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What treatments work for anxiety and depression in children and adolescents with Chronic Fatigue Syndrome? An updated systematic review

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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 to 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 PsychINFO databases from 2015 to 2020.

Participants

Inclusion criteria: 1) < 18 years old; 2) diagnosed with CFS/ME (using Centre for Disease Control and Prevention, National Institute for Health and Care Excellence, or Oxford criteria); 3) validated measures of depression and/or anxiety.

Interventions

Observational studies or randomised controlled trials (RCT).

Comparison

Any or none.

Outcomes

Studies with outcome measures of anxiety, depression, or fatigue on validated assessments.

Results

Of 1040 papers identified, seven were paediatric CFS/ME intervention studies, of which two measured depression and/or anxiety outcomes. One study was an RCT, suggesting the Lightening

Process intervention in addition to specialist medical care (SMC) was more effective at reducing depressive and anxiety symptoms compared to SMC alone. The other was a retrospective observational cohort study evaluating routine specialist care. It measured anxiety and depression at baseline but not at follow-up. Neither study specifically targeted depression nor anxiety.

Conclusion

Very few paediatric CFS/ME intervention studies have been conducted in the last five years. Even fewer measured depression and/or anxiety outcomes (one of which was conducted by our own research team). There is continued lack of evidence identifying effective treatments for comorbid depression and/or anxiety in paediatric CFS/ME. We still do not know what treatment should be offered for these children.

Trial registration number

This review was an update of two previous reviews registered on the Prospective Register of Systematic Review Protocols (PROSPERO):

http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016043488; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016813.

Key words

Paediatric, CFS/ME, chronic fatigue syndrome, anxiety, depression

ARTICLE SUMMARY

Strengths and limitations of study

- This updated review used a systematic approach to identify evidence for treatment approaches for comorbid anxiety and/or depression in paediatric CFS/ME.
- Non-English language articles were included.

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- Authors were contacted and sub-group 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 0.22-1.35) 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 to 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 depressive[10] and anxiety[11] symptoms, there was no consistent treatment approach for children with CFS/ME and comorbid depression or anxiety. Since conducting these reviews in 2015/16, 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 previous reviews considered them separately.

We conducted an updated systematic review by synthesizing the evidence regarding treatments for paediatric CFS/ME and comorbid depression and anxiety since 2015. 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, PsychINFO and Cochrane Library databases. We used the same search strategies from the previous systematic reviews (registered on Prospero: CRD42015016813; CRD42016043488) to repeat the depression and anxiety searches separately.

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Searches were designed with input from an information specialist to include the concepts: paediatric; CFS/ME; anxiety and depression (search strategies are in supplementary material). We updated the searches from when they had last been run (February 2015 for depression search and July 2016 for anxiety search) up until September 2020. The two searches were carried out by different reviewer teams: anxiety search (PC, AR); depression search (KD, 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).

Table 1: Inclusion criteria

	Anxiety Review	Depression Review			
Participants	2. Diagnosed with CFS/ME de	<18 years of age efined using one of these criteria: CDC[12] NICE[1] Oxford[13]			
Interventions	Any study with intervention – e	al cohort studies e.g., observational clinical cohorts, trials, etc.			
Baseline measure	Validated assessment of anxiety	Validated assessment of depression			
Outcome measure	Repeated measures of either anxiety and/or fatigue on psychometrically validated assessments or validated diagnostic interviews.	Repeated measures of either depression and/or fatigue on psychometrically validated assessments or validated diagnostic interviews.			
Language	Non-English language papers	anguage papers were considered for inclusion.			

Study selection

Articles returned from database searches were inputted into Endnote and duplicates removed. Each reviewer 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[12] flowchart.

Data extraction

For all included articles, data were extracted independently by two reviewers (PC, 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.

Quality assessment

PC and AR used Risk of Bias assessment tools[13, 14] to assess methodological quality of the included studies.

Data synthesis

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We conducted a narrative synthesis[15] because there was insufficient comparable data to conduct a meta-analysis as interventions were heterogeneous and a range of outcome measures were reported. For each study, we compared the effects of interventions on outcomes, using mean differences. Different measures of anxiety and depression were used in each study, and one study did not have follow-up data, which limited direct comparison.

Patient and public involvement

No patients were involved.

Ethics approval

This study did not involve human participants.

RESULTS

Studies included

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]. Study 1 was an RCT and study 2 was a retrospective observational cohort study. The PRISMA[12] flowchart is in Figure 1.

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[Figure 1 here]

Quality assessment

The RCT (study 1)[17] was conducted by members of our CFS/ME research team (EC). The study has a low risk of bias 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 study (study 2)[16] 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 one to seven). For the sample of 366 without baseline data for anxiety and depression, 76% returned a follow-up questionnaire on one occasion, whilst 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

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Study 1[17] evaluated the effectiveness of the Lightning Process (LP) intervention alongside 'specialist medical care' (SMC) compared with SMC only. Participants were 100 children (mean age of 14) from a UK specialist centre. Study 2[16] sent questionnaires to over 700 patients who had visited the authors' CFS/ME clinic in Australia in the last 20 years, to assess the outcomes of 'routine specialist care'. Table 2 shows participant characteristics.

Both studies measured anxiety and depression, but neither were primary outcomes. Table 2 summarises study characteristics. Study 1 used the Hospital Anxiety and Depression Scale (HADS)[18] and Spence Children's Anxiety Scale (SCAS)[19] to measure anxiety and depression as secondary outcomes. Study 2 measured anxiety and depression at baseline using the State-Trait Anxiety Inventory (STAI)[20] and Beck Depression Inventory (BDI)[21] scales, respectively but there was no repeated measure of anxiety or depression at follow-up points during or after the intervention. Rather, it investigated whether depression and anxiety scores at baseline differed between participants that reported their main outcome of recovery.

In both studies, there were participants who met the criteria for a clinical diagnosis of depression (HADS score > 8[22] or BDI > 20[21]) and anxiety (STAI score > 39[23], HADS score >8) at baseline.

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Table 2: Pa	rticipant and stu	dy characteris	stics						BMJ Open: fi								
Author, year, country	Study design	Setting	Sam Control	ple size Intervention	Mean ag Control	ge, years (SD) Intervention	Gender Control	· (Female %) Intervention	rst put S/ME diagnostic diatiteria 10	Primary Outcome	Secondary Outcomes	Measure of anxiety/ depression	Treatment specifically targeted to anxiety or depression?	Were the outcomes stratified by those with anxiety/ depression?	Intervention	Control	Length of follow up
Crawley et al, 2018, UK	RCT	Outpatient, secondary care	49	51	14.5 (1.6)	14.7 (1.4)	78	75	년 1136/bmjopen-2021-051358	SF-36 PFS at 6 months	SF-36 PFS at 3 and 12 months; Chalder Fatigue Scale; pain (VAS); anxiety (SCAS and HADS); depression (HADS); school attendance (%); QALY; cost- effectiveness	SCAS, HADS	No	No	Specialist medical care + Lightning Process®	Specialist medical care only	3, 6, 12 months
Rowe et al, 2019, Australia	Observational retrospective	Outpatient, secondary care	did not h	cruited but 366 ave baseline ionnaire)	N/A	14.8	N/A	77	org 1 January 2022. Downloaded from http://bmjopen.bm	Reported recovery‡ and duration of illness	Bell CFIDS disability scale; global rating*; educational outcomes (proportion of work/school attended, use of educational support, visiting teacher service, educational level achieved); illnesses experiences and exacerbations of CFS/ME; and qualitative feedback†	STAI, BDI	No	No	Routine specialist medical care provided in the outpatient clinic	Nil	Mean: 8 years; Range 1- 21 years

Note: SCAS, Spence Children's Anxiety Scale; HADS, Hospital Anxiety and Depression Scale; STAJ, State-Trait Anxiety Inventory; SF-36 PFS, Short-form-3[®] physical function subscale [27]; VAS, visual analogue scale; QALY, quality-adjusted life-years derived from EQ-SD-Y; Global rating was measured on multiple scales of functioning [ind: school/work, stamina, recovery, social and symptomatology] from 1-10, with 10 being "back to normal"; † qualitative freedback included: what was useful/helpful in treatment, their perceived effectiveness, and whether anything could have been handled better; ‡reported precovery was based on the question "Do you feel you are no longer suffering from CFS?" (yes/no). Note: SCAS, Spence Children's Anxiety Scale; HADS, Hospital Anxiety and Depression Scale; STAI, State-Trait Anxiety Inventory; SF-36 PFS, Short-form-3 physical function subscale [27]; VAS, visual analogue scale; QALY, quality-adjusted life-years derived from EQ-5D-Y; Global rating was measured on

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Treatment approaches

The LP intervention (https://lightningprocess.com) evaluated in study 1 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[24]. The intervention in study 2 was routine specialist care delivered at the authors' CFS/ME clinic. Details of the interventions are in Table 3. Neither study .alıy KC' and 'rc C.1. The differences offered an intervention that was specifically designed to target anxiety or depression in CFS/ME. Whilst CBT was an element of the 'SMC' and 'routine specialist care' in both studies, we do not know how many children received CBT-f. The differences and similarities between LP and CBT-f are also unclear [25].

able 3: Descriptions of treatments in the studies Crawley et al 2	018	bmjopen-2021-051358 on 31 Ja Rowe et al 2019
Lightning Process [®]	Specialist Medical Care	Routine specialist care
 Three 4-hour sessions on consecutive days run with groups of two to five young people. Each had a theory session with taught elements on the stress response, how the mind and body interact and how though processes can be either helpful or negative. Sessions were followed by group discussions where the language used was discussed, and in some cases, challenged, and where participants were encouraged to think about what they could take responsibility for and change. In the practical session, participants identified a goal they wished to achieve (such as being able to stand up for a longer period of time) and were given different cognitive strategies before and while the goal was attempted. Participants were also asked to identify a goal to attempt at home. After the course of sessions, young people were offered at least two follow-up phone calls with a Lighting Process practitioner. 	 Based on NICE guidance [1]. Focused on improving sleep and using activity management to establish a baseline level of activity (school, exercise and social) which is then gradually increased. Sessions delivered by a range of professionals including doctors, psychologists, physiotherapists and occupational therapists in family-based rehabilitation consultations. The number and timing of sessions were agreed with the family depending on each adolescents' needs and goals. Those with significant anxiety or low mood were offered additional CBT. 	 A person-centred goal-oriented holistic program which targets educational, physical social and emotional aspects of life. It included: An initial appointment where the young person identifi and rates symptoms they would like help with, outlines their aspirations and is given explanations of illness and management plans available. Development of a management plan in collaboration w parent, chilg and clinician which aims to minimise impa of chronic itness while accommodating for specifics of CFS. A focus on mysical social and emotional aspects includ proactive social contact, academic input, physical activi and a communent to something enjoyable outside the home on a egular basis. An explanation that the consequence of illness can be more damaging than the illness itself and tools on how navigate the Symptom management e.g. sleep, migraine, dizziness, nausea, orthostatic intolerance, concentration difficulti 6-week review appointment to review management pla and change fracessary.

Treatment efficacy

Study 1 showed the LP resulted in a reduction in depression symptoms across *both* the intervention (LP+SMC) and control (SMC) groups, but there was a greater difference reduction in symptoms (based on adjusted mean differences) among participants allocated to the LP+SMC intervention than those allocated to the SMC control. This difference was only statistically significant at the later follow-up time-point of 12 months, not earlier at 6 months. The study showed LP was more effective at reducing anxiety symptoms compared with depression (at both 6 and 12 months follow-up). However, the reduction in anxiety symptoms differed depending on whether they were measured using the HADS or SCAS: at 6 months follow-up, there was a reduction in anxiety symptomatology as measured by both HADS and SCAS, but at the full 12 months follow-up, the improvements in the HADS anxiety score were smaller than when measured by SCAS. But, at both time-points participant numbers were small (43/51 participants at 12 months; 46/51 at 6 months). Outcomes in this study were not stratified by those with depression or anxiety, so we cannot comment on other CFS/ME outcomes in context of comorbid depression or anxiety.

Study 2 measured depressive and anxiety symptomatology at baseline but not post-treatment, so we cannot comment on the effectiveness of their intervention at reducing depression or anxiety. Instead, they 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 i.e. depression nor anxiety were found to be associated with recovery.

Both studies reported improvements in other CFS/ME outcomes following intervention, including physical function, fatigue, and self-reported "recovery". Table 4 shows the summary of outcomes of depression and anxiety and other relevant findings for each included study.

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Table 4: Summary of outcomes for symptoms of depression and anxiety and other relevant findings for included studies

Author, Year, Country	Measure of Depression and Anxiety	Pre treati depression, n		Pre treatment: anxiety, mean (SD)		Post treatmen me	-	By Post treatmer	it: anxiety, mean	Statistical analysis of change in depression, symptomatology		
		Intervention	Control	Intervention	Control	Intervention	Control	रतु मृतtervention	Control	Depression	Anxiety	
Crawley et al. 2018. UK	HADS* (depression and anxiety scales),	7.5 (3.1)	8.1 (4.4)	HADS: 8.8 (4.5) SCAS:	HADS: 10.4 (4.4) SCAS:	6 months: 4.2 12 months:	6 months: 5.9 12 months:	Bennorths: 6.1 Bennorths: 5.3	HADS 6 months: 9.7 12 months: 8.3	Adjusted difference in means† (95%CI, pvalue):	Adjusted differer means† (95%CI, p	
	SCAS* (anxiety scale)			29.8 (16.9)	40.3 (20.1)	2.8	4.6	10 11 12 12 12 12 12 12 12 12 13 13 15 15 15 15 15 15 15 15 15 15	SCAS 6 months: 37.4 12 months: 36.3	6 months: -1.5 (-3.5 to 0.5, p=0.1)	HADS at 6 mon -3.5 (-5.6 to -1.5, p SCAS at 6 mont	
								ven-2021-05		12 months: -1.8 (-3.4 to -0.1, p=0.04)	-10.0 (-18.5 to -1.5, HADS at 12 mor -2.6 (-4.7 to -0.4, p=	
						or D		-2021-051358 on 3			SCAS at 12 mon 14.5 (-22.4 to -6.	
Rowe et al. 2019. Australia	BDI* (depression scale),	13.8 (8.9)	N/A	88.9 (24.9)	N/A	N/A	N/A	N/A 31 January 2022. Do	N/A	were not measur depression and an	because post-treatmer ed. Instead, mean base xiety scores were comp reported recovery‡ and	
	STAI* (anxiety scale)							022. Dow			sing the student's t-tes	
HADS, Hospital Medical Care	Anxiety and Depre	ssion Scale (score	>8 indicates a	diagnosis of depre	ssion); SCAS, S	pence Children's A	nxiety Scale ; BDI, E	ed for http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright.	ventory (score >20 india	cates moderate depression);	STAI, State Trait Anxiety	

pression/anxiety

Summary of other relevant findings

d difference in 95%CI, pvalue):

at 6 months: o -1.5, p=0.001)

at 6 months: 5 to -1.5, p=0.02)

t 12 months: o -0.4, p=0.019);

t 12 months: 2.4 to -6.7, p=)

treatment scores ean baseline ere compared very‡ and those nt's t-test. 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 costeffective.

