BMJ Paediatrics Open

Do treatments for paediatric CFS/ME improve pain? A systematic review.

Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2019-000617
Article Type:	Original research
Date Submitted by the Author:	26-Nov-2019
Complete List of Authors:	Ascough, Caitlin; University of Bristol, Centre for Academic Child Health King, Hayley; University of Bristol, Centre for Academic Child Health Serafimova, Teona; University of Bristol, Centre for Academic Child Health Beasant, Lucy; University of Bristol, Centre for Academic Child Health Jackson, Sophie; University of Bristol, Centre for Academic Child Health Baldock, Luke; University of Bristol, Centre for Academic Child Health Pickering, Anthony; University of Bristol, School of Physiology, Pharmacology & Neuroscience Brooks, Jonathan; University of Bristol, School of Psychological Science Crawley, Esther; University of Bristol, Centre for Academic Child Health
Keywords:	Chronic Fatigue Syndrome, Pain

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Do treatments for paediatric CFS/ME improve pain?

A systematic review.

Caitlin Ascough BMBS BMedSci[a], Hayley King MB ChB MSc[a], Teona Serafimova MBBS MSc[a], Lucy Beasant PhD[a], Sophie Jackson BMBS BMedSci[a], Luke Baldock[a], Anthony Edward Pickering MB ChB BSc PhD FRCA[b], Jonathan C.W. Brooks BSc MSc PhD[c] and Esther Crawley MBBCh, PhD[a]

Affiliations: [a]Centre for Academic Child Health, University of Bristol, Bristol, UK, BS8 1NU; and [b] School of Physiology, Pharmacology & Neuroscience, University of Bristol, Bristol, UK, BS8 1TD; and [c]School of Psychological Science, Priory Road, Bristol, UK, BS8 1TU

Address correspondence to: Dr Caitlin Ascough, Centre for Academic Child Health, University of Bristol, Bristol, BS8 1NU. Email: caitlin.ascough@bristol.ac.uk. Telephone: 0117 42 83072

Abbreviations: CFS - chronic fatigue syndrome; ME – myalgic encephalomyelitis, RCT – randomised controlled trial

Key Words: Chronic Fatigue Syndrome, Pain

Systematic Review Registration Number: CRD42019117540

Word count: 2304

ABSTRACT

Background

Paediatric CFS/ME is common (prevalence 1-2%). Two thirds of children experience moderate or severe pain, which is associated with increased fatigue and poorer physical function. However, we do not know if treatment for CFS/ME improves pain.

Objective

Identify whether specialist treatment of paediatric CFS/ME improves pain.

Methods

We conducted a detailed search in MEDLINE, EMBASE, PsycINFO, and the Cochrane Library. Two researchers independently screened texts published since 1994 with no language restrictions. Inclusion criteria were (1) RCTs & observational studies; (2) Participants aged <19 years with CFS/ME; (3) Measure of pain before and after an intervention.

Results

Of 1898 papers screened, 26 studies investigated treatment for paediatric CFS/ME, 19 of which did not measure pain at any time point. Only five treatment studies measured pain at baseline and follow-up and were included in this review. None of the interventions were specifically targeted at treating pain. Of the included studies, two showed no improvement in pain scores, one suggested an improvement in one subgroup, and two studies identified improvements in pain measures in 'recovered' patients compared to 'non-recovered patients'.

Conclusions

Despite the impact of pain in children with CFS/ME surprisingly few treatment studies measured pain. In those that did measure pain, there is limited evidence that treatment helps improve pain scores. However, patients who recover, appear to have less pain than those who do not recover. More studies are needed to determine if pain in paediatric CFS/ME requires a specific treatment approach, with a particular focus on patients who do not recover following initial treatment.

What is already known on this topic

- CFS/ME is prevalent (1-2%) in adolescents and nearly two thirds of patients report moderate or severe pain.
- Pain is associated with worse fatigue and poorer physical function in adolescents with CFS/ME.

What this study adds

- Despite the prevalence and impact of pain in children with CFS/ME few treatment studies have measured pain as an outcome.
- There is insufficient evidence to suggest that the treatment of fatigue also improves pain in paediatric CFS/ME.
- Patients who recover from CFS/ME appear to have less pain at follow-up than those who do not recover.

INTRODUCTION

Paediatric chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) is relatively common and causes significant suffering for children and their families.[1-3] It affects 1-2% of UK adolescents and is associated with low mood, poor quality of life, and a mean total loss of school attendance of one year.[4, 5] In addition to fatigue, children and young people experience a range of symptoms including headaches, muscle and joint pain, and sore throats.[6]

Pain is a common and disabling symptom in children with CFS/ME. Over 60% of CFS/ME children experience moderate or severe pain (as evidenced by a pain visual analogue scale >40/100) and this is associated with worse fatigue and poorer physical function.[6, 7] This is much higher than in healthy children where between 3.6% and 16.6% will describe severe pain [8]. In adult patients with CFS/ME pain is associated with worse outcomes.[7, 9]

However, the aetiology and pathophysiology of pain in this population is poorly understood and current treatment approaches do not target pain.[10, 11] This systematic review aimed to identify what interventions, if any, have been used to treat pain in children with CFS/ME, and to establish whether interventions used to treat paediatric CFS/ME change pain scores at follow-up.

METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement and the Cochrane Handbook 5.1.[12, 13] The protocol was prospectively registered on Prospero (https://www.crd.york.ac.uk/prospero) under the registration number CRD42019117540.

Search Strategy

We performed a detailed literature search in MEDLINE, EMBASE, PsycINFO, and the Cochrane library. The search was adapted appropriately for each database and there were no language restrictions. We searched trial registration websites for unpublished trials and hand searched reference lists of all included studies. Full details of the search strategy can be seen in supplementary file 1. We searched only for studies published since 1994, as this is when the CDC definition of CFS/ME was introduced[14], and included articles published until 24th January 2019.

Eligibility Criteria

We included randomised controlled trials and observational studies that investigated a treatment or intervention in patients <19 years of age with CFS/ME. A diagnosis of CFS/ME was determined according to NICE (2007)[11], CDC (Fukuda 1994, 2004)[14] or Oxford (1991)[15] criteria. Studies were eligible if they described a measure of pain (quantitative, qualitative, or mixed methods) before and after an intervention. Studies that described self-reported symptoms such as 'abdominal discomfort' and 'muscle aches' were excluded unless they also included an objective or subjective measure of pain.

Study Selection

Two researchers independently screened the abstracts of all studies generated from the literature search. Any discrepancies were discussed and resolved, if necessary, with a third reviewer. The researchers then independently reviewed the full texts of all potentially eligible studies. To identify all available evidence, we reviewed the full text of all studies that described interventions in paediatric CFS/ME. Any studies involving patients both above and below 19 years of age were also reviewed at full text to establish if there was separate data for patients under 19 years.

Data Extraction

Two researchers extracted the data from all studies that met the inclusion criteria using a purpose-designed data extraction form. We collected data on study characteristics (study type, country, sample size), intervention characteristics (type, length of course), pain characteristics (type, severity, pain measure used) and change in pain measure from baseline to follow-up.

Assessment of Risk of Bias

The risk of bias was evaluated in all studies for outcomes relating to pain. The four RCTs were evaluated using the Revised Cochrane risk of bias tool for randomised trials (RoB 2).[16] One study reported pain and assessment in a longitudinal cohort derived from a randomised controlled trial. We chose to evaluate this using the Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool.[17] Assessment was conducted by two independent assessors, who resolved disagreements by discussion.

Data Synthesis

We performed a descriptive analysis of the results, taking into account the methodological quality of the evidence. There was substantial heterogeneity between studies, and we were therefore unable to perform a meta-analysis.

RESULTS

Summary of Included Studies

Figure 1 describes the search results and study selection process. The search identified 1898 studies of which, we reviewed 107 full text papers for eligibility. Six papers were eligible for inclusion with data from five studies.[18-23] Papers were considered to be ineligible because they did not include: CFS/ME patients <19 years of age (n=65); measure pain (n=19); measure pain at both time points (n=1); describe an intervention (n=2); or because they were not published papers of RCTs/observational studies (n=14).

Table 1 details the characteristics of the included studies. Of these studies, four were randomised controlled trials and one was an observational study. The total sample size consisted of 414 adolescents aged between 10 and 18 years with a diagnosis of CFS/ME.

Table 1: Study Characteristics

Author, Year	Country	Study Design	Intervention	Sample at baseline (n)	Sample at follow-up (n, % baseline)	Mean age (range)	Follow-up
Crawley, 2013 2018	UK	RCT	Specialist care and Lightning Process vs specialist care alone	100	61 (61%) 59 (59%)	14	6 months 12 months
Knoop, 2007 [Analysis of data from Stulemeijer, 2005]	Netherlands	RCT	CBT vs. waiting list	69	66 (96%)	15.6 (10-17.2)	5 months
Nijhof, 2013	Netherlands	Cohort Study	CBT (internet-delivered or face-to-face)	83	72 (87%)	15.8 (12-18)	12 months
Sulheim, 2013	Norway	RCT	Low dose clonidine vs. placebo	120	103 (86%)	15.4 (12-18)	8 weeks 30 weeks
Van Geelen, 2011	Netherlands	RCT	6 sessions self-confrontation method vs. 12 sessions self-confrontation method	42	35 (83%)	16.5 (N/A)	4 months 14 months

RCT, randomised controlled trial; CBT, cognitive behavioural therapy

Pain Measurement in Treatment Studies of Paediatric CFS/ME

In total, we identified 26 randomised controlled trials or observational studies that investigated treatment interventions in paediatric CFS/ME. However, 19 of these studies did not measure pain at any timepoint,[24-43] and two studies measured pain at a single timepoint only.[10, 44] They were therefore excluded from this review. Four of the studies included the prevalence of self-reported symptoms e.g. muscle aches, abdominal discomfort, and tender lymph nodes, but did not include additional objective or subjective measures of pain severity.[24, 25, 31, 41] The remaining studies did not discuss pain at all.

