

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

Philippa Clery ¹, Alexander Royston,¹ Katie Driver,¹ Jasmine Bailey,¹ Esther Crawley,^{1,2} Maria Loades^{1,3}

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¹Centre for Academic Child Health, University of Bristol, Bristol, UK

²Paediatric Chronic Fatigue Syndrome Specialist Service, Royal United Hospitals Bath NHS Foundation Trust, Bath, UK

³Department of Psychology, University of Bath, Bath, UK

Correspondence to

Dr Philippa Clery;
philippa.clery@bristol.ac.uk

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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Strengths and limitations of this study

- This review used a systematic approach to identify updated evidence for treatment approaches for comorbid anxiety and/or depression in paediatric chronic fatigue syndrome/myalgic encephalomyelitis, and combined it with previous review results to provide a comprehensive synthesis of all evidence available since 1991.
- Non-English language articles were included.
- Authors were contacted and subgroup data obtained when available.
- Grey literature and unpublished material was not included.
- There was insufficient data to carry out a meta-analysis.

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.^{8 9} 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.⁹ The impact of anxiety on outcomes is less clear. Given that most children with CFS/ME who have anxiety also have depression,⁵ 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.^{10 11} Although CBT-f and a multicomponent inpatient programme showed promise in reducing depressive¹⁰ and anxiety¹¹ 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

Table 1 Inclusion criteria

	Anxiety review	Depression review
Participants	1. Children <18 years of age 2. Diagnosed with CFS/ME defined using one of these criteria: CDC aka Fukuda <i>et al</i> ⁵⁰ NICE ¹ Oxford aka Sharpe <i>et al</i> ⁵¹	
Interventions	Observational cohort studies Any study with intervention—for example, observational clinical cohorts, clinical trials.	
Baseline measure	Validated assessment of anxiety	Validated assessment of depression
Outcome measure	Either an anxiety and/or fatigue measure on psychometrically validated assessments or validated diagnostic interviews.	Either a depression and/or fatigue measure on psychometrically validated assessments or validated diagnostic interviews.
Language	Non-English language papers were considered for inclusion.	

CDC, Centers for Disease Control and Prevention; CFS/ME, chronic fatigue syndrome/myalgic encephalomyelitis; NICE, National Institute for Health and Care Excellence.

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 PRISMA¹² 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.