Overall, 46.5% reported recovery; participants who were followed for >10 years, 68% reported recovery

Mean duration of illness was 5 years

om CFS?" (yes/no).

t Anxiety index; LP, Lightning Process; SMC, Specialist

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. Neither study specifically targeted comorbid anxiety and/or depression. Study 1 showed adding LP to SMC was more effective than SMC alone at reducing both depressive and, to a greater extent, anxiety symptoms. Study 2 did not measure depression or anxiety at follow-up. Study 1 had a small sample size and both studies suffered from bias.

Strengths of this review include the systematic approach, the use of four reviewers, contacting authors for sub-group 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. Whilst HADS[26], SCAS[27], and STAI[20] 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].

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To date, the intervention with the most evidence for improvement in anxiety and depressive symptoms in CFS/ME, when compared to other interventions, such as behavioural-only or pharmacological, is CBT-f[10, 11]. The mechanisms for why CBT-f is effective are unclear because no study targeted anxiety and depression. Our study does not further this debate as the only trial that measured anxiety and depression at follow-up (study 1) did not clearly report whether CBT-f was delivered in the control (SMC) arm.

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[28-30] were excluded from our review for these reasons. For example, studies evaluating Acceptance and Commitment Therapy[28] and Mindfulness-based therapies[29] 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 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 upon researchers to undertake paediatric CFS/ME interventions studies and use validated, diagnostic outcome measures of anxiety and depression.

CONCLUSION

This review highlights both the paucity of intervention studies in children with CFS/ME and the lack of forward movement in identifying effective treatments for paediatric CFS/ME and comorbid depression and anxiety over the last five years. 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. The LP in addition to SMC appears to be effective at reducing depressive and anxiety symptoms, but this is only one study and findings have not been replicated, and it is unclear whether changes are sustained long-term. 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, it remains a priority to focus on these outcomes in future research.

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AUTHOR CONTRIBUTIONS

ML and EC 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.

COMPETING INTERESTS STATEMENT

Professor Crawley acts as a non-paid medical advisor for the Sussex and Kent ME society.

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DATA STATEMENT

Not applicable.

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FIGURES AND TABLES LEGENDS

Figure 1: Flow chart for studies included in the systematic review; based on PRISMA guidelines

Table 1: Inclusion criteria

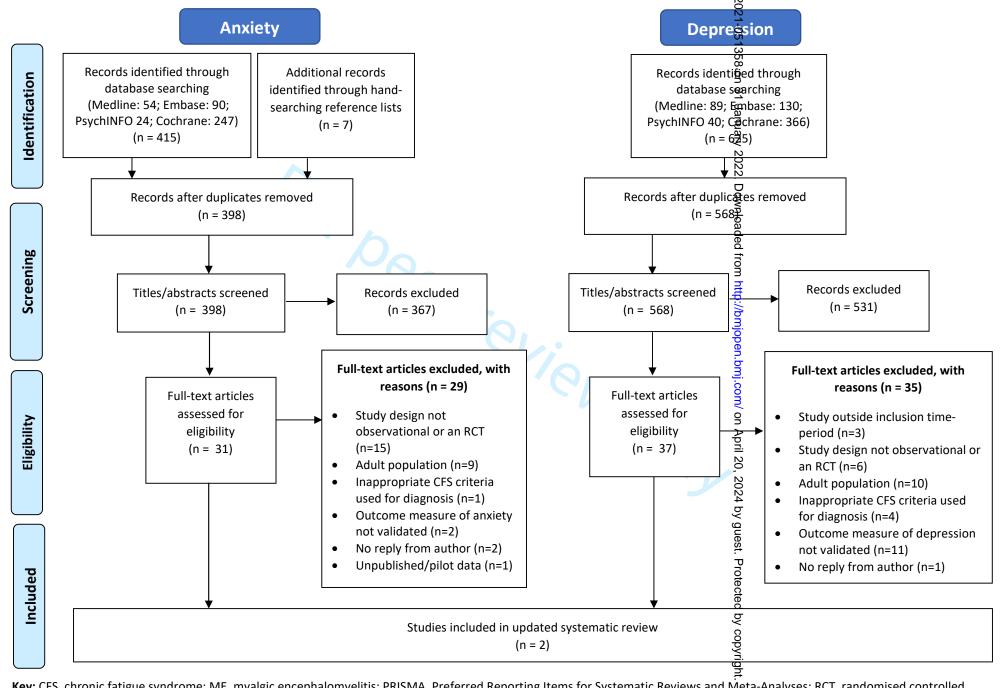
Table 2: Participant and study characteristics

Table 3: Descriptions of treatments in the studies

Table 4: Summary of outcomes for symptoms of depression and anxiety and other relevant findings

for included studies

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Key: CFS, chronic fatigue syndrome; ME, myalgic encephalomyelitis: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trials.

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
- -der 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:

- (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.
- 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

11. exp depression/

12. depress*.tw

13. dysthymi*.tw

16. low mood.tw.

18. 3 and 9 and 17

10. depressive disorder.mp.

14. exp adjustment disorders/

15. adjustment disorder* .mp.

17. 10 or 11 or 12 or 14 or 14 or 15 or 16

19. Limit 18 to yr = "2015 – current"

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PRISMA 2009 Checklist

		BMJ Open 36/bmjope	Page 30 of 3
PRISMA 2	2009	Checklist	
Section/topic	#	Checklist item	Reported on page #
TITLE		3	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT		uary	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
) Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS		p://t	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Table 1 page 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
, Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and apy assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification gof whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
3 4 5		State the principal summary measures (e.g., risk ratio, difference in means).	



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PRISMA 2009 Checklist

Page 31 of 31		BMJ Open 136/bmjope	
PRISMA 20	009	Checklist Checklist	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	N/A
	· ·	Page 1 of 2	
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS		oade	
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICO, follow-up period) and provide the citations.	9-10and Table 2
2 Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summare data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 4
6 Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of gonsistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION	_		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., in complete retrieval of identified research, reporting bias).	17
7 Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of datas; role of funders for the systematic review.	20
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PRISMA 2009 Checklist

	BMJ Open	Page 32 of 3
1	PRISMA 2009 Checklist	136/bmjopen-2021
2 3 4	<i>From:</i> Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The doi:10.1371/journal.pmed1000097 For more information, visit: <u>www.prisma-statement.org</u> . Page 2 of 2	
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What treatments work for anxiety and depression in children and adolescents with Chronic Fatigue Syndrome? An updated systematic review

Journal:	BMJ Open
Manuscript ID	bmjopen-2021-051358.R1
Article Type:	Original research
Date Submitted by the Author:	24-Jul-2021
Complete List of Authors:	Clery, Philippa; University of Bristol, Centre for Academic Child Health Royston, Alexander; University of Bristol, Centre for Academic Child Health Driver, Katie; University of Bristol, Centre for Academic Child Health Bailey, Jasmine; University of Bristol, Centre for Academic Child Health Crawley, Esther; University of Bristol, Centre for Academic Child Health; Royal United Hospitals Bath NHS Foundation Trust, Paediatric Chronic Fatigue Syndrome Specialist Service Loades, Maria; University of Bristol, Centre for Academic Child Health; University of Bath, Department of Psychology
Primary Subject Heading :	Paediatrics
Secondary Subject Heading:	Paediatrics
Keywords:	PAEDIATRICS, Anxiety disorders < PSYCHIATRY, Depression & mood disorders < PSYCHIATRY, MENTAL HEALTH, Child & adolescent psychiatry < PSYCHIATRY

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1	What treatments work for anxiety and depression in children and
2	adolescents with Chronic Fatigue Syndrome? An updated systematic review
3	
4	Philippa Clery ¹ , Alexander Royston ¹ , Katie Driver ¹ , Jasmine Bailey ¹ , Esther Crawley ^{1,2} , Maria Loades ^{1,3}
5	
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1 2		
2 3	1	ABSTRACT
4 5	Ŧ	
6 7	2	Objectives
8 9 10	3	Children with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) experience a higher
11 12	4	prevalence of depression and anxiety compared to age-matched controls. Our previous systematic
13 14 15	5	reviews in 2015/16 found little evidence for effective treatment for children with CFS/ME with
16 17	6	comorbid depression and/or anxiety. This review updates these findings.
18 19 20	7	Design
21 22 23	8	A systematic review. We searched Cochrane library, Medline, Embase and PsychINFO databases
23 24 25	9	from 2015-2020. We combined the updated results with our previous reviews in a narrative
26 27	10	synthesis.
28 29 30 31	11	Participants
32 33	12	Inclusion criteria: <18 years old; diagnosed with CFS/ME (using Centre for Disease Control, National
34 35	13	Institute for Health and Care Excellence, or Oxford criteria); validated measures of depression and/or
36 37 38	14	anxiety.
39 40 41	15	Interventions
42 43	16	Observational studies or randomised controlled trials.
44 45 46	17	Comparison
47 48 49	18	Any or none.
50 51 52	19	Outcomes
53 54 55	20	Studies with outcome measures of anxiety, depression, or fatigue.
56 57 58 59 60	21	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 to 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. Trial registration number Reviews are registered on the Prospective Register of Systematic Review Protocols: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016043488; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016813. Key words Paediatric, CFS/ME, chronic fatigue syndrome, anxiety, depression **ARTICLE SUMMARY** Strengths and limitations of study

2		
3	1	This review used a systematic approach to identify updated evidence for treatment
4 5	-	
6	2	approaches for comorbid anxiety and/or depression in paediatric CFS/ME, and combined it
7 8	3	with previous review results to provide a comprehensive synthesis of all evidence.
9		
10 11	4	 Non-English language articles were included.
12	5	 Authors were contacted and sub-group data obtained when available.
13 14		
15	6	Grey literature and unpublished material was not included.
16 17	7	• There was insufficient data to carry out a meta-analysis.
18		
19 20	8	
21	U	
22 23	9	INTRODUCTION
23 24	9	INTRODUCTION
25 26	10	
20 27	10	Chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) is a common but poorly understood
28 29	11	condition causing disabling fatigue, malaise, myalgia, sleep difficulties, and problems
29 30	40	
31 22	12	concentrating[1]. In children and adolescents (henceforth referred to as children), prevalence is
32 33	13	estimated at 0.55% (95%CI 0.22-1.35) across community, primary care and hospital populations[2].
34		
35 36	14	CFS/ME has long-term impacts on children's physical, cognitive, emotional and social functioning[3,
37	15	4].
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43	17	Children with CFS/ME suffer from higher rates of both depression and anxiety than age-matched
44 45	10	
46	18	population samples. The prevalence estimates of comorbid depression and anxiety are 20%[5] and
47 48	19	29%[6], respectively, compared to 2.1% and 7.2%[7] in adolescents without CFS/ME. In those
40 49		
50	20	attending a specialist CFS/ME service, 61% who meet diagnostic criteria for depression also have an
51 52	21	anxiety disorder[5]. Having comorbid depression and/or anxiety is associated with less favourable
53		
54 55	22	outcomes and may impact on engaging with treatment. Comorbid depression in paediatric CFS/ME
56	23	is associated with greater functional disability, worse fatigue and more pain compared with those
57 58		
59	24	without depression[8, 9]. Low mood, anergia and anhedonia could be barriers to motivation to
60		

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 depressive[10] and anxiety[11] symptoms, there was no consistent treatment approach for children with CFS/ME and comorbid depression or anxiety. Since conducting these reviews in 2015/16, 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 synthesizing 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: What treatment approaches are there for depression and anxiety in children with CFS/ME?

1 2				
2 3 4	1	2. What is known about the	he treatment efficacy of these appro	baches for treating depression and
5 6	2	anxiety in CFS/ME? Do	different approaches have different	outcomes?
7 8 9	3			
9 10				
11 12 13	4	METHODS		
14 15 16	5	Data sources and search strate	egy	
17 18	6	We conducted searches on Me	dline, Embase, PsychINFO and Coch	rane Library databases. We used
19 20 21	7	the same search strategies from	n the previous systematic reviews (r	egistered on Prospero:
21 22 23	8	CRD42015016813; CRD4201604	43488) to repeat the depression and	anxiety searches separately.
24 25	9	Searches were designed with ir	put from an information specialist t	o include the concepts:
26 27	10	paediatric; CFS/ME; anxiety and	d depression (search strategies are i	n supplementary material). We
28 29	11	updated the searches from who	en they had last been run (February	2015 for depression search and
30 31 32	12	July 2016 for anxiety search) up	o until September 2020. The two sea	rches were carried out by
33 34	13	different reviewer teams: anxie	ety search (PC, AR); depression searc	h (KD, JB). Grey literature was not
35 36	14	searched. Reference lists of art	icles for full-text screening were har	nd-searched.
37 38 39	15			
40 41 42 43	16	Inclusion and exclusion Criteria	a	
43 44 45	17	Studies were included if they m	net inclusion criteria (Table 1).	
46 47 48		Table 1: Inclusion criteria		
49 50			Anxiety Review	Depression Review
51 52 53 54 55 56 57		Participants	2. Diagnosed with CFS/ME of CDC a	e <18 years of age defined using one of these criteria: hka Fukuda[12] NICE[1]
58 59 60			Oxford	aka Sharpe[13]

2													
3													
4				al cohort studies									
5		Interventions		, observational clinical cohorts, clinical									
6			tria	als, etc.									
7													
8		Baseline measure	Validated assessment of anxiety	Validated assessment of depression									
9 10													
10													
12			Either an anxiety and/or fatigue	Either a depression and/or fatigue									
13			measure on psychometrically	measure on psychometrically									
14		Outcome measure	validated assessments or	validated assessments or validated									
15			validated diagnostic interviews.	diagnostic interviews.									
16				diagnostic interviews.									
17													
18		Language	Non-English language paper	s were considered for inclusion.									
19 20													
20 21	1												
22													
23	2	Study selection											
24	-												
25													
26	3	Articles returned from databas	e searches were inputted into Endno	te and duplicates removed. Each									
27													
28	4	reviewer conducted title and a	bstract screening independently. Full	texts of potentially eligible									
29													
30	5	articles were screened against	specifically created eligibility checklis	sts. The final articles for inclusion									
31 32													
33	6	were cross-checked between a	Il four reviewers and any conflicts dis	scussed and resolved with input									
34													
35	7	from the senior author (ML) if	necessary. Where information from t	he paper was insufficient to									
36													
37	8	determine eligibility, authors w	vere contacted by email for additiona	l information. If authors did not									
38		C <i>I</i> .											
39	9	reply after two follow-up email	ls, the study was excluded. Figure 1 p	resents the PRISMA[14]									
40		., .											
41	10	flowchart.											
42 43													
43 44													
45	11												
46													
47	12	Data extraction											
48	12	Data extraction											
49													
50	13	For all included articles, data w	ere extracted independently by two	reviewers (PC, AR) using a									
51													
52	14	purpose-designed data extract	ion form to collect information about	t: study design; setting;									
53 54													
54 55	15	recruitment; participant charac	cteristics; CFS/ME definition used for	diagnosis; assessment of									
55 56				<u> </u>									
57	16	depression and anxiety: other	outcomes; treatment and interventio	ons provided: definition of									
58													
59	17	response and treatment/interv	vention outcomes										
60	_,												