Within the included studies, the pain measures used were heterogenous. Three of the five studies used validated pain questionnaires: a pain Visual Analogue Scale,[45] CHQ-87 Bodily Pain Subscale,[46] and Brief Pain Inventory.[47] The remaining two studies, conducted at the same centre, used a mean Daily Observed Pain (DOP) score calculated from a Likert scale of 1 (no pain) to 4 (severe pain) recorded four times a day for twelve consecutive days. Only one study attempted to measure pain using algometry, in addition to subjective measures.[21]

Interventions Used to Treat Pain in Paediatric CFS/ME

The included studies described a range of interventions used to treat children with CFS/ME (Table 2). However, none of the interventions were specifically targeted at treating pain.

All treatments were delivered in the outpatient setting. One of the studies investigated a pharmacological intervention (low dose clonidine)[22] and four studies described behavioural interventions.[19-21, 23] Behavioural interventions used were heterogenous. Two of the trials used cognitive behavioural therapy (CBT), however the structure of the treatment varied. CBT was delivered as both a face-to-face intervention and an online intervention, and the number of sessions ranged from 10 to 22. One trial investigated the Lightning Process which is developed from life coaching and neurolinguistics programming, and another used a programme of self-confrontation, a method used to 'assess and change individual life stories through narrative self-investigation'[23].

Table 2: Study Results

Author, Year	Description of intervention	Intervention targeted at treating pain?	Pain measure used	Change in pain score following intervention
Crawley, 2013 2018	Lightning process course of 3x 4-hour sessions on consecutive days in small groups.	No	Pain visual analogue scale	Intervention group vs. control group -9.3 (-21.1 to 2.6) p=0.124 at 6 months -6.5 (-19.4 to 6.5) p=0.321 at 12 months
Knoop, 2007 [Analysis of data from Stulemeijer, 2005]	CBT 10 sessions in 5 months Two CBT protocols were used. One was for patients with a passive physical activity pattern and another for relatively active patients.	No	Mean daily observed pain score (DOP) calculated from a Likert scale of 1 (no pain) to 4 (very severe pain) done 4x per day for 12 days. % of patients with pain level within range of healthy controls defined as DOP score <2.3	Change in DOP score of CBT group vs waiting list control -2.21 (SD = 3.85) vs -0.36 (SD = 2.19) T=-2.44 p=0.04 % of participants with DOP score within range of healthy controls in CBT group vs waiting list group 56% vs 29% (χ^2 4.38, d.f. = 1, p=0.04)
Nijhof, 2013	CBT 6-month course of either internet-based (FITNET) or face-to-face CBT	No	Mean daily observed pain score (DOP) calculated from a Likert scale of 1 (no pain) to 4 (very severe pain) done 4x per day for 12 days Average pressure pain threshold (kg)	Recovered group vs non-recovered group Average DOP -2.9 (-4.2 to -1.6) p=<0.001 Average pain threshold +1.3 (0.2 to 2.2) p=0.019
Sulheim, 2013	9 weeks daily oral clonidine hydrochloride	No	Brief Pain Inventory average pain score	Clonidine group vs placebo group 0.5 (-0.16 to 1.16), p=0.14 at week 8 0.4 (-0.4 to 1.1), p=0.32 at week 30
Van Geelen, 2011	Self-confrontation method 6 or 12 sessions	No	Bodily pain subscale of CHQ-87	Change in bodily pain score at 4 months 6 sessions 11.8 (SD 28.1) p= >0.05 12 sessions 22.7 (SD 22.5) p= <0.05 Healthy controls 4.0 (SD 13.5) p= >0.05

CBT, cognitive behavioural therapy; DOP, daily observed pain score

Change in Pain Scores Following Treatment

The results of each study are presented in Table 2. Two RCTs showed no improvement in pain scores following treatment.[19, 22] One of these trials, conducted in a sample of 100 patients from the UK, investigated the effectiveness of the Lightning Process in addition to specialist medical care compared to specialist medical care alone. In this trial, fatigue, anxiety, depression, and school attendance improved. Pain, measured on a visual analogue scale (0 – 100) was similar between assessment and follow up at 6-months (adjusted difference in means -9.3 (95% CI (-21.1 – 2.6), p 0.124).[19] The second trial investigated treatment with low dose clonidine and found no change in scores on a Brief Pain Inventory compared to a placebo.[22]