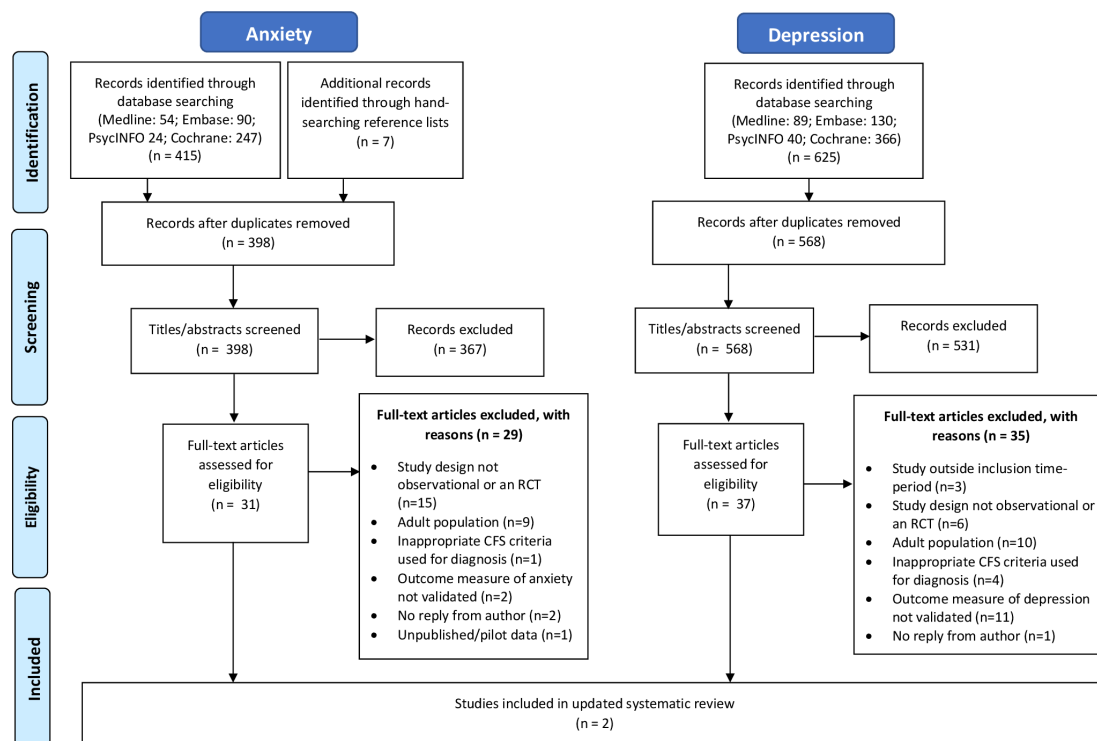


Figure 1 Flow chart for studies included in the systematic review; based on PRISMA guidelines. CFS, chronic fatigue syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trials.

Quality assessment

PC and AR used Risk of Bias (ROB) assessment tools^{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^{10 11} to conduct a narrative synthesis,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.^{16 17} One was a randomised controlled trial (RCT),¹⁷ one was a retrospective observational cohort study.¹⁶ The PRISMA¹² flow chart is in figure 1.

The previous systematic reviews for depression¹⁰ (search conducted in 2015) and anxiety¹¹ (search conducted

in 2016) found 362 and 1274 references, respectively. After full-text screening, the depression search returned nine eligible studies (one RCT,¹⁸ and eight observational studies^{19–26}), and the anxiety search returned nine eligible papers from eight studies (three RCTs,^{27–30} six observational studies^{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)¹³). Of the RCTs, all six had an overall rating of ‘low’ ROB (as defined by the Cochrane ROB-2 scale).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.^{10 11}

In this paper, we report in detail on the quality assessment of the two new studies found in the updated search.

The RCT¹⁷ 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

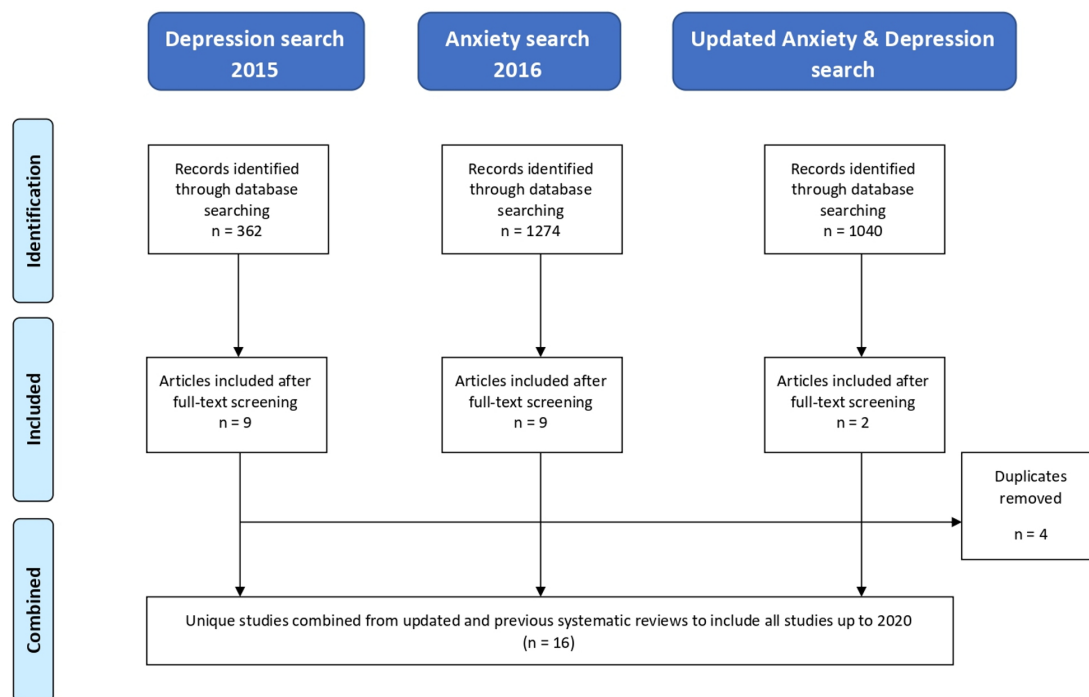


Figure 2 Flow chart of studies combined from updated review and previous reviews.