1		
2		
3	1	
4 5		
6	2	Quality assessment
7	2	
8		
9	3	PC and AR used Risk of Bias assessment tools[15, 16] to assess methodological quality of the
10		
11 12	4	included studies.
13		
14	5	
15	0	
16		
17 18	6	Data synthesis
19		
20	7	We combined results from the included studies identified in the updated search with findings from
21		
22	8	the two previous systematic reviews[10, 11] to conduct a narrative synthesis[17], providing an
23		
24 25	9	overview of all longitudinal studies that have been evaluated in this clinical cohort since 1991 (when
26		
27	10	CFS/ME was scientifically defined). There was insufficient comparable data to conduct a meta-
28		
29	11	analysis as interventions were heterogeneous and a range of outcome measures were reported. For
30		
31 32	12	each of the new studies, the effects of interventions on outcomes using mean differences were
33		
34	13	compared.
35		
36	14	
37		
38 39	4 -	
40	15	Patient and public involvement
41		
42	16	No patients were involved.
43		
44 45	17	No patients were involved.
45 46	17	
47		
48	18	Ethics approval
49		
50	19	This study did not involve human participants.
51 52	19	
53		
54	20	
55		
56	21	RESULTS
57 58	4 1	
50 59		
60	22	Studies included

1	In the updated search (2015-2020), a total of 625 and 415 references were found by database
2	searching for the depression and anxiety searches, respectively. After full-text screening, both
3	searches returned the same two eligible studies[18, 19]. One was an RCT[19], one was a
4	retrospective observational cohort study[18]. The PRISMA[14] flowchart is in Figure 1.
5	[Figure 1 here]
6	
7	The previous systematic reviews for depression[10] (search conducted in 2015) and anxiety[11]
8	(search conducted in 2016) found 362 and 1274 references, respectively. After full-text screening,
9	the depression search returned nine eligible studies (one RCT[20], and eight observational[21-28]),
10	and the anxiety search returned nine eligible papers from eight studies (three RCTs[29-32], six
11	observational studies[21, 23, 24, 27, 33, 34]). Four of the studies from these two searches were the
12	same.
13	Therefore, in total, 16 eligible studies were included in the narrative synthesis review. Figure 2
14	shows a flowchart combining studies from this updated search with studies identified from previous
15	reviews.
16	[Figure 2 here]
17	
18	Quality assessment
19	For detailed reporting on the quality assessment of studies from the previous searches, please refer
20	to our previous two reviews[10, 11]. In this paper we report on the quality assessment of the two
21	new studies found in the updated search.
22	

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The RCT[19] was conducted by members of our CFS/ME research team (EC). The study has a low risk of bias 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 study[18] 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 one to seven). For the sample of 366 without baseline data for anxiety and depression, 76% returned a follow-up questionnaire on one occasion, whilst 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

1	The two studies identified in the updated search were: an RCT evaluating the 'Lightning Process'
2	intervention alongside 'specialist medical care' compared with 'specialist medical care' alone[19];
3	and an observational cohort study assessing 'routine specialist care' over a 20-year period[18].
4	Studies from the previous reviews included the following. Four RCTs evaluating: inpatient
5	programmes with predominantly behavioural approaches[20, 30], an online CBT programme[31, 32],
6	and intravenous gammaglobulin[29]; eight observational cohort studies evaluating: CBT[21, 27, 34],
7	CBT with pharmacotherapy[26, 33], an anti-viral treatment[28], and an inpatient programme[25];
8	and two prospective observational community studies that did not assess a specified
9	intervention[23, 24]. Follow-up times varied from immediately post-treatment to 21 years. Total
10	number of participants included across all studies was 965. Most sample sizes were small but ranged
11	between one and 418. Participant ages ranged between 11 and 18. Most studies were conducted
12	across Europe (UK, Netherlands, Spain) and Australia. One was in Japan, one in the USA (Table 2).
13	
13	
13 14	None of the studies identified were specifically aimed at treating anxiety or depression in children
	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
14	
14 15	with CFS/ME (all primary outcomes were measures of fatigue or recovery). Anxiety and/or
14 15 16	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
14 15 16 17	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)[35], Spence Children's Anxiety Scale
14 15 16 17 18	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)[35], Spence Children's Anxiety Scale (SCAS)[36], the State-Trait Anxiety Inventory for Children (STAIC)[37], the Multidimensional Anxiety
14 15 16 17 18 19	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)[35], Spence Children's Anxiety Scale (SCAS)[36], the State-Trait Anxiety Inventory for Children (STAIC)[37], the Multidimensional Anxiety Scale for Children (MASC)[38], Spielberger State Trait Anxiety Questionnaire (SSTAQ)[39], Beck
14 15 16 17 18 19 20	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)[35], Spence Children's Anxiety Scale (SCAS)[36], the State-Trait Anxiety Inventory for Children (STAIC)[37], the Multidimensional Anxiety Scale for Children (MASC)[38], Spielberger State Trait Anxiety Questionnaire (SSTAQ)[39], Beck Depression Inventory (BDI)[40], Children's Depression Inventory[41], the Birleson Depression
14 15 16 17 18 19 20 21	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)[35], Spence Children's Anxiety Scale (SCAS)[36], the State-Trait Anxiety Inventory for Children (STAIC)[37], the Multidimensional Anxiety Scale for Children (MASC)[38], Spielberger State Trait Anxiety Questionnaire (SSTAQ)[39], Beck Depression Inventory (BDI)[40], Children's Depression Inventory[41], the Birleson Depression Scale[42], and Zung's Self-rating depression scale[43]. One study used a diagnostic interview, the
14 15 16 17 18 19 20 21 21 22	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)[35], Spence Children's Anxiety Scale (SCAS)[36], the State-Trait Anxiety Inventory for Children (STAIC)[37], the Multidimensional Anxiety Scale for Children (MASC)[38], Spielberger State Trait Anxiety Questionnaire (SSTAQ)[39], Beck Depression Inventory (BDI)[40], Children's Depression Inventory[41], the Birleson Depression Scale[42], and Zung's Self-rating depression scale[43]. One study used a diagnostic interview, the Development and Well-Being Assessment (DAWBA)[44]. Six studies (including the two identified in

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Table 2: Participant and study characteristics

Author (year),	• •	Study design	Setting	Sample size		Mean age, years		Gender, Female %			Primary	Measure of	Treatment specifically	Outcomes stratified by	Intervention	Control	Length of
country	depression or both?			Control	Intervention /case	Control	Intervention /case	Control	Intervent /case	O diagnostic on criteria	Outcome	anxiety/ depression	specifically targeted to anxiety or depression?	those with anxiety/			follow up
a) Studies Iden	tified in Updat	ed Review											•	•			
Rowe et al (2019) [18], Australia	Both	Observational retrospective	Outpatient secondary care	N/A	418 (789 recruited but 366 did not have baseline questionnaire)	N/A	14.8	N/A	-	CDC/Fukuda	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 program which targets educational, physical, social and emotional aspects of life.	N/A	Mean: 8 years; Range 1- years
Crawley et al (2018)[19], UK	Both	RCT	Outpatient secondary care	49	51	14.5	14.7	78%	75%	NICE NICE NICE 0021-051358 on 31 January 2022	SF-36 PFS at 6 months	SCAS, HADS	No	No	Specialist medical care (Based on NICE guidance) + Lightning Process® (3 x 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 (e.g. stand up for longer) and are given cognitive strategies.)	Specialist medical care only	3, 6, 12 months
(b) Studies Ider	tified in Previo	ous Reviews															
Henderson (2014)[28], USA	Depression	Observational , retrospective, case-series	Outpatient secondary care	N/A	15 (14 at follow- up)	N/A	15.46	N/A	73%	CDC/Fukuda	Fatigue self- assessment scores (CFSI, FSS, FSI, MFSI)	CDI	No	Yes	Valacyclovir (antiviral) medication, initially 500mg BID, increasing after 2-3 weeks. Duration of treatment ranged from 3 to 60 months (mean 27.9 months).	N/A	Varied po treatmen
Rimes et al (2014)[34], UK	Anxiety	Observational case-control	Outpatient secondary care	36 healthy controls	49 (24 at follow- up)	15	14.9	58%	63%	CDC/Fukuda , Oxford/ Sharpe	School attendance	SCAS	No	No	CBT via telephone based guided self-help. 6 fortnightly sessions, 30mins duration	N/A	6 months
Nijhof et al (2012[31], 2013[32]), Netherlands	Anxiety	RCT	Outpatient secondary care	67 (63 at follow-up)	68 (64 at follow- up)	15.8	15.9	85%		CDC/Fukuda	School attendance, absence of severe fatigue and normal physical functioning	STAIC	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
										rotected by							

Lloyd et al (2012)[27], UK	Both	Observational	Outpatient secondary care	N/A	63 (52 at follow- up)	N/A	Median 15	N/A	63%	BMJ (Oxford/ Sharpe	Fatigue (Chalder Fatigue Questionnaire Total) and school attendance	SCAS, Birleson Depression Scale	No	No	CBT via telephone based guided self-help. 6 fortnightly sessions, 30mins duration	N/A	6 months
Kawatani et al (2011)[26], Japan	Depression	Observational	Outpatient secondary care	N/A	19	N/A	13.6	N/A	63%) Dpen: first publish	Jason et al [45]	Chalder's Fatigue Scale	Zung self- rating depression scale	No	No	CBT (average of 5 sessions over 6 months) and pharmacotherapy (antidepressants, antihypotensives, hypnotic agents)	N/A	6 months
Gordon, Knapman & Lubitz (2010)[20], Australia	Depression	RCT	Inpatient secondary care	Aerobic group: 11	Resistance group: 11	Aerobic group: 16.2	Resistance group: 15.6	Not report	ted	ed as 10.1136/bmjopen-2021-05135	CDC/Fukuda	Exercise tolerance (time to fatigue)	BDI	No	No	4 week inpatient programme inclu therapy, psychological/psychiatric at school. Patients randomised to either gra- training or progressive resistance for 5 days/week for 4 weeks. The training consisted of 20-40 minute cycling and treadmill exercise. The resistance training involved 16 exe with single set, moderate load and	ded aerobic exercise training programme graded aerobic es of stationary e progressive ercises performed	
Gordon & Lubitz (2009)[25], Australia	Depression	Observational	Inpatient secondary care	N/A	16	N/A	16	Not report	ted	8 on 31 January 2022. Downlo	CDC/Fukuda	Physical and physiological measures e.g. aerobic capacity (VO ₂ peak), time to fatigue, physical component score of SF-36	BDI	No	No	4 week inpatient programme including graded exercise therapy, psychological/psychiatric support, attendance at school, recreation and leisure intervention.	N/A	Post- treatment
iaz Caneja et I (2007)[33], pain	Anxiety	Observational case study	Outpatient secondary care	N/A	1	N/A	15	N/A	100%	paded from http	Oxford/ Sharpe	Self-reported fatigue, pain symptoms	MASC	No	No	CBT + fluoxetine (initially 10mg daily, increased after 1 week to 20 mg)	N/A	3 months
times 2007)[23], JK	Both	Observational prospective	Community	N/A	1 case of CFS at time 1; 4 cases of CFS at time 2	N/A	13	Not report	ted	;;//bmjopen.bmj.com/	CDC/Fukuda	Incidence and prevalence of fatigue, chronic fatigue and CFS	DAWBA	No	No	None specifically stated or evaluated	N/A	4-6 months
/an de Putte et al 2007)[24], Jetherlands	Both	Observational prospective	Community	N/A	40 at baseline, 36 at follow-up	N/A	16	N/A	78%	on April 20, 202	CDC/Fukuda	Fatigue	SSTAQ, CDI	No	No	None specifically stated or evaluated	N/A	18 months
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Wright et al (2005)[30], UK	Anxiety	RCT	Outpatient secondary care	6 (5 at follow-up)	7 (6 at follow- up)	12.9		66%	57%	Oxford/ Sharpe	Global Health on Child Health Questionnaire	HADS	No	Ν
									BMJ Open: first published as					
Denborough et al (2003)[22], Australia	Depression	Observational	Inpatient secondary care	N/A	39 (19 at follow- up)	N/A	16.2	N/A	90% 90%	CDC/Fukuda	Global assessment of functioning, Chronic Fatigue Illness Disability Scale, FSS	BDI	No	Ν
Chalder et al (2002)[21], UK	Both	Observational	Outpatient secondary care	N/A	23	N/A	14.5	N/A	051358 87% 1358 on 3.	Oxford/ Sharpe	The fatigue questionnaire, school attendance	HADS	No	٦
Rowe et al (1997)[29], Australia	Anxiety	RCT	Outpatient secondary care	35	36	15.6	15.3	75%	1 January 2022. Download	CDC/Fukuda	Functional score including school attendance, school work, social activity and physical activity	SSTAQ	No	1
Multidimensional Fatigue Symptom	Anxiety Scale for Inventory-Short	· Children; DAWBA, Form; Global rating	Development an was measured or	d Well-Being Ass n multiple scales	ria, also known as Sha sessment; SSTAQ, Spie of functioning (incl. s re no longer suffering	elberger St chool/wor	ate-Trait Anxiety k, stamina, recove	Questionnaire; SF	kiety Scale; HAD -36 PFS, Short-fogn nptomatology) frer	lospital Anxiety and I n-36 physical functior	Depression Scale; ST n subscale; CFSI, Chr	onic Fatigue S	yndrome Sympto	om Inve
									ip://bmjopen.bmj.com/ on					
									n/ on April 20,					
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STAIRway to Health intervention is a structured rehabilitation programme including conceptualising CFS as having both physical and psychological components, formulating and addressing vicious cycles around activity, sleep, social isolation, physical deconditioning, and developing adaptive coping strategies whilst challenging negative and unhelpful attributions about illness and the future.	Pacing - focuses on limiting activity to the changing needs and responses of the body by avoiding overexertion and managing energy within an overall limit	1 year
4 week inpatient programme, focused on graded exercise using hydrotherapy and physiotherapy.	N/A	6 months
CBT based rehabiliation programme. Up to 15 sessions, 1 hour duration.	N/A	6 months
3 monthly infusions of gammaglobulin	3 monthly infusions of placebo	3 and 6 months

n); BDI, Beck's Depression Inventory; CDI, Children's Depression Inventory; MASC, S, Fatigue Severity Scale; FSI, Fatigue Symptom Inventory; MFSI, Multidimensional l/helpful in treatment, their perceived effectiveness, and whether anything could have

1 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[18]; one evaluated the Lightening Process outpatient intervention[19]; one evaluated the 'STAIRway to health' outpatient intervention[30]; six evaluated various outpatient CBT programmes[21, 26, 27, 31-34]; two evaluated outpatient pharmacological interventions (antivirals[28] and gammaglobulins[29]); three evaluated inpatient programmes focussed on graded exercise therapy[20, 22, 25]; and two were epidemiological observational studies so were uninformative about interventions[23, 24].

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 (e.g. inpatient treatment, consecutive daily four-hour outpatient sessions, and fortnightly 30-minute phone calls), duration of treatment (days to years), and modality (e.g. face-to-face, telephone, and online). The antiviral and gammaglobuin 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 (a) the updated review, and (b) 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.