The remaining three studies reported some improvement in pain measures.[20, 21, 23] Two of the studies compared DOP scores in patients that were deemed to have 'recovered' from CFS/ME with those that had 'not recovered'.[20, 21] Different definitions of recovery were used in each study. One of the largest trials to date enrolled a subgroup of patients from the FITNET study in the Netherlands and reported an association between "recovery" from CFS/ME and improved pressure pain thresholds and DOP scores. All participants were treated with 6 months of internet-based or face-to-face CBT and follow-up measures were obtained at 12 months. After the trial was reported, the authors submitted an additional, peer reviewed, letter to the editor evaluating pain. Here, they compared pain levels in those who had recovered to those who had not recovered. Within this, they described higher mean pressure pain thresholds and lower mean DOP scores in 'recovered' patients (39 of 72 patients) compared to 'non recovered' patients. However, due to a relatively small sample size, confidence intervals were large, and the study was not controlled.[21]

Another study presented a post-hoc analysis of data that had not previously been reported in an original RCT, comparing CBT to a 'waiting list' control. Following 10 sessions of CBT 21/32 patients were classed as 'recovered' and had lower mean DOP scores than 'non-recovered' patients. This finding was replicated when comparing patients receiving CBT with the waiting list control group. However, the mean DOP score in adolescents, who had completed the course of CBT but were not classed as 'recovered', increased at 6-month follow-up.[20]

The final study assessed a 'self-confrontation method' of behavioural therapy that is not used in the NHS. Patients who received 12 sessions of self-confrontation exhibited improved scores on a Bodily Pain Subscale at 4 months, whereas patients who received 6 sessions had no significant change. Sample sizes in each group were small and confidence intervals were large [23].

Risk of Bias

Figure 2 describes the risk of bias in the RCTs. One was deemed low risk of bias and one was deemed moderate risk of bias. The remaining two were at high risk of bias following assessment. The ROBINS-I tool suggested the longitudinal cohort study following an RCT was at high risk of bias.

DISCUSSION

This is the first systematic review investigating interventions used to treat pain in paediatric CFS/ME and whether they change pain scores at follow-up. We did not identify any interventions that specifically targeted pain. Surprisingly few of the CFS/ME intervention studies (<20%) identified measured pain despite the fact that pain is one of the most common and important Patient Reported Outcomes experienced by children with CFS/ME. In those studies that did measure pain, there is limited evidence that specialist CFS/ME treatment improves pain scores. However, in those that do recover, pain is less compared to those that do not recover.

Strengths and limitations

Strengths of this study include its comprehensive search strategy and rigorous study selection process. We ran a detailed search in four databases, hand searched reference lists for additional papers and, in order to reduce the risk of publication bias, hand searched trial registration websites to identify unpublished studies. We included papers that were not written in the English language. During screening two independent researchers reviewed the full texts of all treatment studies in children with CFS/ME to ensure that we identified any studies in which pain was measured as a secondary outcome but not discussed in the abstract.

This review has a number of limitations. Substantial heterogeneity in the pain measures used and intervention types made comparison between studies challenging and we were unable to carry out a meta-analysis. Four studies were excluded because the secondary outcomes measured were ambiguous and it was not possible to confirm the presence or degree of pain. This included self-reported symptoms such as 'abdominal discomfort', 'muscle aches', and 'tender lymph nodes'.

In addition to this, none of the studies reported data on the use of pain medications by participants. It is therefore unclear to what extent pain medications may be responsible for improvements in pain scores. Further, one of the studies involved clonidine as an intervention. While this was employed to attenuate sympathetic and adrenocortical hyperactivity, it is also known to have an analgesic action.

One study compared different durations of the same intervention (self-confrontation method). Improved pain scores cited following 12 self-confrontation sessions could be a consequence of an increased numbers of sessions or represent the natural time course of the pain.

Almost all the studies were conducted outside of the UK and therefore the findings may not be applicable to the NHS. All patients were referred from secondary care and therefore the results may not be generalisable to patients looked after in a primary care setting. The generalisability of the findings is also limited by the fact that two of the studies excluded patients with psychiatric comorbidities and another study only included patients with mild or moderate CFS/ME.

We were also unable to locate one full text paper despite contacting the author directly, and at the time of publication there are two ongoing randomised controlled treatment trials in paediatric CFS/ME [48, 49] for which results are not yet available.

CONCLUSION

Despite the prevalence and impact of pain in children with CFS/ME, it is surprising how few treatment studies have measured pain. There is limited evidence that current treatments improve pain in paediatric CFS/ME, especially in patients who do not recover following initial treatment. Future research should investigate appropriate methods to measure pain in children with CFS/ME. This will enable large, well-powered RCTs investigating different treatment approaches to pain in this population.