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,^{18 28} an online CBT programme^{29 30} and intravenous gammaglobulin²⁷; eight observational cohort studies evaluating: CBT,^{19 25 32} CBT with pharmacotherapy,^{24 31} an antiviral treatment²⁶ and an inpatient programme²³; 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),³³ Spence Children’s Anxiety Scale (SCAS),³⁴ the State-Trait Anxiety Inventory for Children,³⁵ the Multidimensional Anxiety Scale for Children,³⁶ Spielberger State Trait Anxiety Questionnaire,³⁷ Beck Depression Inventory,³⁸ Children’s Depression

Table 2 Participant and study characteristics

Author (year), country	Anxiety, depression or both?	Study design	Sample size		Mean age, years		Gender, female %		CFS/ME diagnostic criteria	Primary outcome	Measure of anxiety/depression	Treatment specifically targeted to anxiety or depression?	Outcomes stratified by those with anxiety/depression?	Intervention	Control	Length of follow-up
			Control	Intervention	Control	Intervention	Control	Intervention								
(A) Studies identified in updated review																
Rowe (2019), Australia ⁶	Both	Observational retrospective	N/A	418 (789 recruited but 366 did not have baseline questionnaire)	N/A	14.8	N/A	77%	CDC/ Fukuda et al	Reported recovery [†] and duration of illness	STAI, BDI	No	No	Routine specialist medical care provided in the outpatient clinic. Described as a person-centred goal-oriented holistic programme which targets educational, physical, social and emotional aspects of life.	N/A	Mean: 8 years; range 1-21 years
Crawley (2018), UK ¹⁷	Both	RCT	49	51	14.5	14.7	78%	75%	NICE	SF-36 PFS at 6 months	SCAS, HADS	No	No	Specialist medical care (Based on NICE guideline) - Lightning Process (>4 hour sessions on consecutive days with groups of 2-5 young people. Theory sessions teach the stress response, how the mind and body interact and how thought processes can be either helpful or negative. Practical sessions involve participants identifying a goal (eg, stand up for longer) and are given cognitive strategies.)	Specialist medical care only	3, 6, 12 months
(B) Studies identified in previous reviews																
Henderson (2014), USA ²⁸	Depression	Observational, retrospective, case-series	N/A	15 (14 at follow-up)	N/A	15.46	N/A	73%	CDC/ Fukuda et al	Fatigue self-assessment scores (CFSS, FSS, FSI, MFS)	CDI	No	Yes	Velavolour (antiviral) medication, initially 500 mg Twice daily, increasing after 2-3 weeks. Duration of treatment ranged from 3 to 60 months (mean 27.9 months).	N/A	Varied post-treatment
Rimes (2014), UK ³²	Anxiety	Observational case-control	36 healthy controls	49 (24 at follow-up)	15	14.9	58%	63%	CDC/ Fukuda et al/Oxford/ Sharpe et al	School attendance	SCAS	No	No	CBT via telephone based guided self-help, 6 fortnightly sessions, 30 mins duration	N/A	6 months
Nijhof (2012, 2013, Netherlands) ²⁹⁻³⁰	Anxiety	Both RCTs	67 (63 at follow-up)	68 (64 at follow-up)	15.8	15.9	85%	79%	CDC/ Fukuda et al	School attendance absence of severe fatigue and normal physical functioning	STAI	No	No	Internet delivered CBT consisting of psychoeducation and 21 modules, with parallel child and parent sessions. FITNET therapist individually tailored intervention and initially responded to emails weekly, decreasing to fortnightly. Mean treatment duration 26.2 weeks (SD 7.3).	Treatment as usual including CBT (66%) rehabilitation treatment (22%) physical treatment (mostly graded exercise therapy; (49%) or alternative treatment (24%)	2.5 years
Lloyd (2012), UK ³⁵	Both	Observational	N/A	63 (62 at follow-up)	N/A	Median 15	N/A	63%	Oxford/ Sharpe et al	Fatigue (Chalder Fatigue Questionnaire Total) and school attendance	SCAS, Bireson Depression Scale	No	No	CBT via telephone based guided self-help, 6 fortnightly sessions, 30 mins duration	N/A	6 months
Kawatani (2011), Japan ³⁴	Depression	Observational	N/A	19	N/A	13.6	N/A	63%	Jason et al ³²	Chalder's Fatigue Scale	Zung self-rating depression scale	No	No	CBT (average of 5 sessions over 6 months) and pharmacotherapy (antidepressants, anxiolytics, hypnotic agents)	N/A	6 months

Continued

Inventory,³⁹ the Birlerson Depression Scale⁴⁰ and Zung's Self-rating depression scale.⁴¹ One study used a diagnostic interview, the Development and Well-Being Assessment.⁴² Six studies (including the two identified in the updated review) measured both anxiety and depression; five measured depression only; and five anxiety only (table 2).