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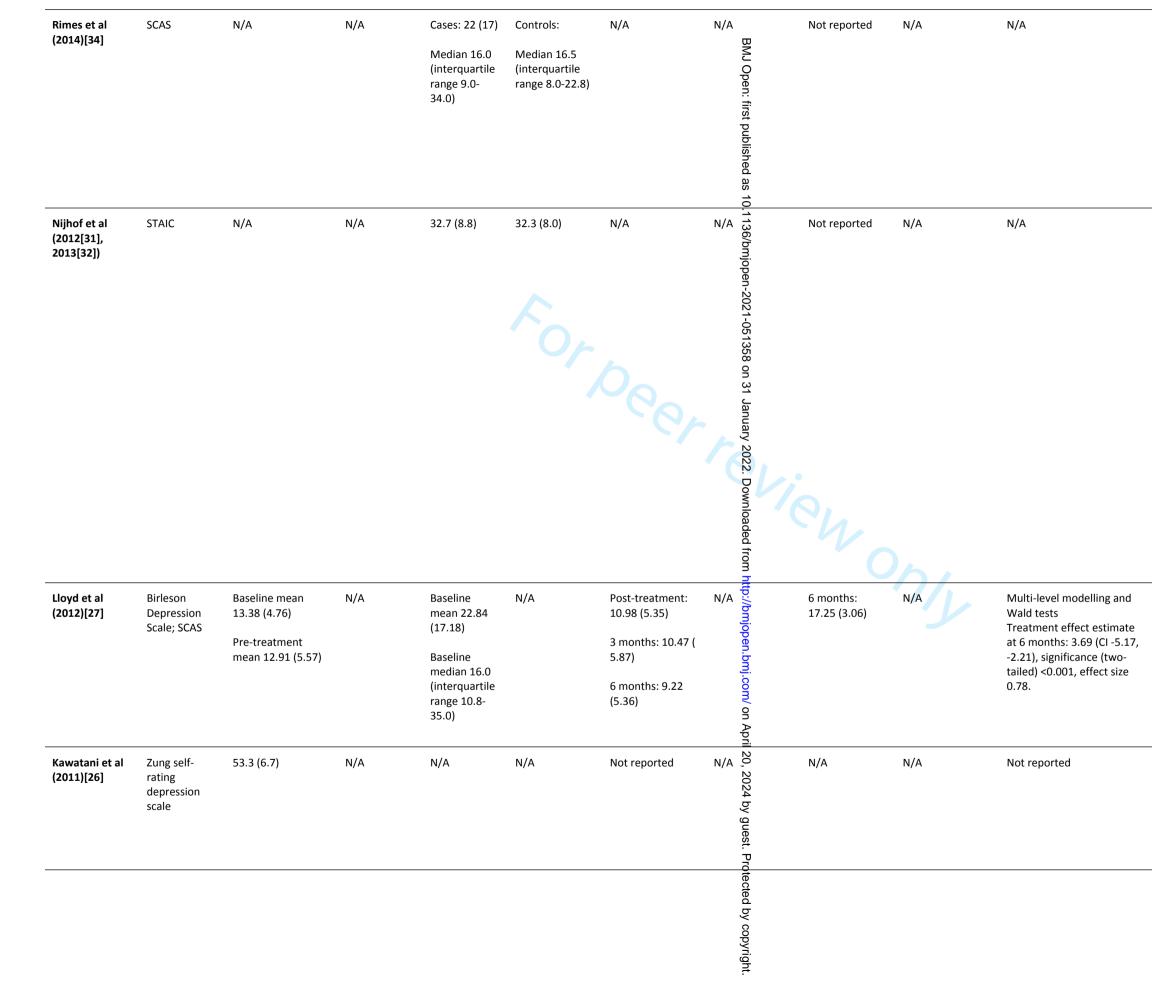
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	Measure of Depression and Anxiety	Pre treatment: depression, mean(SD)		Pre treatment: anxiety, mean(SD)		Post treatment: depression		Post treatment: anxiety, mean(SD)		Statistical analysis of change in depression/anxiety symptomatology		Summary of other relevant findings
		Intervention	Control	Intervention /case	Control	Intervention /case	Contres	Intervention /case	Control	Depression	Anxiety	
(a) Studies Ider	ntified in Updated Re	eview					ned					
Rowe et al (2019)[18]	BDI* (depression scale), STAI*	13.8 (8.9)	N/A	88.9 (24.9)	N/A	N/A	as 10.1136/bmj N/A	N/A	N/A	measured. Instead, mean ba scores were compared betw	se post-treatment scores were not aseline depression and anxiety veen those who reported d not, using the student's t-test.	Overall, 46.5% reported recovery; participants who were followed for years, 68% reported recovery Mean duration of illness was 5 yea
Crawley et al (2018)[19]	(anxiety scale) 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	openths: 5.9 6 months: 5.9 12 mogS1358 on 31 January 2022. Downloaded fi	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 means ⁺ (95%Cl, pvalue): 6 months: -1.5 (-3.5 to 0.5, p=0.1) 12 months: -1.8 (-3.4 to -0.1, p=0.04)	Adjusted difference in means [†] (95%Cl, pvalue): HADS at 6 months: -3.5 (-5.6 to -1.5, p=0.001) SCAS at 6 months: -10.0 (-18.5 to -1.5, p=0.02) HADS at 12 months: -2.6 (-4.7 to -0.4, p=0.019); SCAS at 12 months: 14.5 (-22.4 to -6.7, p<0.001)	At 6 months, participants allocated LP in addition to SMC (intervention had better physical function and fatigue at than those allocated to S (control). At 12 months, participants allocated 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 Ider	ntified in Previous Re	eviews					om h					
			NI / A	N/A	N/A	Not reported	N/A	N/A	N/A	Not reported	N/A	
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			/bmjopen.bmj.com/ on April 20, 2024			Not reported		All patients reported at least 80% rated improvement. Significant reduction in FSS, MSFI (all subsca



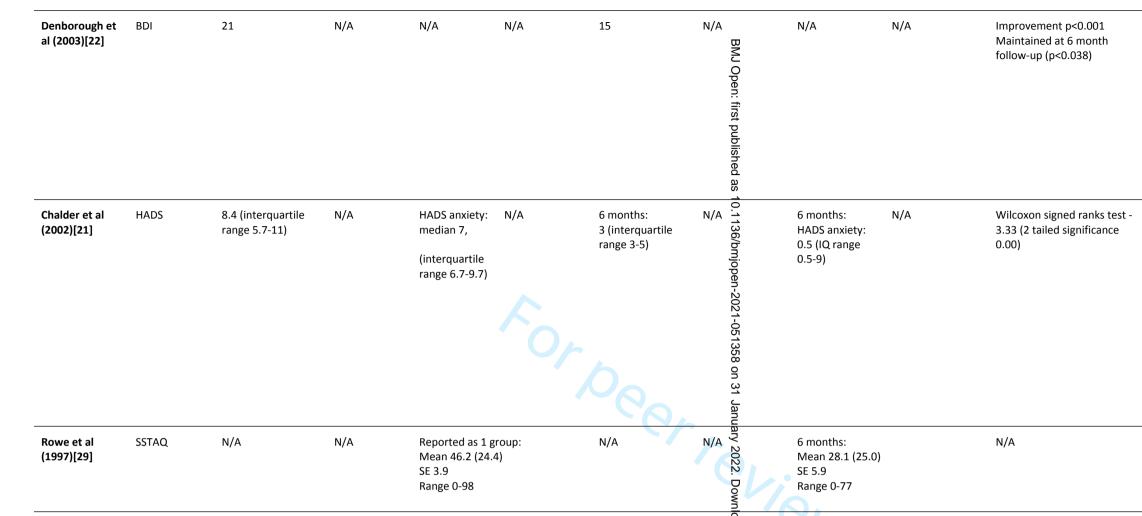
T value (21)= 2.1. p=0.005	Adolescents with CFS had reduced cortisol excretion throughout the day compared to healthy controls. There was significant improvement in school attendance after treatment from 24% to 49%. There was reduction in fatigue after treatment, however the results were not significant.
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 (57 [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 0.96-1.06), P = 0.66
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

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).

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Gordon, Knapman & Lubitz (2010)[20]	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 (677) MC Open: first pu	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. Signif improvement in BDI scores in both arms.
Gordon & Lubitz (2009)[25]	BDI	19.88 (8.62)	N/A	N/A	N/A	11.44 (10.98)	N/A as 1	N/A	N/A	Paired t test p value 0.001, sig 0.008	N/A	Significant improvement in Fatigue Severity scores.
Diaz Caneja et al (2007)[33]	MASC	N/A	N/A	Not stated. Raised levels of social anxiety and physical symptoms of anxiety	N/A	N/A	10.1136/bmjopen-2021-0	Not stated although it is reported that anxiety improved	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, although she still complained of tiredness and pain, she was attend classes daily.
Rimes (2007)[23]	DAWBA	Only states "3 of 4 had at least 1 psychiatric diagnosis at baseline"	N/A	Only states "3 of 4 had at least 1 psychiatric diagnosis at baseline"	N/A	N/A	551358 on 31 January 2022. Dow	N/A	N/A	Not reported	Not reported	Of the 4 participants who develop CFS/ME over the follow-up period 4 had at least 1 psychiatric diagno baseline, 3 had reported being 'm more tired and worn out than usu over the last month' at time 1, 2 participants had frequent headact time 1, 1 also had sleep problems post-exertional malaise at time 1.
Van de Putte et al (2007)[24]	CDI at baseline only; HADS (anxiety)	11.7(6.1)	N/A	36.9 (7.8)	N/A	Not stated	nloaded from http://b	Not stated	N/A	Not reported	Not reported	47% of adolescents 'fully recover (below score that is mean plus 2 subjective fatigue distribution in l adolescents).
Wright et al (2005)[30]	HADS (anxiety)	N/A	N/A	10.17 (3.71)	6.80 (3.56)	N/A	mjopen.bmj.com/ on April 20, 2024 by ∧∕	Post-treatment: 6.00 (3.63)	Post-treatment: 6.60 (4.73)	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) school attendance improved mar in the intervention (STAIRway) ar compared to little improvement i activity scores in the control (Pac arm, and a deterioration in schoo attendance. Global health (child a clinician rated) improved in both although more in the STAIRway a than the pacing arm.
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Note: *higher score=more symptoms, poorer function; † adjusted for age, gender, baseline outcome, SCAS and visual analogue scale; ‡reported recovery was Besed on the question "Do you feel you are no longer suffering from CFS?" (yes/no).

HADS, Hospital Anxiety and Depression Scale (score >8 indicates a diagnosis of depression); SCAS, Spence Children's Anxiety Scale ; BDI, Beck's Depression Inventory; CDI, Children's Depression Inventory; CDI, Children's Depression Inventory; MASC, Multidimensional Anxiety Scale for Children; DAWBA, Development and Well-Being Assessment; SSTAQ, Spielberger State-Trait Anxiety Questionnaire; SF-36 PP3, Short-form-36 physical function subscale; CFSI, Chronic Fatigue Syndrome Symptom Inventory; FSS, Fatigue Severity Scale; FSI, Fatigue Symptom Inventory; MFSI, Multidimensional Fatigue Symptom Inventory-Short Form; LP, Lightning Process; SMC, Specialist Medical Care http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright

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.
Wilcoxon signed ranks test (significance 2 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.
T value (df) 2.63 (56) Sig p value 0.01	Significant mean functional improvement in both groups.

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1 <u>1</u>. <u>Outpatient programmes</u>

The two new studies from this updated review evaluated two outpatient programmes. Crawley et al[19] compared adding the Lightening Process intervention (https://lightningprocess.com) to specialist care (recommended by NICE[1]), to specialist medical care alone. The Lightening 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[46]. It is delivered in intensive three, four-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[18]. Routine specialist care offers a "person-centered goal-oriented holistic programme" to "target educational, physical, social and emotional aspects of life". This includes symptom management (e.g. 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 i.e.
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-minute telephone calls), duration of treatment (12 weeks to one year), and whether pharmacotherapy was offered alongside CBT (anti-depressants and anti-hypotensives). Three observational studies showed that face-to-face and telephone CBT resulted in improved depression, anxiety, functioning and social adjustment[21, 27, 34]. An RCT showed that participants who received internet-based CBT demonstrated improvement in fatigue and school attendance at 6-months follow up, compared to participants who received usual care[32]. 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[26], or reported on only a single case-study[33]. In terms of behavioural approaches, the STAIRway to Health – an incremental rehabilitation intervention – showed greater improvement in anxiety levels, when compared with a 'pacing' intervention in an RCT[30]. Pharmacological studies showed insufficient evidence for improving anxiety or depressive symptoms with intravenous gammaglobulin infusions or vancyclovir respectively[28, 29]

25 <u>2.</u> Inpatient programmes

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As per our previous review[10], three studies[20, 22, 25] 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[22]). However: they did not measure anxiety symptoms; internalising problems at 6-months returned to pre-admission levels; two studies did not have follow-up data[20, 25]; 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

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what the best interventions are for treating anxiety and/or depression in paediatric CFS/ME
 patients.

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4 Strengths of the updated review include the systematic approach, the use of four reviewers, 5 contacting authors for sub-group data, and not limiting results to English language. The limitations 6 are the lack of eligible studies and insufficient data available for a meta-analysis. Only two papers 7 were eligible for inclusion, of which one did not provide sufficient follow-up data to comment on the 8 treatment efficacy of the intervention on depression and anxiety. Neither intervention was 9 specifically designed to measure the impact on depression and anxiety and therefore studies were 10 inadequately powered to measure this. Studies were not stratified by those who met criteria for 11 clinical diagnoses of depression/anxiety reducing our ability to analyse effectiveness. Furthermore, 12 neither study used diagnostic interviews for anxiety and depression, relying instead on 13 questionnaires. Whilst HADS[47], SCAS[48], and STAI[37] questionnaires are validated for use in 14 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 15 diagnostic interviews in paediatric CFS/ME populations[5]. 16 17 18 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 to other 19 20 interventions, such as behavioural-only or pharmacological, is CBT[10, 11]. The 'Lightening Process' 21 programme, 'STAIRway to Health' intervention, and a 4-week multicomponent inpatient 22 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 23 24 mechanisms for why CBT could be effective are unclear because no study targeted anxiety and 25 depression. Further, multi-component outpatient and inpatient interventions make it difficult to

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identify the effective element of interventions. Our updated review does not further this debate because, whilst 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[49]. 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[50-52] were excluded from our review for these reasons. For example, studies evaluating Acceptance and Commitment Therapy[50] and Mindfulness-based therapies[51] 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 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 upon

researchers to undertake paediatric CFS/ME interventions studies and use validated, diagnostic
 outcome measures of anxiety and depression.

4 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.