FUNDING

This work was supported by the UKFPO Academic Foundation Programme.

PATIENT AND PUBLIC INVOLVEMENT

A young person's CFS/ME patient advisory group identified pain in fatigue as an important topic for further research.

CONFLICTS OF INTEREST

One of the authors of this systematic review (EC) was also an author of one of the included papers. However, to avoid a conflict of interest, EC was not involved in the study selection, data extraction, or assessment of risk of bias.

AUTHORS CONTRIBUTIONS

CA conducted the review and wrote the first draft of the paper. CA, HK, LB and SJ reviewed titles and abstracts and extracted data. TS and LB completed the risk of bias assessments. TP and JB advised on the interpretation of pain scores. The idea for the study was ECs. All the authors reviewed drafts of the paper and all approved the final submitted version.

REFERENCES

1. Rangel L, Garralda ME, Levin M, Roberts H. The course of severe chronic fatigue syndrome in childhood. JRSocMed. 2000;93(3):129-34.
2. Crawley E. The epidemiology of chronic fatigue syndrome/myalgic encephalitis in children. Arch Dis Child. 2014;99(2):171-4.
3. Parslow R, Patel A, Beasant L, Haywood K, Johnson D, Crawley E. What matters to children with CFS/ME? A conceptual model as the first stage in developing a PROM. Archives of disease in childhood. 2015;100(12):1141-7.
4. Crawley E, Sterne JA. Association between school absence and physical function in paediatric chronic fatigue syndrome/myalgic encephalopathy. Arch Dis Child. 2009;94(10):752-6.
5. Crawley EM, Emond AM, Sterne JA. Unidentified Chronic Fatigue Syndrome/myalgic encephalomyelitis (CFS/ME) is a major cause of school absence: surveillance outcomes from school-based clinics. BMJ Open. 2011;1(2):e000252.
6. May M, Emond A, Crawley E. Phenotypes of chronic fatigue syndrome in children and young people. Arch Dis Child. 2010;95(4):245-9.
7. Collin SM, Nuevo R, van de Putte EM, Nijhof SL, Crawley E. Chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) is different in children compared to in adults: a study of UK and Dutch clinical cohorts. BMJ open. 2015;5(10):e008830.
8. Perquin CW, Hazebroek-Kampschreur AA, Hunfeld JA, Bohnen AM, van Suijlekom-Smit LW, Passchier J, et al. Pain in children and adolescents: a common experience. Pain. 2000;87(1):51-8.
9. Crawley E, Collin SM, White PD, Rimes K, Sterne JA, May MT, et al. Treatment outcome in adults with chronic fatigue syndrome: a prospective study in England based on the CFS/ME National Outcomes Database. QJM. 2013;106(6):555-65.
10. Winger A, Kvarstein G, Wyller VB, Sulheim D, Fagermoen E, Smastuen MC, et al. Pain and pressure pain thresholds in adolescents with chronic fatigue syndrome and healthy controls: A cross-sectional study. 2014;4(10):e005920.
11. NICE. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): Diagnosis and management of CFS/ME in adults and children (NICE guidelines CG53). London; 2007 2007. Report No.: CG53.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7).
13. Handbook for Systematic Reviews of Interventions, (2011).
14. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994;121(12):953-9.
15. Sharpe MC, Archard LC, Banatvala JE, Borysiewicz LK, Clare AW, David A, et al. A report--chronic fatigue syndrome: guidelines for research. J R Soc Med. 1991;84(2):118-21.
16. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj-Brit Med J. 2019;366.
17. Sterne JAC, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. Bmj-Brit Med J. 2016;355.
18. Crawley E, Mills N, Hollingworth W, Deans Z, Sterne JA, Donovan JL, et al. Comparing specialist medical care with specialist medical care plus the Lightning Process for chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME): study protocol for a randomised controlled trial (SMILE Trial). Trials. 2013;14:444.
19. Crawley EM, Gaunt DM, Garfield K, Hollingworth W, Sterne JAC, Beasant L, et al. Clinical and cost-effectiveness of the Lightning Process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial. Arch Dis Child. 2017.