Treatment approaches and their efficacy treating anxiety and/or depression in paediatric CFS/ME

Of the 16 studies: one study evaluated routine specialist outpatient care¹⁶; one evaluated the Lightning Process outpatient intervention¹⁷; one evaluated the 'STAIRway to health' outpatient intervention²⁸; six evaluated various outpatient CBT programmes^{19 24 25 29–32}; two evaluated outpatient pharmacological interventions (antivirals²⁶ and gammaglobulins²⁷); three evaluated inpatient programmes focused on graded exercise therapy^{18 20 23}; and two were epidemiological observational studies so were uninformative about interventions.^{21 22}

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*¹⁷ compared adding the Lightning Process intervention (<https://lightningprocess.com>) to specialist care (recommended by National Institute for Health and Care Excellence (NICE)¹), 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.⁴³ 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 Lightning Process intervention (in addition to specialist medical care) arm than those allocated to the specialist medical care-only control. The Lightning 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.¹⁶ 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,^{10 11} 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 antihypertensives). Three observational studies showed that face-to-face and telephone CBT resulted in improved depression, anxiety, functioning and social adjustment.^{19 25 32} 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.³⁰ 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,²⁴ or reported on only a single case-study.³¹ In terms of behavioural approaches,

Table 3 Summary of outcomes for symptoms of depression and anxiety and other relevant findings for included studies

Study	Measure of depression and anxiety	Pre treatment: depression, mean (SD)		Pre treatment: anxiety, mean (SD)		Post treatment: depression, mean (SD)		Post treatment: anxiety, mean (SD)		Statistical analysis of change in depression/anxiety symptomatology		Summary of other relevant findings
		Intervention /case	Control	Intervention /case	Control	Intervention /case	Control	Intervention /case	Control	Depression	Anxiety	
(A) Studies identified in updated review												
Rowe (2019) ¹⁶	BDI* (depression scale), STAI* (anxiety scale)	13.8 (8.9)	N/A	88.9 (24.9)	N/A	N/A	N/A	N/A	N/A	No statistical change because post-treatment scores were not measured. Instead, mean baseline depression and anxiety scores were compared between those who reported recovery† and those who did not, using the Student's t-test.	Overall, 46.5% reported recovery; participants who were followed for >10 years, 68% reported recovery. Mean duration of illness was 5 years	
Crawley et al (2018) ¹⁷	HADS* (depression and anxiety scales), SCAS* (anxiety scale)	7.5 (3.1)	8.1 (4.4)	HADS: 8.8 (4.5) SCAS: 29.8 (16.9)	HADS: 10.4 (4.4) SCAS: 40.3 (20.1)	6 months: 4.2 12 months: 2.8	6 months: 5.9 12 months: 4.6	HADS 6 months: 6.1 12 months: 5.3 SCAS 6 months: 24.7 12 months: 19.6	HADS 6 months: 9.7 12 months: 8.3 SCAS 6 months: 37.4 12 months: 36.3	Adjusted difference in mean† (95% CI, p value): HADS at 6 months: -3.5 (-5.6 to -1.5, 0.001) SCAS at 6 months: -1.5 (-3.5 to 0.5, 0.1) 12 months: -10.0 (-18.5 to -1.5, 0.02) -1.8 (-3.4 to 0.04) HADS at 12 months: -2.6 (-4.7 to -0.4, 0.019) SCAS at 12 months: 14.5 (-22.4 to -6.7, <0.001)	At 6 months, participants allocated to LP in addition to SMC (intervention) had better physical function and fatigue at than those allocated to SMC (control). At 12 months, participants allocated to LP in addition to SMC (intervention) had better fatigue and school attendance than those in SMC (control). Adding LP to SMC is cost-effective.	
(B) Studies identified in previous reviews												
Henderson (2014) ²⁸	CDI	14 (2.83) 4 patients with mood disorder: 16.8 (1.92) 11 patients without mood disorder: 12.73 (2.00)	N/A	N/A	N/A	Not reported	N/A	N/A	N/A	Not reported	N/A	All patients reported at least 80% self-rated improvement. Significant reduction in FSS, MSFI (all subscales).
Rimes et al (2014) ³²	SCAS	N/A	N/A	Cases: 22 (17) Median 16.0 (IQR 9.0–34.0)	Controls: Median 16.5 (IQR 8.0–22.8)	N/A	N/A	Not reported	N/A	N/A	T value (21)=2.1. p=0.005	Adolescents with OFS had reduced cortisol excretion throughout the day compared with healthy controls. There was significant improvement in school attendance after treatment from 24% to 49%. There was reduction in fatigue after treatment, however the results were not significant.