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23 AUTHOR CONTRIBUTIONS

2		
3	1	ML and EC conceptualised this study. PC, AR, KD, and JB performed data collection, synthesis and
4		
5 6	2	interpretation. PC wrote the manuscript. All authors contributed to manuscript revisions, have read
7	3	the final manuscript and approved it for publication. All authors agree to be accountable for all
8 9	5	the marmanuscript and approved it for publication. An authors agree to be accountable for an
10	4	aspects of the work.
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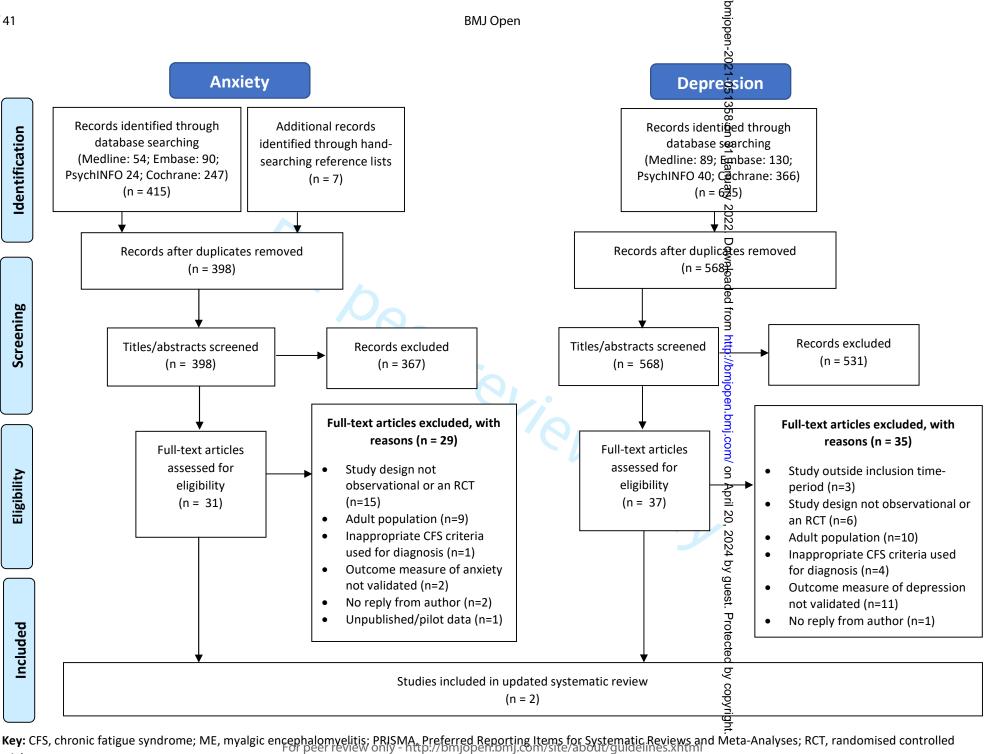
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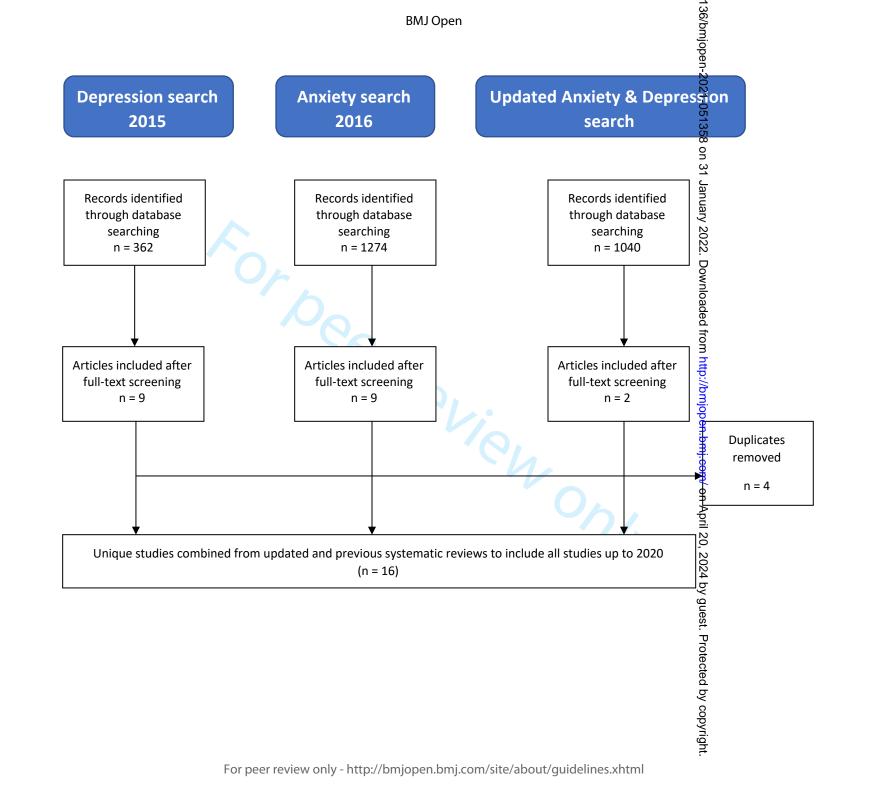
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37 38	15		
39 40			
40 41 42	16	FIGUR	ES AND TABLES LEGENDS
43 44	17	Figure	1: Flow chart for studies included in the systematic review; based on PRISMA guidelines
45 46 47	18	Figure	2: Flow chart of studies combined from updated review and previous reviews
48			
49 50 51	19	Table 1	L: Inclusion criteria
52 53	20	Table 2	2: Participant and study characteristics
54 55	21	Table 3	3: Summary of outcomes for symptoms of depression and anxiety and other relevant findings
56 57	22	foring	uded studies
58 59 60	22		



trials.





Identification

Included

Combined

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
- -der 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:

- (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.
- 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

11. exp depression/

12. depress*.tw

13. dysthymi*.tw

16. low mood.tw.

18. 3 and 9 and 17

10. depressive disorder.mp.

14. exp adjustment disorders/

15. adjustment disorder* .mp.

17. 10 or 11 or 12 or 14 or 14 or 15 or 16

19. Limit 18 to yr = "2015 – current"

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PRISMA 2009 Checklist

		BMJ Open	Page 40 of
PRISMA 2	009	BMJ Open 36/bmj open-2021	
Section/topic	#	Checklist item	Reported on page #
TITLE		<u> </u>	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT		uary v	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provid registration information including registration number.	e 3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered language, publication status) used as criteria for eligibility, giving rationale.	, Table 1 page 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable included in the meta-analysis).	e, 7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and apy assumptions and simplifications made.	6 t
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification \vec{R} of whether this wa done at the study or outcome level), and how this information is to be used in any data synthesis.	s 8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). ⁰ ⁰ ¹	7



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PRISMA 2009 Checklist

Page 41 of 41		BMJ Open 136/bmjope	
PRISMA 20)09	Checklist ^{njopen} -2021-	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	N/A
/	· ·	Page 1 of 2	
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS		o adde	
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICO, follow-up period) and provide the citations.	9-10and Table 2
2 Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 4
6 Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of gonsistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION	1		
2 Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., in complete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
	1		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of datas; role of funders for the systematic review.	20
12 <u></u> 13 14 15 16		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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PRISMA 2009 Checklist

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1	PRISMA 2009 Checklist		Page 42 of Page 42 of
2 3 4	From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses:		-
5	<i>From:</i> Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: doi:10.1371/journal.pmed1000097 For more information, visit: <u>www.prisma-statement.org</u> . Page 2 of 2		1355
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BMJ Open

What treatments work for anxiety and depression in children and adolescents with Chronic Fatigue Syndrome? An updated systematic review

Journal:	BMJ Open
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1	What treatments work for anxiety and depression in children and
2	adolescents with Chronic Fatigue Syndrome? An updated systematic review
3	
4	Philippa Clery ¹ , Alexander Royston ¹ , Katie Driver ¹ , Jasmine Bailey ¹ , Esther Crawley ^{1,2} , Maria Loades ^{1,3}
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16	Word count: 3624
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1 2		
3 4	1	ABSTRACT
5 6 7	2	Objectives
8 9 10	3	Children with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) experience a higher
11 12	4	prevalence of depression and anxiety compared to age-matched controls. Our previous systematic
13 14	5	reviews in 2015/16 found little evidence for effective treatment for children with CFS/ME with
15 16 17	6	comorbid depression and/or anxiety. This review updates these findings.
18 19 20	7	Design
21 22 23	8	A systematic review. We searched Cochrane library, Medline, Embase and PsychINFO databases
23 24 25	9	from 2015-2020. We combined the updated results with our previous reviews in a narrative
26 27	10	synthesis.
28 29 30	11	Participants
31 32 33	12	Inclusion criteria: <18 years old; diagnosed with CFS/ME (using Centre for Disease Control, National
34 35	13	Institute for Health and Care Excellence, or Oxford criteria); validated measures of depression and/or
36 37	14	anxiety.
38 39 40 41	15	Interventions
42 43	16	Observational studies or randomised controlled trials.
44 45 46	17	Comparison
47 48 49	18	Any or none.
50 51 52	19	Outcomes
53 54 55	20	Studies with outcome measures of anxiety, depression, or fatigue.
56 57 58 59 60	21	Results

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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 to 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. Trial registration number Reviews are registered on the Prospective Register of Systematic Review Protocols: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016043488; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015016813. Key words Paediatric, CFS/ME, chronic fatigue syndrome, anxiety, depression **ARTICLE SUMMARY** Strengths and limitations of study

1 2									
3 4	1	• This review used a systematic approach to identify updated evidence for treatment							
5 6	2	approaches for comorbid anxiety and/or depression in paediatric CFS/ME, and combined it							
7 8 9	3	with previous review results to provide a comprehensive synthesis of all evidence.							
9 10 11	4	Non-English language articles were included.							
12 13	5	Authors were contacted and sub-group data obtained when available.							
14 15	6	Grey literature and unpublished material was not included.							
16 17 18	7	There was insufficient data to carry out a meta-analysis.							
19 20	8								
21 22									
23 24	9	INTRODUCTION							
25 26 27	10	Chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) is a common but poorly understood							
27 28 29	11	condition causing disabling fatigue, malaise, myalgia, sleep difficulties, and problems							
30 31	12	concentrating[1]. In children and adolescents (henceforth referred to as children), prevalence is							
32 33	13	estimated at 0.55% (95%CI 0.22-1.35) across community, primary care and hospital populations[2							
34 35 36	14	CFS/ME has long-term impacts on children's physical, cognitive, emotional and social functioning[3,							
37 38	15	4].							
39 40	16								
41 42									
43 44	17	Children with CFS/ME suffer from higher rates of both depression and anxiety than age-matched							
45 46	18	population samples. The prevalence estimates of comorbid depression and anxiety are 20%[5] and							
47 48 40	19	29%[6], respectively, compared to 2.1% and 7.2%[7] in adolescents without CFS/ME. In those							
49 50 51	20	attending a specialist CFS/ME service, 61% who meet diagnostic criteria for depression also have an							
52 53	21	anxiety disorder[5]. Having comorbid depression and/or anxiety is associated with less favourable							
54 55	22	outcomes and may impact on engaging with treatment. Comorbid depression in paediatric CFS/ME							
56 57	23	is associated with greater functional disability, worse fatigue and more pain compared with those							
58 59 60	24	without depression[8, 9]. Low mood, anergia and anhedonia could be barriers to motivation to							

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2								
3 4	1	engage in behavioural treatment approaches and Cognitive Behavioural Therapy-for-fatigue (CBT-f).						
5 6	2	Depressive symptoms are therefore likely to require tailored treatment[9]. The impact of anxiety on						
7 8	3	outcomes is less clear. Given that most children with CFS/ME who have anxiety also have						
9 10 11	4	depression[5], it is important to explore treatments for both.						
12 13	5							
14								
15 16 17	6	Despite the high prevalence of comorbid mental health problems, there is little evidence about the						
18 19	7	effectiveness of treatments. Our two previous systematic reviews looking at depression and anxiety						
20 21	8	outcomes in existing CFS/ME intervention studies found that no specifically adapted treatments had						
22 23 24	9	been trialled to target depression and anxiety in paediatric CFS/ME[10, 11]. Although CBT-f and a						
24 25 26	10	multicomponent inpatient programme showed promise in reducing depressive[10] and anxiety[11]						
27 28	11	symptoms, there was no consistent treatment approach for children with CFS/ME and comorbid						
29 30	12	depression or anxiety. Since conducting these reviews in 2015/16, further intervention studies may						
31 32	13	have been published. It is important and timely to review the current evidence to provide an update						
33 34 35	14	on what treatments should be offered to this population. Further, it is important to consider anxiety						
36 37	15	and depression together given their overlap, whereas our previous reviews considered them						
38 39	16	separately.						
40								
41	17							
42 43								
44 45	18	We conducted an updated systematic review by synthesizing the evidence regarding treatments for						
46 47	19	paediatric CFS/ME and comorbid depression and anxiety since 2015. We combined these findings						
48 49	20	with results from our previous systematic reviews (1991-2015) to give an overview of all						
50 51 52	21	interventions evaluated since 1991 (when CFS/ME was scientifically defined). Specifically, we aimed						
52 53 54	22	to address the following:						
55 56 57 58 59 60	23	1. What treatment approaches are there for depression and anxiety in children with CFS/ME?						

1 2							
2 3 4	1	2. What is known about the second sec	he treatment efficacy of these appro	paches for treating depression and			
5 6	2	anxiety in CFS/ME? Do different approaches have different outcomes?					
7 8	3						
9 10							
11 12 13	4	METHODS					
14 15 16	5	Data sources and search strate	gy				
17 18	6	We conducted searches on Me	dline, Embase, PsychINFO and Coch	rane Library databases. We used			
19 20 21	7	the same search strategies from	n the previous systematic reviews (r	egistered on Prospero:			
21 22 23	8	CRD42015016813; CRD4201604	43488) to repeat the depression and	anxiety searches separately.			
24 25	9	Searches were designed with in	put from an information specialist t	o include the concepts:			
26 27	10	paediatric; CFS/ME; anxiety and depression (search strategies are in supplementary material). We					
28 29 30	11	updated the searches from when they had last been run (February 2015 for depression search and					
31 32	12	July 2016 for anxiety search) up until September 2020. The two searches were carried out by					
33 34	13	different reviewer teams: anxie	ety search (PC, AR); depression searc	ch (KD, JB). Grey literature was not			
35 36	14	searched. Reference lists of art	icles for full-text screening were har	nd-searched.			
37 38 39	15						
40 41 42	16	Inclusion and exclusion Criteria Studies were included if they met inclusion criteria (Table 1).					
43 44 45	17	Studies were included if they met inclusion criteria (Table 1).					
46 47 48		Table 1: Inclusion criteria					
49 50			Anxiety Review	Depression Review			
51 52 53 54				n <18 years of age defined using one of these criteria:			
55 56 57 58 59		Participants CDC aka Fukuda[12] NICE[1] Oxford aka Sharpe[13]					
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3								
4			Observation	al cohort studies				
5		Interventions	Any study with intervention – e.g.,	, observational clinical cohorts, clinical				
6			tria	als, etc.				
7								
8		Deceline measure	Validated according to familiate	Validated accompant of degreesion				
9		Baseline measure	Validated assessment of anxiety	Validated assessment of depression				
10								
11								
12			Either an anxiety and/or fatigue	Either a depression and/or fatigue				
13		Outcome measure	measure on psychometrically	measure on psychometrically				
14 15		Outcome measure	validated assessments or	validated assessments or validated				
16			validated diagnostic interviews.	diagnostic interviews.				
17								
18								
19		Language	Non-English language paper	s were considered for inclusion.				
20	1		I					
21	-							
22								
23	2	Study selection						
24								
25			\mathbf{O}					
26	3	Articles returned from databas	e searches were inputted into Endno	te and duplicates removed. Each				
27 29								
28 29	4	reviewer conducted title and a	bstract screening independently. Full	texts of potentially eligible				
29 30								
30	5	articles were screened against specifically created eligibility checklists. The final articles for inclusion						
32								
33	6	were cross-checked between all four reviewers and any conflicts discussed and resolved with input						
34								
35	7	from the senior author (ML) if necessary. Where information from the paper was insufficient to						
36								
37	8	determine eligibility, authors w	vere contacted by email for additionation	l information. If authors did not				
38								
39	9	reply after two follow-up emai	ls, the study was excluded. Figure 1 p	resents the PRISMA[14]				
40 41								
41	10	flowchart.						
43								
44								
45	11							
46								
47	12	Data extraction						
48	12	Data extraction						
49								
50	13	For all included articles, data w	ere extracted independently by two	reviewers (PC, AR) using a				
51								
52	14	4 purpose-designed data extraction form to collect information about: study design; setting;						
53								
54 55	15	15 recruitment; participant characteristics; CFS/ME definition used for diagnosis; assessment of						
55 56								
57	16	depression and anxiety: other	outcomes; treatment and interventio	ons provided: definition of				
58	10	appression and anxiety, other		no provided, definition of				
59	17	response and treatment/interv	vention outcomes					
60	11	response and treatment/interv	chilon outcomes.					