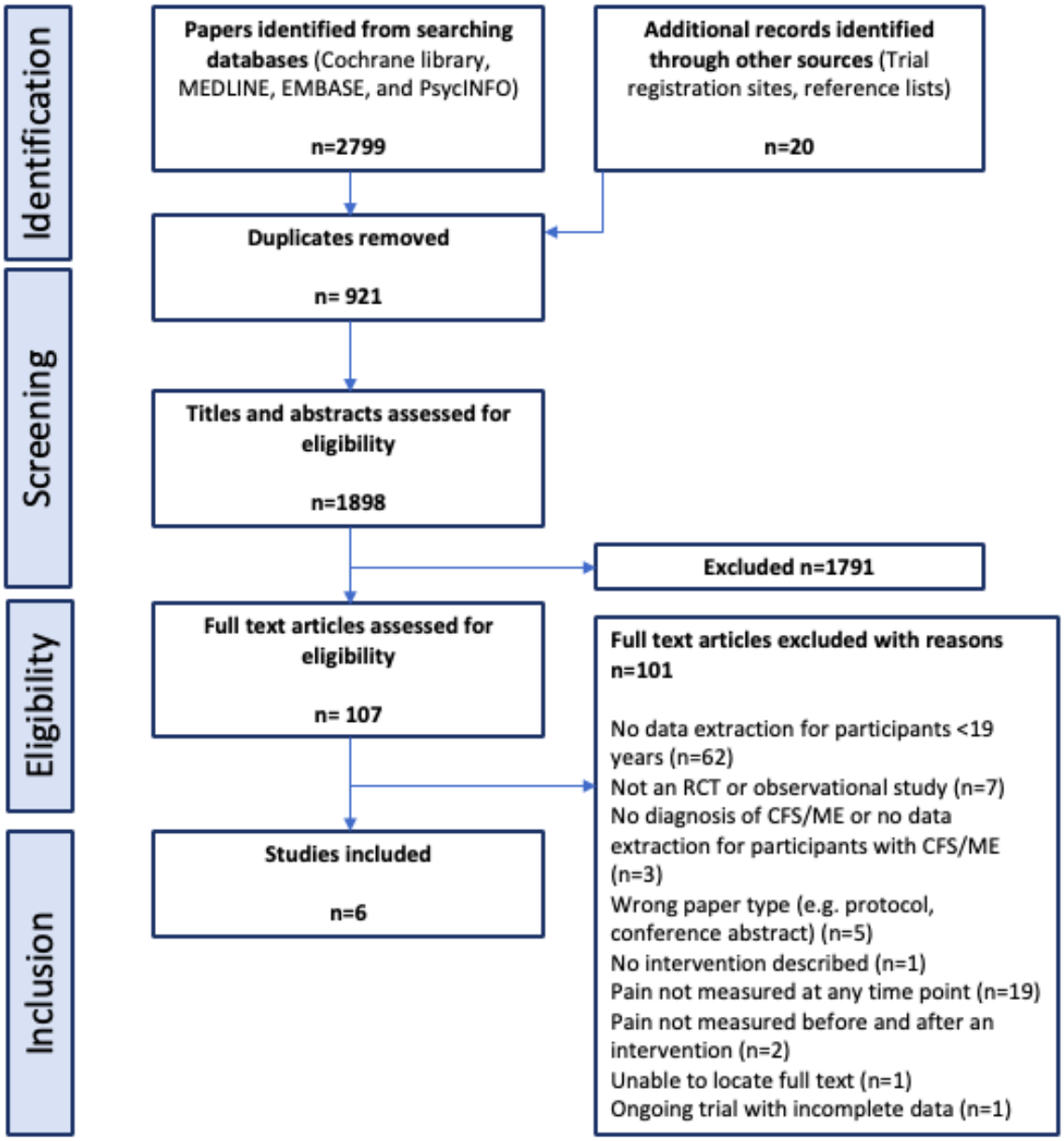
20. Knoop H, Stulemeijer M, Prins JB, van der Meer JW, Bleijenberg G. Is cognitive behaviour therapy for chronic fatigue syndrome also effective for pain symptoms? Behav Res Ther. 2007;45(9):2034-43.
21. Nijhof SL, Priesterbach LP, Bleijenberg G, Engelbert RH, van de Putte EM. Functional improvement is accompanied by reduced pain in adolescent chronic fatigue syndrome. Pain Med. 2013;14(9):1435-8.
22. Sulheim D, Fagermoen E, Winger A, Andersen AM, Godang K, Muller F, et al. Disease mechanisms and clonidine treatment in adolescent chronic fatigue syndrome: a combined cross-sectional and randomized clinical trial. JAMA Pediatr. 2014;168(4):351-60.
23. van Geelen SM, Fuchs CE, Sinnema G, van de Putte EM, van GR, Hermans HJ, et al. Self-investigation in adolescent chronic fatigue syndrome: narrative changes and health improvement. PatientEduc Couns. 2011;83(2):227-33.
24. Al-Haggar M S, Al-Naggar Z A, Abdel-Salam M A. Biofeedback and cognitive behavioural therapy for Egypian adolescents suffering from chronic fatigue syndrome. . J Paediatric Neurol. 2006;4:8.
25. Ashby B, Wright B, Jordan J. Chronic Fatigue Syndrome: An Evaluation of a Community Based Management Programme for Adolescents and their Families. Child and Adolescent Mental Health. 2006;11(1):13-8.
26. Chalder T, Tong J, Deary V. Family cognitive behaviour therapy for chronic fatigue syndrome: an uncontrolled study. Arch Dis Child. 2002;86(2):95-7.
27. Chalder T, Deary V, Husain K, Walwyn R. Family-focused cognitive behaviour therapy versus psycho-education for chronic fatigue syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. Psychol Med. 2010;40(8):1269-79.
28. Gordon B, Lubitz L. Promising outcomes of an adolescent chronic fatigue syndrome inpatient programme. JPaediatrChild Health. 2009;45(5):286-90.
29. Gordon BA, Knapman LM, Lubitz L. Graduated exercise training and progressive resistance training in adolescents with chronic fatigue syndrome: a randomized controlled pilot study. Clin Rehabil. 2010;24(12):1072-9.
30. Khawaja S, Van Boxel P. Chronic fatigue syndrome in childhood: seven-year follow-up study. Psychiatric Bulletin. 1998;22(4):198-202.
31. Knoop H, Stulemeijer M, de Jong LW, Fiselier TJ, Bleijenberg G. Efficacy of cognitive behavioral therapy for adolescents with chronic fatigue syndrome: long-term follow-up of a randomized, controlled trial. Pediatrics. 2008;121(3):e619-e25.
32. Lim A, Lubitz L. Chronic fatigue syndrome: successful outcome of an intensive inpatient programme. J Paediatr Child Health. 2002;38(3):295-9.
33. Lloyd S, Chalder T, Rimes KA. Family-focused cognitive behaviour therapy versus psycho-education for adolescents with chronic fatigue syndrome: Long-term follow-up of an RCT. BehavResTher. 2012;50(11):719-25.
34. Lloyd S, Chalder T, Sallis HM, Rimes KA. Telephone-based guided self-help for adolescents with chronic fatigue syndrome: A non-randomised cohort study. BehavResTher. 2012;50(1):304-12.
35. Loades ME, Chalder T. Same, Same But Different? Cognitive Behavioural Treatment Approaches for Paediatric CFS/ME and Depression - CORRIGENDUM. Behav Cogn Psychother. 2017;45(4):432.
36. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. Lancet. 2012;379(9824):1412-8.
37. Nijhof SL, Priesterbach LP, Uiterwaal CS, Bleijenberg G, Kimpen JL, van de Putte EM. Internet-based therapy for adolescents with chronic fatigue syndrome: long-term follow-up. Pediatrics. 2013;131(6):e1788-95.
38. Rimes KA, Papadopoulos AS, Cleare AJ, Chalder T. Cortisol output in adolescents with chronic fatigue syndrome: Pilot study on the comparison with healthy adolescents and change after cognitive behavioural guided self-help treatment. J Psychosom Res. 2014;77(5):409-14.

