with CFS/ME identified only two new studies published since 2015 (one of which was conducted by members of our own research team) exposing the lack of progress in this field. One study (an RCT) showed that adding the Lightening Process intervention to specialist medical care was more effective than specialist medical care alone at reducing both depressive and, to a greater extent, anxiety symptoms. The other study (an observational cohort evaluating routine specialist care) did not measure depression or anxiety at follow-up. Combined with our results from previous reviews, we identified 16 studies of 11 different interventions for paediatric CFS/ME since 1991 that include measures of anxiety and/or depression. Of these, six did not provide follow-up measurements of anxiety and/or depression post-intervention, and none of the interventions in the studies specifically targeted comorbid anxiety and/or depression. The results of this updated review do not appreciably alter what is already known from previous reviews, that there is insufficient evidence to conclude what the best interventions are for treating anxiety and/or depression in paediatric CFS/ME patients.

Strengths of the updated review include the systematic approach, the use of four reviewers, contacting authors for subgroup data, and not limiting results to English language. The limitations are the lack of eligible studies and insufficient data available for a meta-analysis. Only two papers were eligible for inclusion, of which one did not provide sufficient follow-up data to comment on the treatment efficacy of the intervention on depression and anxiety. Neither intervention was specifically designed to measure the impact on depression and anxiety and therefore studies were inadequately powered to measure this. Studies were not stratified by those who met criteria for clinical diagnoses of depression/anxiety reducing our ability to analyse effectiveness. Furthermore, neither study used diagnostic interviews for anxiety and depression, relying instead on questionnaires. While HADS, SCAS and STA questionnaires are validated for use in adolescents, only the RCADS (Revised Children’s Anxiety and Depression scale), which is derived from the SCAS, has been found to have sufficient discriminative accuracy against gold standard diagnostic interviews in paediatric CFS/ME populations.

In conjunction with our previous reviews, we show that currently the interventions with most evidence for improvement in anxiety and depressive symptoms in CFS/ME, when compared with other interventions, such as behavioural-only or pharmacological, is CBT. The ‘Lightening Process’ programme, ‘STAIRway to Health’ intervention, and a 4-week multicomponent inpatient rehabilitation programme show promising results for improving anxiety and/or depressive symptoms in single RCTs, but sample sizes are small and results have not been replicated. The mechanisms for why CBT could be effective are unclear because no study targeted anxiety and depression. Further, multicomponent outpatient and inpatient interventions make it difficult to identify the effective element of interventions. Our updated review does not further this debate because, while CBT is an element of ‘specialist medical care’ and ‘routine specialist care’ interventions in the new studies, we do not know how many participants received CBT or how it was delivered. Additionally, results are not stratified by those with anxiety and/or depression. Furthermore, the differences and similarities between the Lightening Process and CBT are also unclear. It should also be noted that the draft NICE guideline (expected publication date August 2021: https://www.nice.org.uk/guidance/NG10091/documents/draft-guideline) does not recommend the Lightening Process for management of CFS (although this is not specifically aimed at anxiety and depression).

Other cognitive and behavioural based approaches are being trialled in CFS/ME, but are limited in contributing to our understanding of their efficacy for anxiety and depressive symptoms in CFS/ME because of a failure to include paediatric CFS/ME populations or those diagnosed with CFS/ME using recognised criteria, or measure anxiety and depressive symptoms in the 20%–30% of children that experience them. Three studies were excluded from our review for these reasons. For example, studies evaluating acceptance and commitment therapy and mindfulness-based therapies show promising results in improving the physical health, symptom burden and ‘emotional distress’ in children with functional somatic syndromes including CFS/ME but were excluded from this review because data for adolescent participants with CFS/ME were aggregated with those with other somatic syndromes including CFS/ME but were excluded from this review.
syndromes, and the studies only measured general wellbeing outcomes rather than specifically validated anxiety and/or depression outcomes.

There is a pressing need for more work in this area to identify efficacious treatments for anxiety and depressive symptoms in paediatric CFS/ME so they can be used in clinical practice. We call on researchers to undertake paediatric CFS/ME interventions studies and use validated, diagnostic outcome measures of anxiety and depression.