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4 5		
6	2	Quality assessment
7	2	Quality assessment
8		
9	3	PC and AR used Risk of Bias assessment tools[15, 16] to assess methodological quality of the
10		
11 12	4	included studies.
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14	5	
15	5	
16		
17	6	Data synthesis
18 19		
20	7	We combined results from the included studies identified in the updated search with findings from
21		
22	8	the two previous systematic reviews[10, 11] to conduct a narrative synthesis[17], providing an
23		
24 25	9	overview of all longitudinal studies that have been evaluated in this clinical cohort since 1991 (when
26		
27	10	CFS/ME was scientifically defined). There was insufficient comparable data to conduct a meta-
28		
29	11	analysis as interventions were heterogeneous and a range of outcome measures were reported. For
30		
31 32	12	each of the new studies, the effects of interventions on outcomes using mean differences were
33		
34	13	compared.
35		
36	14	
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38 39	4 5	Detient and multipline investore
40	15	Patient and public involvement
41		No patients were involved.
42	16	No patients were involved.
43		
44 45	17	
46	17	
47		
48	18	Ethics approval
49		
50 51	19	This study did not involve human participants.
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56 57	21	RESULTS
57 58		
59		
60	22	Studies included

1	In the updated search (2015-2020), a total of 625 and 415 references were found by database
2	searching for the depression and anxiety searches, respectively. After full-text screening, both
3	searches returned the same two eligible studies[18, 19]. One was an RCT[19], one was a
4	retrospective observational cohort study[18]. The PRISMA[14] flowchart is in Figure 1.
5	[Figure 1 here]
6	
7	The previous systematic reviews for depression[10] (search conducted in 2015) and anxiety[11]
8	(search conducted in 2016) found 362 and 1274 references, respectively. After full-text screening,
9	the depression search returned nine eligible studies (one RCT[20], and eight observational[21-28]),
10	and the anxiety search returned nine eligible papers from eight studies (three RCTs[29-32], six
11	observational studies[21, 23, 24, 27, 33, 34]). Four of the studies from these two searches were the
12	same.
13	Therefore, in total, 16 eligible studies were included in the narrative synthesis review. Figure 2
14	shows a flowchart combining studies from this updated search with studies identified from previous
15	reviews.
16	[Figure 2 here]
17	
18	Quality assessment
19	Of the total 16 studies in this review, ten were observational and six were RCTs. Of the observational
20	studies, five had an overall risk of bias as "unclear", and five had "high" risk of bias (as defined by the
21	Cochrane risk of bias scale, ROBINS-I[15]). Of the RCTs, all six had an overall rating of "low" risk of
22	bias (as defined by the Cochrane risk of bias scale (ROB-2[16]). See supplementary material for the
23	quality assessment table. For detailed reporting on the quality assessment of studies from the

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previous searches, please refer to our previous two reviews[10, 11]. In this paper we report in detail 1 2 on the quality assessment of the two new studies found in the updated search.

4 The RCT[19] was conducted by members of our CFS/ME research team (EC). The study has a low risk 5 of bias from the concealed allocation randomisation process, minimal deviation from how 6 interventions were intended to be delivered, and appropriate intention-to-treat analysis. Outcome 7 measurement is biased because of self-reported measures, but this is standard for behavioural 8 treatments. It is also biased due to loss to follow-up. In the control arm at 3 months, 13 of 49 (27%) 9 were lost to follow-up and at the primary outcome of 6 months, 12 of 49 (24%) were not included in 10 analysis. In the intervention arm 8 of 51 (16%) were lost to follow-up at 3 months and 7 of 51 (14%) 11 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 12 erie 13 related to the outcome.

14

The retrospective observational study[18] is also biased due to poor follow-up rates at any one time 15 16 point (making comparison difficult), and no pre-published analysis plan. In the cohort, there are two 17 samples; one with baseline data for anxiety and depression and one without. Follow-up 18 questionnaires were mailed to all participants on a number of occasions between January 2008 and 19 June 2011. This produced a range of follow-up time points (1-21 years) after illness onset, meaning 20 some patients would not have had contact with the clinic for a long time when they were sent the 21 questionnaire, so it is likely that both disease status and time since illness influenced outcome data. 22 Of the 489 patients who were sent baseline questionnaires, 74% returned a follow-up questionnaire 23 on at least one occasion (range one to seven). For the sample of 366 without baseline data for 24 anxiety and depression, 76% returned a follow-up questionnaire on one occasion, whilst only 8%

returned a questionnaire on more than one occasion. Outcome measures were also self-reported,
 and many participants did not complete all measures.

4 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' alone[19]; and an observational cohort study assessing 'routine specialist care' over a 20-year period[18]. Studies from the previous reviews included the following. Four RCTs evaluating: inpatient programmes with predominantly behavioural approaches[20, 30], an online CBT programme[31, 32], and intravenous gammaglobulin[29]; eight observational cohort studies evaluating: CBT[21, 27, 34], CBT with pharmacotherapy[26, 33], an anti-viral treatment[28], and an inpatient programme[25]; and two prospective observational community studies that did not assess a specified intervention[23, 24]. 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)[35], Spence Children's Anxiety Scale (SCAS)[36], the State-Trait Anxiety Inventory for Children (STAIC)[37], the Multidimensional Anxiety Scale for Children (MASC)[38], Spielberger State Trait Anxiety Questionnaire (SSTAQ)[39], Beck Depression Inventory (BDI)[40], Children's Depression Inventory[41], the Birleson Depression

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1 Scale[42], and Zung's Self-rating depression scale[43]. One study used a diagnostic interview, the 2 Development and Well-Being Assessment (DAWBA)[44]. Six studies (including the two identified in 3 the updated review) measured both anxiety and depression; five measured depression only; and five 4 anxiety only (Table 2). to beet terien only

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Table 2: Participant and study characteristics

Author (year), country	Anxiety, depression or both?	Study design	Setting	Control	mple size Intervention /case	Control	n age, years Intervention /case	Control	er, Female % Oppose Intervention /case firs	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 o follow up
(a) Studies Ident	tified in Updat	ed Review							t put				•	•			
Rowe et al (2019) [18], Australia	Both	Observational retrospective	Outpatient secondary care	N/A	418 (789 recruited but 366 did not have baseline questionnaire)	N/A	14.8	N/A	77% shed as 10.1136/bm	CDC/Fukuda	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 program which targets educational, physical, social and emotional aspects of life.	N/A	Mean: 8 years; Range 1 years
Crawley et al (2018)[19], UK	Both	RCT	Outpatient secondary care	49	51	14.5	14.7	78%	ppen-2021-051358 on 31 January 2022 75%	NICE	SF-36 PFS at 6 months	SCAS, HADS	No	No	Specialist medical care (Based on NICE guidance) + Lightning Process® (3 x 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 (e.g. stand up for longer) and are given cognitive strategies.)	Specialist medical care only	3, 6, 12 months
(b) Studies Ident	tified in Previo	ous Reviews							Do								
Henderson (2014)[28], USA	Depression	Observational , retrospective, case-series	Outpatient secondary care	N/A	15 (14 at follow- up)	N/A	15.46	N/A	73% 73% http://t	CDC/Fukuda	Fatigue self- assessment scores (CFSI, FSS, FSI, MFSI)	CDI	No	Yes	Valacyclovir (antiviral) medication, initially 500mg BID, increasing after 2-3 weeks. Duration of treatment ranged from 3 to 60 months (mean 27.9 months).	N/A	Varied treatm
Rimes et al (2014)[34], UK	Anxiety	Observational case-control	Outpatient secondary care	36 healthy controls	49 (24 at follow- up)	15	14.9	58%	63% jopen.bm	CDC/Fukuda , Oxford/ Sharpe	School attendance	SCAS	No	No	CBT via telephone based guided self-help. 6 fortnightly sessions, 30mins duration	N/A	6 mont
Nijhof et al (2012[31], 2013[32]), Netherlands	Anxiety	Both RCTs	Outpatient secondary care	67 (63 at follow-up)	68 (64 at follow- up)	15.8	15.9	85%	j.com/ on April 20, 2024 by guest 1 79%	CDC/Fukuda	School attendance, absence of severe fatigue and normal physical functioning	STAIC	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 yea
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Lloyd et al (2012)[27], UK	Both	Observational	Outpatient secondary care	N/A	63 (52 at follow- up)	N/A	Median 15	N/A	63%	BMJ O	Oxford/ Sharpe	Fatigue (Chalder Fatigue Questionnaire Total) and school attendance	SCAS, Birleson Depression Scale	No	No
Kawatani et al (2011)[26], Japan	Depression	Observational	Outpatient secondary care	N/A	19	N/A	13.6	N/A	63%	pen: first published	Jason et al [45]	Chalder's Fatigue Scale	Zung self- rating depression scale	No	No
Gordon, Knapman & Lubitz (2010)[20], Australia	Depression	RCT	Inpatient secondary care	Aerobic group: 11	Resistance group: 11	Aerobic group: 16.2	Resistance group: 15.6	Not reporte		ad as 10.1136/bmjopen-2021-051358	CDC/Fukuda	Exercise tolerance (time to fatigue)	BDI	No	No
Gordon & Lubitz (2009)[25], Australia	Depression	Observational	Inpatient secondary care	N/A	16	N/A	16	Not reporte		58 on 31 January 2022. Downlo	CDC/Fukuda	Physical and physiological measures e.g. aerobic capacity (VO ₂ peak), time to fatigue, physical component score of SF-36	BDI	No	No
Diaz Caneja et al (2007)[33], Spain	Anxiety	Observational case study		N/A	1	N/A	15	N/A	100%	paded from http:	Oxford/ Sharpe	Self-reported fatigue, pain symptoms	MASC	No	No
Rimes (2007)[23], UK	Both	Observational prospective	Community	N/A	1 case of CFS at time 1; 4 cases of CFS at time 2	N/A	13	Not reporte		://bmjopen.bmj.com/ o	CDC/Fukuda	Incidence and prevalence of fatigue, chronic fatigue and CFS	DAWBA	No	No
Van de Putte et al (2007)[24], Netherlands	Both	Observational prospective	Community	N/A	40 at baseline, 36 at follow-up	N/A	16	N/A			CDC/Fukuda	Fatigue	SSTAQ, CDI	No	No
										n April 20, 2024 by guest. Protected by copyright					

CBT via telephone based guided self-help. 6 fortnightly sessions, 30mins duration	N/A	6 months
CBT (average of 5 sessions over 6 months) and pharmacotherapy (antidepressants, antihypotensives, hypnotic agents)	N/A	6 months
4 week inpatient programme inclue therapy, psychological/psychiatric at school.		Post- treatment
Patients randomised to either grad training or progressive resistance t for 5 days/week for 4 weeks. The g training consisted of 20-40 minutes cycling and treadmill exercise. The resistance training involved 16 exe with single set, moderate load and	raining programme raded aerobic s of stationary progressive rcises performed	
4 week inpatient programme including graded exercise therapy, psychological/psychiatric support, attendance at school, recreation and leisure intervention.	N/A	Post- treatment
CBT + fluoxetine (initially 10mg daily, increased after 1 week to 20 mg)	N/A	3 months
None specifically stated or evaluated	N/A	4-6 months

Wright et al (2005)[30], UK	Anxiety	RCT	Outpatient secondary care	6 (5 at follow-up)	7 (6 at follow- up)	12.9		66%	57%		0xford/ harpe	Global Health on Child Health Questionnaire	HADS	No	No
										BMJ Open: first published as					
Denborough et al (2003)[22], Australia	Depression	Observational	Inpatient secondary care	N/A	39 (19 at follow- up)	N/A	16.2	N/A	90%	0.1136/bmiopen-2021-C	DC/Fukuda	Global assessment of functioning, Chronic Fatigue Illness Disability Scale, FSS	BDI	No	No
Chalder et al (2002)[21], UK	Both	Observational	Outpatient secondary care	N/A	23	N/A	14.5	N/A	87%	<u>б</u> с) 0	Dxford/ harpe	The fatigue questionnaire, school attendance	HADS	No	No
Rowe et al (1997)[29], Australia	Anxiety	RCT	Outpatient secondary care	35	36	15.6	15.3	75%	58%	U January 2022. Download	DC/Fukuda	Functional score including school attendance, school work, social activity and physical activity	SSTAQ	No	No

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be the transformed base of the n); BDI, Beck's Depression Inventory; CDI, Children's Depression Inventory; MASC,

STAIRway to Health intervention is a structured rehabilitation programme including conceptualising CFS as having both physical and psychological components, formulating and addressing vicious cycles around activity, sleep, social isolation, physical deconditioning, and developing adaptive coping strategies whilst challenging negative and unhelpful attributions about illness and the future.	Pacing - focuses on limiting activity to the changing needs and responses of the body by avoiding overexertion and managing energy within an overall limit	1 year
4 week inpatient programme, focused on graded exercise using hydrotherapy and physiotherapy.	N/A	6 months
CBT based rehabiliation programme. Up to 15 sessions, 1 hour duration.	N/A	6 months
3 monthly infusions of gammaglobulin	3 monthly infusions of placebo	3 and 6 months

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1 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[18]; one evaluated the Lightening Process outpatient intervention[19]; one evaluated the 'STAIRway to health' outpatient intervention[30]; six evaluated various outpatient CBT programmes[21, 26, 27, 31-34]; two evaluated outpatient pharmacological interventions (antivirals[28] and gammaglobulins[29]); three evaluated inpatient programmes focussed on graded exercise therapy[20, 22, 25]; and two were epidemiological observational studies so were uninformative about interventions[23, 24].

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 (e.g. inpatient treatment, consecutive daily four-hour outpatient sessions, and fortnightly 30-minute phone calls), duration of treatment (days to years), and modality (e.g. face-to-face, telephone, and online). The antiviral and gammaglobuin 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 (a) the updated review, and (b) 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.