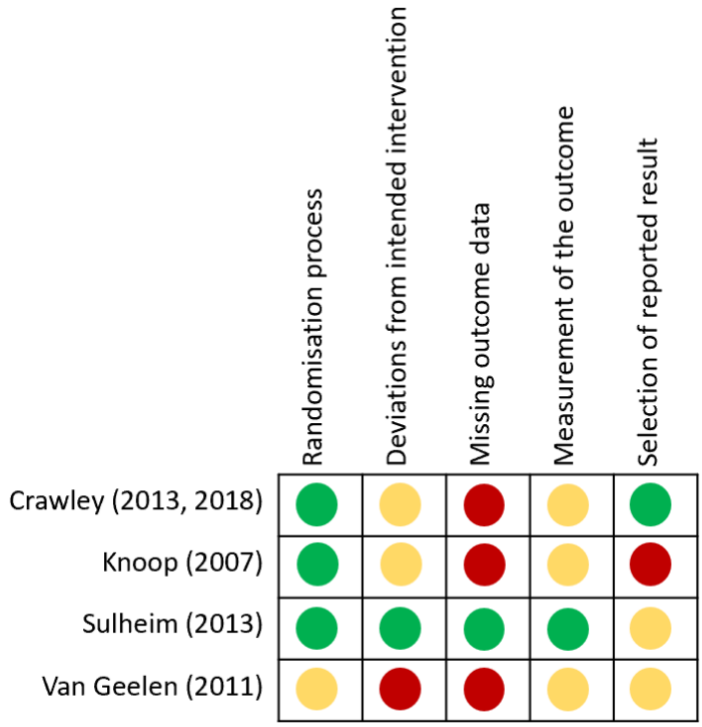
39. Rowe KS. Double-blind randomized controlled trial to assess the efficacy of intravenous gammaglobulin for the management of chronic fatigue syndrome in adolescents. J PsychiatrRes. 1997;31(1):133-47.
40. Rowe KSJJoCFS. Five-year follow-up of young people with chronic fatigue syndrome following the double blind randomised controlled intravenous gammaglobulin trial. 1999;5(3-4):97-107.
41. Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ. 2005;330(7481):14.
42. Viner R, Gregorowski A, Wine C, Bladen M, Fisher D, Miller M, et al. Outpatient rehabilitative treatment of chronic fatigue syndrome (CFS/ME). ArchDisChild. 2004;89(7):615-9.
43. Wright B, Ashby B, Beverley D, Calvert E, Jordan J, Miles J, et al. A feasibility study comparing two treatment approaches for chronic fatigue syndrome in adolescents. Arch Dis Child. 2005;90(4):369-72.
44. van Geelen SM, Bakker RJ, Kuis W, van de Putte EM. Adolescent chronic fatigue syndrome: a follow-up study. Arch Pediatr Adolesc Med. 2010;164(9):810-4.
45. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain. 1983;17(1):45-56.
46. Witherspoon D, Drotar D, Greenley R, Zebracki K, Palermo T, Burant C. Exploratory and confirmatory factor analyses of the Child Health Questionnaire-Child Form 87 (CHQ-CF87) with children chronic conditions and healthy children. J Dev Behav Pediatr. 2006;27(5):448-.
47. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994;23(2):129-38.
48. Nijhof SL, Bleijenberg G, Uiterwaal CSPM, Kimpen JLL, van de Putte EM. Fatigue In Teenagers on the interNET - The FITNET Trial. A randomized clinical trial of web-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome: study protocol. [ISRCTN59878666]. BMC Neurol. 2011;11:23.
49. Brigden A, Beasant L, Hollingworth W, Metcalfe C, Gaunt D, Mills N, et al. Managed Activity Graded Exercise iN Teenagers and pre-Adolescents (MAGENTA) feasibility randomised controlled trial: study protocol. BMJ open. 2016;6(e011255).