CONCLUSION
This updated review highlights both the paucity of intervention studies in children with CFS/ME since 1991 and the lack of forward movement in identifying effective treatments for paediatric CFS/ME and comorbid depression and anxiety over the last five years. The overall quality of the literature remains poor and calls for paediatric CFS/ME intervention studies to target anxiety and depression, measure outcomes with validated scales, or report outcomes in subsets of patients with clinical diagnoses of anxiety and depression, have not been met. Given that comorbid anxiety and depression in paediatric CFS/ME are associated with worse outcomes, unlikely to remit spontaneously without treatment, and can be incompatible with following standard CFS/ME treatment guidance, this needs to be addressed. Future research should improve the quality of the literature by using validated scales (as well as analyse correlation between scales) and measure anxiety and/or depression as primary outcomes in large intervention studies of comorbid anxiety and/or depression in paediatric CFS/ME.

Twitter Philippa Clery @PhilippaClery

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Contributors ML and EC (guarantor) conceptualised this study, PC, AR, KD and JB performed data collection, synthesis and interpretation. PC wrote the manuscript. All authors contributed to manuscript revisions, have read the final manuscript and approved it for publication. All authors agree to be accountable for all aspects of the work.

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Disclaimer The views expressed in this publication are those of the authors and not necessarily those of the NHS, NIHR or the Department of Health and Social Care.

Competing interests EC acts as a non-paid medical advisor for the Sussex and Kent ME society.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. Data sharing not applicable as no datasets were generated or analysed for this study.

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5 Loades ME, Read R, Smith L, et al. How common are depression and anxiety in adolescents with chronic fatigue syndrome (CFS) and how should we screen for these mental health co-morbidities? a clinical cohort study. Eur Child Adolesc Psychiatry 2021;30:1733–43.
10 Loades ME, Shels EA, Crawley E. Treatment for paediatric chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ ME) and comorbid depression: a systematic review. BMJ Open 2016;6:e012271.


41 Zung WW. A self-rating depression scale. *Arch Gen Psychiatry* 1965;12:63–70.


Supplementary Material

Appendix 1: Search Strategies

Search strategy for Anxiety searches:

1. (adolesc* or preadolesc* or pre-adolesc* or boy* or girl* or child* or infan* or preschool* or pre-school* or juvenil* or minor* or pe?diatri* or pubescen* or pre-pubescen* or prepubescen* or puberty or teen* or young* or youth* or school* or high-school* or highschool* or sibling* or schoolchild* or school child* or children).tw.

2. exp Adolescent/ or exp Child/ or exp Child, Preschool/ or exp Infant/ or exp Minors/ or exp Pediatrics/

3. 1 or 2

4. Chronic Fatigue Syndrome.tw

5. myalgic encephal*.tw.

6. chronic fatigue syndrome*.mp.

7. myalgic encephal*.mp.

8. anxiety disorder/

9. exp anxiety disorder

10. exp obsessive-compulsive disorder

11. exp panic

12. anxi*.tw

13. generali#ed anxiety disorder.tw

14. obsessive compulsive.tw

15. OCD.tw

16. Phobia*.tw

17. Social anxiety.tw

18. Separation anxiety.tw
19. Panic.tw
20. exp Chronic Fatigue Syndrome/
21. exp Anxiety Disorders/ or exp Social Phobia/ or exp Panic Disorder/ or exp Anxiety/ or exp Social Anxiety
22. exp Separation Anxiety Disorder/ or Separation Anxiety/
23. exp Generalized Anxiety Disorder
24. exp Obsessive Compulsive Disorder
25. exp Phobias/
26. 4 or 5 or 6 or 7 or 20
27. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 21 or 22 or 23 or 24 or 25
28. 3 and 26 and 27
29. Limit 28 to yr="2016-current"

Search strategy for Depression searches:

1. (adolesc* or preadolesc* or pre-adolesc* or boy* or girl* or child* or infan* or preschool* or pre-school* or juvenil* or minor* or pe?diatri* or pubescen* or pre-pubescen* or prepubescen* or puberty or teen* or young* or youth* or school* or high-school* or highschool* or sibling* or schoolchild* or school child* or children).tw.
2. exp Adolescent/ or exp Child/ or exp Child, Preschool/ or exp Infant/ or exp Minors/ or exp Pediatrics/
3. 1 or 2
4. chronic fatigue syndrome*.mp.
5. exp Chronic Fatigue Syndrome
6. Chronic Fatigue Syndrome.tw
7. myalgic encephal*.mp.
8. myalgic encephal*.tw.
9. 4 or 5 or 6 or 7 or 8
10. depressive disorder.mp.
11. exp depression/
12. depress*.tw
13. dysthym*.tw
14. exp adjustment disorders/
15. adjustment disorder*.mp.
16. low mood.tw.
17. 10 or 11 or 12 or 14 or 14 or 15 or 16
18. 3 and 9 and 17
19. Limit 18 to yr = “2015 – current
Appendix 2: Quality Assessment

Supplementary Table 1: Quality Assessment of all studies included in this updated review, using Cochrane Risk of Bias scales ROBINS-I and RoB-2

### (a) Observational Studies

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Did the study address a clearly focused issue?</th>
<th>Was the cohort recruited in an acceptable way?</th>
<th>Was the exposure accurately measured to minimise bias?</th>
<th>Was the outcome accurately measured to minimise bias?</th>
<th>Confounding factors?</th>
<th>Follow-up of subjects complete enough and long enough?</th>
<th>Overall Rating using Cochrane risk of bias scale ROBINS-I (low/unclear/high)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chalder et al (2002)</td>
<td>Yes, No.</td>
<td>Yes</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Can’t tell, yes</td>
<td>Can’t tell, yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Diaz-Caneja et al (2007)</td>
<td>Can’t tell, No</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
<td>Can’t tell</td>
<td>Yes</td>
<td>Yes, no</td>
<td>High</td>
</tr>
<tr>
<td>Lloyd et al (2012);</td>
<td>Yes, No</td>
<td>Yes</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Can’t tell, yes</td>
<td>Can’t tell, yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Rimes et al (2014)</td>
<td>Yes, No</td>
<td>Yes</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Can’t tell, yes</td>
<td>Unclear</td>
<td>Unklear</td>
</tr>
<tr>
<td>Van de Putte et al (2007)</td>
<td>Yes, No</td>
<td>Yes</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Can’t tell, yes</td>
<td>Can’t tell, yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Kawatani et al (2011)</td>
<td>Yes, No</td>
<td>Yes (Case control)</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>No, Yes</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Gordon and Lubitz (2009)</td>
<td>Yes, No</td>
<td>Yes (Case series)</td>
<td>No</td>
<td>No</td>
<td>Can’t tell</td>
<td>Yes, No</td>
<td>High*</td>
</tr>
<tr>
<td>Henderson (2014)</td>
<td>Yes, No</td>
<td>No (Case series)</td>
<td>No</td>
<td>No</td>
<td>Can’t tell</td>
<td>No, Yes</td>
<td>High*</td>
</tr>
<tr>
<td>Denborough et al (2003)</td>
<td>Yes, No</td>
<td>Yes (Case series)</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Yes, Yes</td>
<td>High*</td>
<td></td>
</tr>
<tr>
<td>Rowe (2019)</td>
<td>No, No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes, Yes</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

### (b) Randomised controlled trials

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Did the trial address a clearly focused issue?</th>
<th>Was the assignment of patients, healthcare</th>
<th>Were the groups</th>
<th>Aside from the experimental</th>
<th>Were all of the patients who</th>
<th>Overall Rating using Cochrane risk of bias scale RoB-2 (low/unclear/high)</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Focused issue?</th>
<th>Patients to treatments randomised?</th>
<th>Professionals and research staff blinded?</th>
<th>Similar at the start of the trial?</th>
<th>Investigation, were the groups treated equally?</th>
<th>Entered the trial properly accounted for at its conclusion?</th>
<th>RoB 2 (low/unclear/high)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nijhof et al (2012); Nijhof et al (2013)</td>
<td>Yes, no</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Can’t tell</td>
<td>Low</td>
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<td>Rowe (1997)</td>
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<td>Wright et al (2005)</td>
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<td>Gordon et al (2010)</td>
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<td>Crawley et al (2018)</td>
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