Study	Measure of Depression and Anxiety	Pre treatment: depres mean(SD)	ssion,	Pre treatment: mean(SD)	anxiety,	Post treatment: de mean(SD)	en: first	Post treatment: a	anxiety, mean(SD)	Statistical analysis of chang symptomatology	e in depression/anxiety	Summary of other relevant finding
		Intervention	Control	Intervention /case	Control	Intervention /case	Contre Contre	Intervention /case	Control	Depression	Anxiety	
a) Studies Ident	tified in Updated Re	eview					and a					
Rowe et al (2019)[18]	BDI* (depression scale), STAI* (anxiety scale)	13.8 (8.9)	N/A	88.9 (24.9)	N/A	N/A	as 10.1136/bmjop ∕A	N/A	N/A	measured. Instead, mean ba scores were compared betw	se post-treatment scores were not aseline depression and anxiety veen those who reported d not, using the student's t-test.	Overall, 46.5% reported recovery; participants who were followed fo years, 68% reported recovery Mean duration of illness was 5 yea
Crawley et al (2018)[19]	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 montos: 5.9 12 montos: 4.6 1358 on 31 January 2022. Downloaded fr	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 means ⁺ (95%Cl, pvalue): 6 months: -1.5 (-3.5 to 0.5, p=0.1) 12 months: -1.8 (-3.4 to -0.1, p=0.04)	Adjusted difference in means ⁺ (95%Cl, pvalue): HADS at 6 months: -3.5 (-5.6 to -1.5, p=0.001) SCAS at 6 months: -10.0 (-18.5 to -1.5, p=0.02) HADS at 12 months: -2.6 (-4.7 to -0.4, p=0.019); SCAS at 12 months: 14.5 (-22.4 to -6.7, p<0.001)	At 6 months, participants allocated LP in addition to SMC (intervention had better physical function and fatigue at than those allocated to S (control). At 12 months, participants allocated LP in addition to SMC (intervention had better fatigue and school attendance than those in SMC (control). Adding LP to SMC is cost-effective.
(h) Chudiaa Idam							om					
(b) Studies iden	tified in Previous Re						<u>₹</u>					
Henderson (2014)[28]	CDI	Aeviews 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	http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protect	N/A	N/A	Not reported	N/A	All patients reported at least 80% s rated improvement. Significant reduction in FSS, MSFI (all subscale

2021231. 20212321. 2021	Rimes et al (2014)[34]	SCAS	N/A	N/A	Cases: 22 (17) Median 16.0 (interquartile range 9.0- 34.0)	Controls: Median 16.5 (interquartile range 8.0-22.8)	N/A	BMJ Open: first published as N∕A	Not reported	N/A	N/A	T value (21)= 2.1. p=0.005	Adolescents with CFS had reduce cortisol excretion throughout the compared to healthy controls. There was significant improvement school attendance after treatment from 24% to 49%. There was reduction in fatigue and treatment, however the results we not significant.
Lloyd et al (2012)[27] Birleson Depression Scale; SCAS Baseline mean 13.38 (4.76) N/A Baseline mean 22.84 (17.18) N/A Post-treatment: 10.98 (5.35) N/A M/A Post-treatment: 10.98 (5.35) N/A Multi-level modelling and Wald tests Multi-level modelling and Wald tests Multi-level modelling and Wald tests Multi-level modelling and Wald tests Multi-level modelling and tests <	Nijhof et al (2012[31], 2013[32])	STAIC	N/A	N/A				136/bmjopen N∕A	Not reported	N/A	N/A	Not reported	At 6 months additional analyses main findings with adjustments f anxiety, depression, and primary outcomes, had no effects on the results. When looking at factors related t
(2011)[26]rating depression scale20 depression scale20 P P P20 P P P20 P P P P20 P P P P20 P P P P20 P P P P20 P P P20 P P P20 P P P20 P P P20 P P P20 P P20 P P20 P P20 P P20 P P20 P P20 P P20 P P20 P<		Depression	13.38 (4.76) Pre-treatment	N/A	mean 22.84 (17.18) Baseline median 16.0 (interquartile range 10.8-	N/A	10.98 (5.35) 3 months: 10.47 (5.87) 6 months: 9.22			N/A	Wald tests Treatment effect estimate at 6 months: 3.69 (CI -5.17, -2.21), significance (two- tailed) <0.001, effect size	tests Treatment effect estimate at 6 months: 0.49, significance (two-tailed) 0.003, effect size	
		rating depression	53.3 (6.7)	N/A	N/A	N/A	Not reported	pril 20, 2024 by guest. Protec	N/A	N/A	Not reported	N/A	improvement in performance st scores (self-reported impact on

Gordon, Knapman & Lubitz (2010)[20]	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 (@7) AL Open: first put	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 & Lubitz (2009)[25]	BDI	19.88 (8.62)	N/A	N/A	N/A	11.44 (10.98)	N/A as	N/A	N/A	Paired t test p value 0.001, sig 0.008	N/A	Significant improvement in Fatigue Severity scores.
Diaz Caneja et al (2007)[33]	MASC	N/A	N/A	Not stated. Raised levels of social anxiety and physical symptoms of anxiety	N/A	N/A	10.1136/bmjopen-2021-0	Not stated although it is reported that anxiety improved	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 (2007)[23]	DAWBA	Only states "3 of 4 had at least 1 psychiatric diagnosis at baseline"	N/A	Only states "3 of 4 had at least 1 psychiatric diagnosis at baseline"	N/A	N/A	051358 on 31 January 2022. Dowr N∕A	N/A	N/A	Not reported	Not reported	Of the 4 participants who developed CFS/ME over the follow-up period, 3 of 4 had at least 1 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.
al (2007)[24]	CDI at baseline only; HADS (anxiety)	11.7(6.1)	N/A	36.9 (7.8)	N/A	Not stated	wnloaded from http://	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).
	HADS (anxiety)	N/A	N/A	10.17 (3.71)	6.80 (3.56)	N/A	/bmjopen.bmj.com/ on April 20, 2024 by N	Post-treatment: 6.00 (3.63)	Post-treatment: 6.60 (4.73)	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 to 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.
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Denborough et al (2003)[22]	BDI	21	N/A	N/A	N/A	15	BMJ Open: first published as 1	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.
Chalder et al (2002)[21]	HADS	8.4 (interquartile range 5.7-11)	N/A	HADS anxiety: median 7, (interquartile range 6.7-9.7)	N/A	6 months: 3 (interquartile range 3-5)	0.1136/bmjopen-2021-051358 on 31 Janu ∧∕	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 2 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 et al (1997)[29]	SSTAQ	N/A	N/A	Reported as 1 g Mean 46.2 (24.4 SE 3.9 Range 0-98		N/A	uary 2022. Down	6 months: Mean 28.1 (25.0) SE 5.9 Range 0-77)	N/A	T value (df) 2.63 (56) Sig p value 0.01	Significant mean functional improvement in both groups.

Note: *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).

HADS, Hospital Anxiety and Depression Scale (score >8 indicates a diagnosis of depression); SCAS, Spence Children's Anxiety Scale ; BDI, Beck's Depression Inventory; CDI, Children's Depression Inventory; CDI, Children's Depression Inventory; MASC, Multidimensional Anxiety Scale for Children; DAWBA, Development and Well-Being Assessment; SSTAQ, Spielberger State-Trait Anxiety Questionnaire; SF-36 PE, Short-form-36 physical function subscale; CFSI, Chronic Fatigue Syndrome Symptom Inventory; FSS, Fatigue Severity Scale; FSI, Fatigue Symptom Inventory; MFSI, Multidimensional Fatigue Symptom Inventory-Short Form; LP, Lightning Process; SMC, Specialist Medical Care http://bmjopen.bmj.com/ on April 20, 2024 by guest. Protected by copyright

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<u>1.</u> Outpatient programmes

The two new studies from this updated review evaluated two outpatient programmes. Crawley et al[19] compared adding the Lightening Process intervention (https://lightningprocess.com) to specialist care (recommended by NICE[1]), to specialist medical care alone. The Lightening 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[46]. It is delivered in intensive three, four-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[18]. Routine specialist care offers a "person-centered goal-oriented holistic programme" to "target educational, physical, social and emotional aspects of life". This includes symptom management (e.g. 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

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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 i.e.
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 econsults), intensity (15 weekly, hourly therapist-led sessions; six fortnightly 30-minute telephone calls), duration of treatment (12 weeks to one year), and whether pharmacotherapy was offered alongside CBT (anti-depressants and anti-hypotensives). Three observational studies showed that face-to-face and telephone CBT resulted in improved depression, anxiety, functioning and social adjustment[21, 27, 34]. An RCT showed that participants who received internet-based CBT demonstrated improvement in fatigue and school attendance at 6-months follow up, compared to participants who received usual care[32]. 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[26], or reported on only a single case-study[33]. In terms of behavioural approaches, the STAIRway to Health – an incremental rehabilitation intervention – showed greater improvement in anxiety levels, when compared with a 'pacing' intervention in an RCT[30]. Pharmacological studies showed insufficient evidence for improving anxiety or depressive symptoms with intravenous gammaglobulin infusions or vancyclovir respectively[28, 29]

25 <u>2.</u> Inpatient programmes

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As per our previous review[10], three studies[20, 22, 25] 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[22]). However: they did not measure anxiety symptoms; internalising problems at 6-months returned to pre-admission levels; two studies did not have follow-up data[20, 25]; 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

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what the best interventions are for treating anxiety and/or depression in paediatric CFS/ME
 patients.

4 Strengths of the updated review include the systematic approach, the use of four reviewers, 5 contacting authors for sub-group data, and not limiting results to English language. The limitations 6 are the lack of eligible studies and insufficient data available for a meta-analysis. Only two papers 7 were eligible for inclusion, of which one did not provide sufficient follow-up data to comment on the 8 treatment efficacy of the intervention on depression and anxiety. Neither intervention was 9 specifically designed to measure the impact on depression and anxiety and therefore studies were 10 inadequately powered to measure this. Studies were not stratified by those who met criteria for 11 clinical diagnoses of depression/anxiety reducing our ability to analyse effectiveness. Furthermore, 12 neither study used diagnostic interviews for anxiety and depression, relying instead on 13 questionnaires. Whilst HADS[47], SCAS[48], and STAI[37] questionnaires are validated for use in 14 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 15 diagnostic interviews in paediatric CFS/ME populations[5]. 16 17

18 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 to other 19 20 interventions, such as behavioural-only or pharmacological, is CBT[10, 11]. The 'Lightening Process' 21 programme, 'STAIRway to Health' intervention, and a 4-week multicomponent inpatient 22 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 23 24 mechanisms for why CBT could be effective are unclear because no study targeted anxiety and 25 depression. Further, multi-component outpatient and inpatient interventions make it difficult to 60

identify the effective element of interventions. Our updated review does not further this debate because, whilst 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[49]. 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[50-52] were excluded from our review for these reasons. For example, studies evaluating Acceptance and Commitment Therapy[50] and Mindfulness-based therapies[51] 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 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 upon

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researchers to undertake paediatric CFS/ME interventions studies and use validated, diagnostic
 outcome measures of anxiety and depression.

4 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.

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23 AUTHOR CONTRIBUTIONS

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1	ML and EC conceptualised this study. PC, AR, KD, and JB performed data collection, synthesis and
2	interpretation. PC wrote the manuscript. All authors contributed to manuscript revisions, have read
3	the final manuscript and approved it for publication. All authors agree to be accountable for all
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5	
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15	DATA STATEMENT
16	Not applicable.
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5 6 7	2		syndrome in a 15-year-old girl. Anales de Pediatria 2007;67(1):74-77 doi:
7 8 9	3		10.1157/13108085
10 11	4	34.	Rimes KA, Papadopoulos A, Cleare AJ, et al. Cortisol output in adolescents with
12 13	5		chronic fatigue syndrome: Pilot study on the comparison with healthy adolescents
14 15 16	6		and change after cognitive behavioural guided self-help treatment. J Psychosom Res
17 18	7		2014;77(5):409-414 doi: 10.1016/j.jpsychores.2014.08.018
19 20	8	35.	Zigmond AS and Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr
21 22 23	9		Scand 1983;67(6):361-70 doi:10.1111/j.1600-0447.1983.tb09716.x
24	-		
25 26	10	36.	Spence SH, Barrett PM and Turner CM. Psychometric properties of the Spence
27 28 29	11		Children's Anxiety Scale with young adolescents. J Anxiety Disord 2003;17(6):605-
30 31	12		625 doi:10.1016/s0887-6185(02)00236-0
32 33	13	37.	Spielberger CD. Manual for the state trait anxiety inventory for children. Palo Alto:
34 35 36	14		Consulting Psychologists Press 1973.
37 38	15	38.	March JS, Parker JD, Sullivan K, et al. The Multidimensional Anxiety Scale for Children
39 40 41	16		(MASC): Factor Structure, Reliability, and Validity. J Am Acad of Child & Adolesc
41 42 43	17		Psychiatry 1997;36(4):554-565 doi: 10.1097/00004583-199704000-00019
44 45	18	39.	Spielberger C. Self-evaluation questionnaire state trait anxiety inventory. Palo Alto,
46 47 48	19		CA: Consulting Psychologists Press. 1977
49 50	20	40.	Beck AT, Steer RA and Carbin MG. Psychometric properties of the Beck Depression
51 52 53	21		Inventory: Twenty-five years of evaluation. Clin Psychol Rev 1988;8(1):77-100
54 55	22		doi:10.1016/0272-7358(88)90050-5
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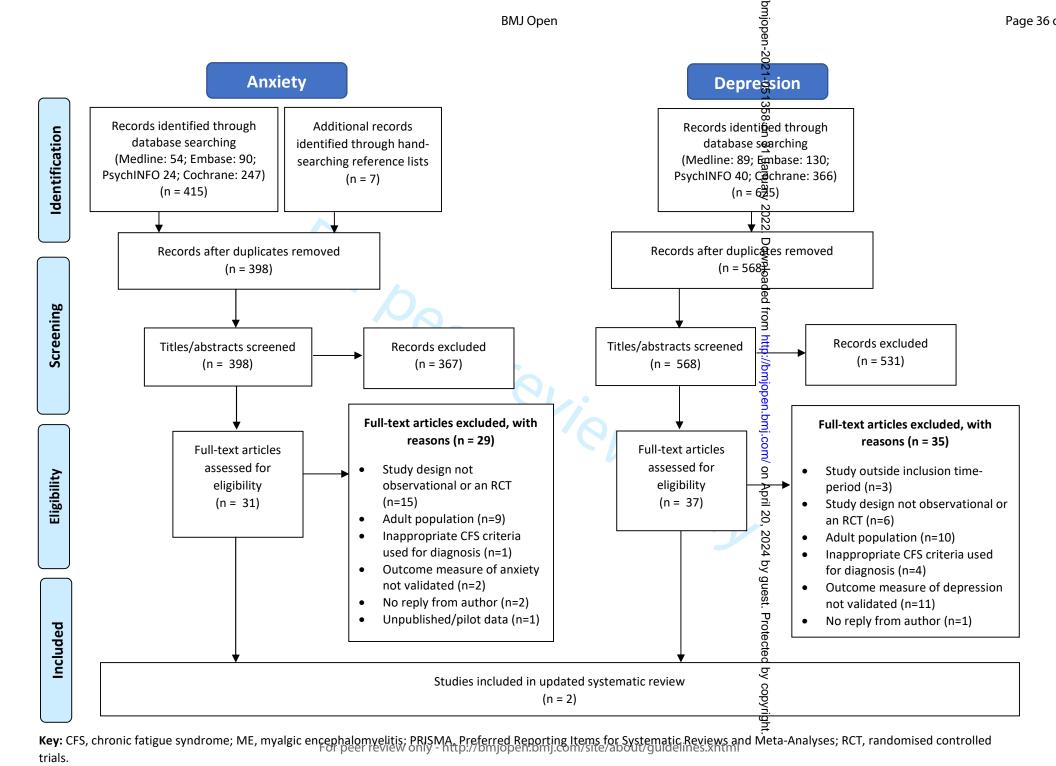
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- 3 4	1	41.	Saylor CF, Finch A, Spirito A, et al. The children's depression inventory: a systematic
5 6	2		evaluation of psychometric properties. J Consult Clin Psychol 1984;52(6):955-67 doi:
7 8 9	3		10.1037//0022-006x.52.6.955
10 11	4	42.	Birleson P, Hudson I, Buchanan D, et al. Clinical Evaluation of a Self-rating Scale for
12 13 14	5		Deprressive Disorder in Childhood (Depression Self-Rating Scale). J Child Psychol
14 15 16	6		<i>Psychiatry</i> 1987;28(1):43-60 doi: 10.1111/j.1469-7610.1987.tb00651.x
17 18	7	43.	Zung W. A self-rating depression scale. Arch Gen Psychiatry 1965;12:63-70 doi:
19 20 21	8		10.1001/archpsyc.1965.01720310065008
22 23	9	44.	Goodman R, Ford T, Richards H, et al. The Development and Well-Being Assessment:
24 25 26	10		description and initial validation of an integrated assessment of child and adolescent
20 27 28	11		psychopathology. J Child Psychol Psychiatry 2000;41(5): 645-55
29 30	12	45.	Jason LA, Jordan K, Miike T, et al. A Pediatric Case Definition for Myalgic
31 32 33	13		Encephalomyelitis and Chronic Fatigue Syndrome. Journal of Chronic Fatigue
34 35	14		<i>Syndrome</i> 2006;13(2-3):1-44 doi: 10.1300/J092v13n02 01
36 37	15	46.	Reme SE, Archer N, and Chalder T. Experiences of young people who have
38 39 40	16		undergone the Lightning Process to treat chronic fatigue syndrome/myalgic
41 42	10		encephalomyelitisa qualitative study. <i>Br J Health Psychol</i> 2013;18(3):508-25 doi:
43 44			
45 46 47	18	47	10.1111/j.2044-8287.2012.02093.x
48 49	19	47.	White D, Leach C, Sims R, et al. Validation of the Hospital Anxiety and Depression
50 51	20		Scale for use with adolescents. Br J Psychiatry 1999;(175):452-454
52 53 54	21		doi:10.1192/bjp.175.5.452
55 56	22	48.	Orgilés M, Fernández-Martínez I, Guillén-Riquelme A, et al. A systematic review of
57 58	23		the factor structure and reliability of the Spence Children's Anxiety Scale. J Affect
59 60	24		Disord 2016(190):333-340 doi:10.1016/j.jad.2015.09.055