Continued

Table 3 Continued

Study	Measure of depression and anxiety	Pre treatment: depression, mean (SD)		Pre treatment: anxiety, mean (SD)		Post treatment: depression, mean (SD)		Post treatment: anxiety, mean (SD)		Statistical analysis of change in depression/anxiety symptomatology		Summary of other relevant findings
		Intervention /case	Control	Intervention /case	Control	Intervention /case	Control	Intervention /case	Control	Depression	Anxiety	
Nijhof <i>et al</i> (2012, 2013) ^{29,30}	STAIC	N/A	N/A	32.7 (8.8)	32.3 (8.0)	N/A	N/A	Not reported	N/A	N/A	Not reported	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<0.0001), absence of severe fatigue (67 (85%) vs 17 (27%), 3.2, 2.1–4.9; p<0.0001), and normal physical functioning (52 (78%) vs 13 (20%), 3.8, 2.3–6.3; p<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
Lloyd <i>et al</i> (2012) ²⁵	Birleson Depression Scale; SCAS	Baseline mean 13.38 (4.76) Pre-treatment mean 12.91 (5.57)	N/A	Baseline mean 22.84 (17.18) Baseline median 16.0 (IQR 10.8–35.0)	N/A	Post-treatment: 10.98 (5.35) 3 months: 10.47 (5.87) 6 months: 9.22 (5.36)	N/A	6 months: 17.25 (3.06)	N/A	Multi-level modelling and Wald tests Treatment effect estimate at 6 months: 0.49, CI -5.17 to -2.21, significance (two-tailed) 0.003, effect size 0.16	Multi-level modelling and Wald tests Treatment effect estimate at 6 months: 0.49, significance (two-tailed) 0.003, effect size 0.16	Significant improvement in fatigue and school attendance, with reductions in depression and impairment and increased adjustment at 6 months
Kawatani <i>et al</i> (2011) ²⁴	Zung Self-Rating Depression Scale	53.3 (6.7)	N/A	N/A	N/A	Not reported	N/A	N/A	N/A	Not reported	N/A	No significant change between baseline fatigue scores and fatigue scores 6 months follow-up. Significant improvement in performance status scores (self-reported impact on functioning).
Gordon <i>et al</i> (2010) ¹⁸	BDI	Resistance arm: 20.9 (11.3)	Aerobic arm: 16.4 (4.3)	N/A	N/A	Resistance arm: 14.2 (10.0)	Aerobic arm: 12.2 (6.7)	N/A	N/A	Resistance arm Difference -6.7±8.5 p=0.03 Aerobic arm Difference -4.2±4.8 p=0.002	N/A	There was no control group. Significant improvement in BDI scores in both arms.
Gordon and Lubitz (2009) ²³	BDI	19.88 (8.62)	N/A	N/A	N/A	11.44 (10.98)	N/A	N/A	N/A	Paired t-test p value 0.001, sig 0.008	N/A	Significant improvement in Fatigue Severity scores.