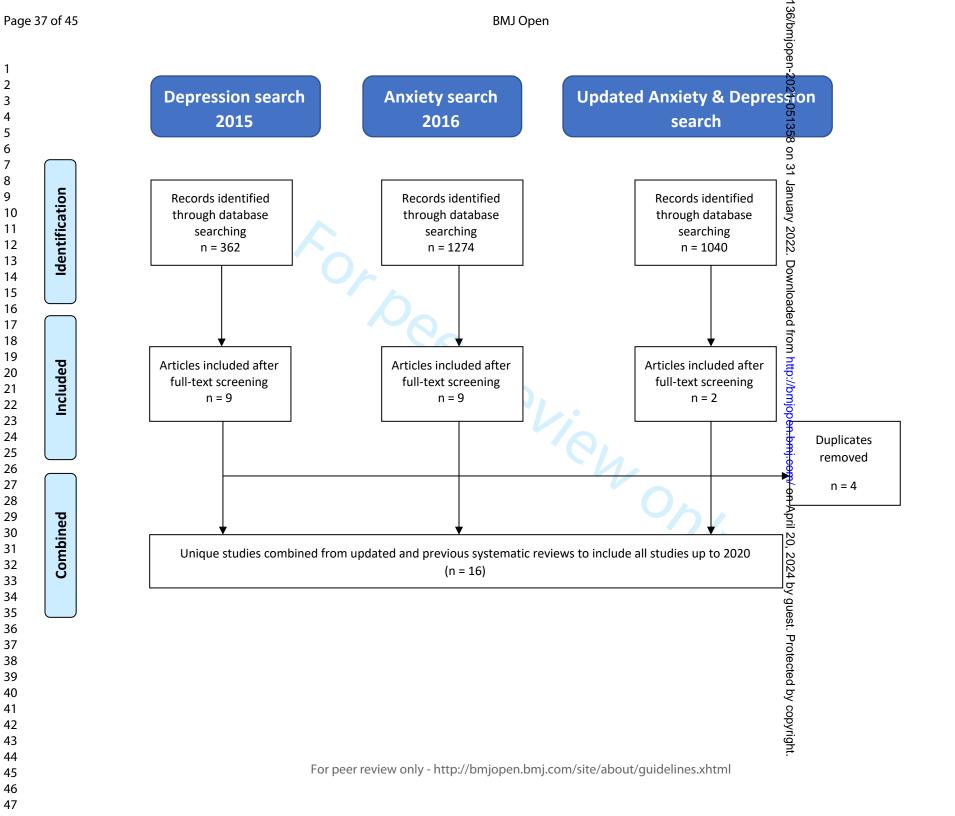
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3 4	1	49.	Anderson E, Loades M, Starbuck J, et al. CBT repackaged or a novel treatment? The
5 6 7	2		Lightning Process [®] compared with specialist medical care for paediatric Chronic
7 8 9	3		Fatigue Syndrome. Biomedicine, Health & Behavior 2021;1-20 doi:
10 11 12	4		10.1080/21641846.2021.1935373
13 14	5	50.	Kallesøe K, Schröder A, Wicksell R, et al. Feasibility of group-based acceptance and
15 16 17	6		commitment therapy for adolescents (AHEAD) with multiple functional somatic
18 19	7		syndromes: a pilot study. BMC Psychiatry 2020;20(1):457 doi:10.1186/s12888-020-
20 21 22	8		02862-z
23 24	9	51.	Ali A, Weiss T, Dutton A, et al. Mindfulness-Based Stress Reduction for Adolescents
25 26 27	10		with Functional Somatic Syndromes: A Pilot Cohort Study. J Pediatr 2017;183:184-
28 29	11		190 doi:10.1016/j.jpeds.2016.12.053
30 31 32	12	52.	Kluck BN, Junghans-Rutelonis AN, Jones AE, et al. Adolescent Chronic Fatigue and
33 34	13		Orthostatic Intolerance. Clinical Pediatrics 2017;56(1):85-89
35 36 37	14		doi:10.1177/0009922816644730
38 39	15		
40 41 42 43	16	FIGUR	RES AND TABLES LEGENDS
44 45	17	Figure	1: Flow chart for studies included in the systematic review; based on PRISMA guidelines
46 47 48	18	Figure	2: Flow chart of studies combined from updated review and previous reviews
49 50 51	19	Table	1: Inclusion criteria
52 53 54	20	Table :	2: Participant and study characteristics
55 56	21	Table	3: Summary of outcomes for symptoms of depression and anxiety and other relevant findings
57 58 59 60	22	for inc	luded studies





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

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3	19. Panic.tw
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6	20. exp Chronic Fatigue Syndrome/
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8	21. exp Anxiety Disorders/ or exp Social Phobia/ or exp Panic Disorder/ or exp Anxiety/ or exp
9	
10	Social Anxiety
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12	22. exp Separation Anxiety Disorder/ or Separation Anxiety/
13	
14 15	23. exp Generalized Anxiety Disorder
16	
17	24. exp Obsessive Compulsive Disorder
18	
19	25. exp Phobias/
20	
21	26. 4 or 5 or 6 or 7 or 20
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23	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
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25 26	28. 3 and 26 and 27
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28	29. Limit 28 to yr="2016-current"
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31 32	Search strategy for Depression searches:
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31 32 33 34 35	Search strategy for Depression searches: 1. (adolesc* or preadolesc* or pre-adolesc* or boy* or girl* or child* or infan* or preschool* or
31 32 33 34 35 36	
31 32 33 34 35 36 37	
31 32 33 34 35 36	 (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
31 32 33 34 35 36 37 38	1. (adolesc* or preadolesc* or pre-adolesc* or boy* or girl* or child* or infan* or preschool* or
31 32 33 34 35 36 37 38 39 40 41	 (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
31 32 33 34 35 36 37 38 39 40 41 42	 (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
31 32 33 34 35 36 37 38 39 40 41 42 43	 (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.
31 32 33 34 35 36 37 38 39 40 41 42 43 44	 (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
31 32 33 34 35 36 37 38 39 40 41 42 43 44	 (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.
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	 (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.
31 32 33 34 35 36 37 38 39 40 41 42 43 44	 (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. exp Adolescent/ or exp Child/ or exp Child, Preschool/ or exp Infant/ or exp Minors/ or exp
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47	 (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. exp Adolescent/ or exp Child/ or exp Child, Preschool/ or exp Infant/ or exp Minors/ or exp
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50	 (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. exp Adolescent/ or exp Child/ or exp Child, Preschool/ or exp Infant/ or exp Minors/ or exp Pediatrics/
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51	 (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. exp Adolescent/ or exp Child/ or exp Child, Preschool/ or exp Infant/ or exp Minors/ or exp Pediatrics/
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52	 (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. exp Adolescent/ or exp Child/ or exp Child, Preschool/ or exp Infant/ or exp Minors/ or exp Pediatrics/ 1 or 2
31 32 33 34 35 36 37 38 39 40 41 42 43 40 41 42 43 44 45 46 47 48 49 50 51 52 53	 (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. exp Adolescent/ or exp Child/ or exp Child, Preschool/ or exp Infant/ or exp Minors/ or exp Pediatrics/ 1 or 2
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54	 (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. exp Adolescent/ or exp Child/ or exp Child, Preschool/ or exp Infant/ or exp Minors/ or exp Pediatrics/ 1 or 2 chronic fatigue syndrome*.mp.
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55	 (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. exp Adolescent/ or exp Child/ or exp Child, Preschool/ or exp Infant/ or exp Minors/ or exp Pediatrics/ 1 or 2 chronic fatigue syndrome*.mp. exp Chronic Fatigue Syndrome
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54	 (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 puberty or teen* or young* or youth* or school* or high-school* or highschool* or sibling* or schoolchild* or school child* or children).tw. exp Adolescent/ or exp Child/ or exp Child, Preschool/ or exp Infant/ or exp Minors/ or exp Pediatrics/ 1 or 2 chronic fatigue syndrome*.mp.
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31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57	 (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. exp Adolescent/ or exp Child/ or exp Child, Preschool/ or exp Infant/ or exp Minors/ or exp Pediatrics/ 1 or 2 chronic fatigue syndrome*.mp. exp Chronic Fatigue Syndrome

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- 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. dysthymi*.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
- ent **19.** Limit 18 to yr = "2015 – current

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Appendix 2: Quality Assessment

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

	Did the study					<u> </u>	
	address a clearly focused issue? Was this the outcome of interest to this review?	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Confounding factors?	Py Follow-up of subjects complete enough and long enough?	Overall Rating using Cochrane risk of bias scale ROBINS-I (low/unclear/higl
Chalder et al (2002)	Yes, No.	Yes	Yes	Yes	Can't tell	Can't tell, yes	Unclear
Diaz-Caneja et al (2007)	Can't tell, No	Can't tell	Can't tell	Can't tell	Yes	Yes, no	High
Lloyd et al (2012); Rimes et al (2014)	Yes, No	Yes	Yes	Yes	Can't tell	Can't tell, yes	Unclear
Rimes et al (2007)	Yes, No	Yes	Yes	Yes	Can't tell	Can't tell, yes	Unclear
Van de Putte et al (2007)	Yes, No	Yes	Yes	Yes	Can't tell	Can't tell, yes	Unclear
Kawatani et al (2011)	Yes, No	Yes (Case control)	Yes	Yes	Can't tell	S No, Yes	High
	Yes, No	Yes (Case series)	No	No	Can't tell	i Yes, No	High*
Henderson (2014)	Yes, No	No (Case series)	No	No	Can't tell	No, Yes	High*
	Yes, No	Yes (Case series)	No	Yes		by the second se	High*
Rowe (2019)	No, No	No	Yes	No	No	မှု Yes, Yes	Unclear
(b) Randomised controlled tr	rials	Pro					
	Did the trial	Was the	Were patients,	Were the	Aside from the	The second secon	Overall Rating
	address a clearly	assignment of	healthcare	groups	experimental	patients who	using Cochrane
I						by cc	
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1 2 3 4 5 6 7		focused issue? Was this the outcome of interest to this review?	patients to treatments randomised?	professionals and research staff blinded?	similar at the start of the trial?	investigation, were the groups treated equally?	entered the trial properly accounted for at its conclusion?	risk of bias scale RoB 2 (low/unclear/high)
8 9 10	Nijhof et al (2012); Nijhof et al (2013)	Yes, no	Yes	No	Yes		Can't tell	Low
11 12	Rowe (1997)	Yes, no	Yes	Yes	Yes		Yes	Low
13 14	Wright et al (2005)	Yes. no	Yes	No	Yes	Yes	Can't tell	Low
15 16	Gordon et al (2010)	Yes, no	Yes	No (pts), No (HCPs), Yes (assessors)	Yes	Yes	Yes	Low
17 18	Crawley et al (2018)	Yes, no	Yes		Yes	Yes	³ Yes	Low
20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42						Yes	http://bmineer.hmi.com/ on April 20 2024 by quest Protected by convrict	5
43 44			For peer review o	nly - http://bmjopen.br	nj.com/site/abou	ıt/guidelines.xhtml		

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PRISMA 2009 Checklist

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PRISMA 2	2009	Checklist	
Section/topic	#	Checklist item	Reported on page #
TITLE	· · · · ·	<u> </u>	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT		uary vary	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
) Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS		tp://b	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Table 1 page 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
, Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and apy assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification gof whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
3 4 5		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	



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PRISMA 2009 Checklist

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1 2 3	PRISMA 20)09	Checklist	
4 5	Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	N/A
6 7		II	Page 1 of 2	
, 8 9	Section/topic	#	Checklist item	Reported on page #
1 1 12	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
13	Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	g N/A
10	RESULTS		o a a de	
17	Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	t 8
19 20 2	Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOs, follow-up period) and provide the citations.	d 9-10and Table 2
22	Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9
23 24 24	Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 4
26	Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of gonsistency.	N/A
27	Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-9
29	Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
30 31	DISCUSSION	<u> </u>		
32		24	Summarize the main findings including the strength of evidence for each main outcome; con $\frac{8}{4}$ der their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-18
34 35 36		25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., in complete retrieval of identified research, reporting bias).	17
37		26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
38	FUNDING	1		
4(4 ⁻	Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	e 20
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PRISMA

PRISMA 2009 Checklist

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1 2	PRISMA 2009 Checklist		136/bmjopen-2021	
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