Continued



Table 3 Continued

Study	Measure of depression and anxiety	Pre treatment: depression, mean (SD)		Pre treatment: anxiety, mean (SD)		Post treatment: depression, mean (SD)		Post treatment: anxiety, mean (SD)		Statistical analysis of change in depression/anxiety symptomatology		Summary of other relevant findings
		Intervention /case	Control	Intervention /case	Control	Intervention /case	Control	Intervention /case	Control	Depression	Anxiety	
Diaz-Caneja <i>et al</i> (2007) ³¹	MASC	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Not reported	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.
Rimes <i>et al</i> (2007) ³¹	DAWBA	Only states '3 of 4 had at least one psychiatric diagnosis at baseline'	N/A	Only states '3 of 4 had at least one psychiatric diagnosis at baseline'	N/A	N/A	N/A	N/A	N/A	Not reported	Not reported	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.
Van de Putte <i>et al</i> (2007) ²²	CDI at baseline only; HADS (anxiety)	11.7 (6.1)	N/A	36.9 (7.8)	N/A	Not stated	N/A	Not stated	N/A	Not reported	Not reported	47% of adolescents 'fully recovered' (below score that is mean plus 2 SD of subjective fatigue distribution in health adolescents).
Wright <i>et al</i> (2005) ²³	HADS (anxiety)	N/A	N/A	10.17 (3.71)	6.80 (3.56)	N/A	6.00 (3.63)	Post-treatment: 6.60 (4.73)	N/A	N/A	Analysis of covariance for anxiety, controlling for baseline score. Difference -1.60 (-8.31-5.10) F 0.3 (df 1,8) p=0.6	Activity (child and clinician rated) and school attendance improved markedly in the intervention (STAIRWay) 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 STAIRWay arm than the Pacing arm.
Denborough <i>et al</i> (2003) ³⁰	BDI	21	N/A	N/A	N/A	15	N/A	N/A	N/A	Improvement p<0.001 Maintained at 6 month follow-up (p<0.038)	N/A	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.

Continued

Table 3 Continued

Study	Measure of depression and anxiety	Pre treatment: depression, mean (SD)		Pre treatment: anxiety, mean (SD)		Post treatment: depression, mean (SD)		Post treatment: anxiety, mean (SD)		Statistical analysis of change in depression/anxiety symptomatology		Summary of other relevant findings
		Intervention /case	Control	Intervention /case	Control	Intervention /case	Control	Intervention /case	Control	Depression	Anxiety	
Chalder <i>et al</i> (2002) ¹⁹	HADS	8.4 (IQR 5.7–11)	N/A	HADS anxiety: median 7, (IQR 6.7–9.7)	N/A	6 months: 3 (IQR 3–5)	N/A	6 months: HADS anxiety: 0.5 (IQ range 0.5–9)	N/A	Wilcoxon signed ranks test –3.33 (2 tailed significance 0.00)	Wilcoxon signed ranks test (significance two tailed) HADS anxiety: 2.02 (0.04)	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.
Rowe (1997) ²⁷	SSTAQ	N/A	N/A	Reported as one group: Mean 46.2 (24.4) SE 3.9 Range 0–98	N/A	N/A	N/A	6 months: Mean 28.1 (25.0) SE 5.9 Range 0–77	N/A	N/A	T value (df) 2.63 (56) Sig p value 0.01	Significant mean functional improvement in both groups.

¹⁹Higher score=more symptoms, poorer function.

²⁷Adjusted for age, gender, baseline outcomes, SCAS and Visual Analogue Scale.

²⁸Reported 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; MFSI, Multidimensional Fatigue Symptom Inventory-Short Form; N/A, not available; SCAS, Spence Children's Anxiety Scale; SMC, Specialist Medical Care; SSTAQ, Spielberger State-Trait Anxiety Questionnaire; STA(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.²⁸ Pharmacological studies showed insufficient evidence for improving anxiety or depressive symptoms with intravenous gammaglobulin infusions or vancyclovir respectively.^{26 27}

Inpatient programmes

As per our previous review,¹⁰ three studies^{18 20 23} 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 study²⁰. However, they did not measure anxiety symptoms; internalising problems at 6 months returned to preadmission levels; two studies did not have follow-up data^{18 23}; 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 Lightning 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,⁴⁴ SCAS⁴⁵ and STAI³⁵ 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.⁵

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.^{10 11} The ‘Lightning 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 Lightning Process and CBT are also unclear.⁴⁶ It should also be noted that the draft NICE guideline (expected publication date August 2021: <https://www.nice.org.uk/guidance/gid-ng10091/documents/draft-guideline>) does not recommend the Lightning 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%^{5 6} of children that experience them. Three studies^{47–49} were excluded from our review for these reasons. For example, studies evaluating acceptance and commitment therapy⁴⁷ and mindfulness-based therapies⁴⁸ 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, and the studies only measured general well-being 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 intervention 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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ORCID iD

Philippa Clery <http://orcid.org/0000-0002-6770-4454>

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