FIGURE LEGENDS

Figure 1. PRISMA flow diagram detailing the study selection process.

Figure 2. Assessment of risk of bias using the Revised Cochrane Risk of Bias Tool for Randomised Trials (RoB 2).[16]





Appendix 1: Search Strategy

MEDLINE/EMBASE

Paediatric

#1 exp Adolescent/
#2 exp Child/
#3 exp Child, Preschool/
#4 exp Infant/
#5 exp Minors/
#6 exp Pediatric/
#7 (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.

CFS/ME

#8 exp Fatigue Syndrome, Chronic/
#9 Chronic Fatigue Syndrome.tw
#10 myalgic encephal*.tw.
#11 CFS.tw
#12 fatigue syndrome*.mp.
#13 chronic fatigue syndrome*.mp.
#14 myalgic encephal*.mp.

Randomised control trial/observational

#15 Clinical Trial/
#16 Controlled Clinical Trial/
#17 Randomized Controlled Trial/
#18 controlled clinical trial.mp
#19 randomi?ed control* trial.mp
#20 (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).mp
#21 placebo*.mp
#22 trial.mp
#23 (control* adj3 (trial* or study or studies)).mp
#24 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp
#25 ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).mp
#26 Clinical Study/
#27 Feasibility Studies/
#28 Observational study/
#29 study.mp

#30 (#1 or #2 or #3 or #4 or #5 or #6 or #7)
#31 (#8 or #9 or #10 or #11 or #12 or #13 or #14)
#32 (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29)
#33 (#30 and #31 and #32)
#34 (Limit #32 to yr=’1994-current

BMJ Paediatrics Open

Interventions to treat pain in paediatric CFS/ME: A systematic review

Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2019-000617.R1
Article Type:	Original research
Date Submitted by the Author:	06-Jan-2020
Complete List of Authors:	Ascough, Caitlin; University of Bristol, Centre for Academic Child Health King, Hayley; University of Bristol, Centre for Academic Child Health Serafimova, Teona; University of Bristol, Centre for Academic Child Health Beasant, Lucy; University of Bristol, Centre for Academic Child Health Jackson, Sophie; University of Bristol, Centre for Academic Child Health Baldock, Luke; University of Bristol, Centre for Academic Child Health Pickering, Anthony; University of Bristol, School of Physiology, Pharmacology & Neuroscience Brooks, Jonathan; University of Bristol, School of Psychological Science Crawley, Esther; University of Bristol, Centre for Academic Child Health
Keywords:	Chronic Fatigue Syndrome, Pain

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Interventions to treat pain in paediatric CFS/ME: A systematic review

Caitlin Ascough BMBS BMedSci[a], Hayley King MB ChB MSc[a], Teona Serafimova MBBS MSc[a], Lucy Beasant PhD[a], Sophie Jackson BMBS BMedSci[a], Luke Baldock[a], Anthony Edward Pickering MB ChB BSc PhD FRCA[b], Jonathan C.W. Brooks BSc MSc PhD[c] and Esther Crawley MBBCh, PhD[a]

Affiliations: [a]Centre for Academic Child Health, University of Bristol, Bristol, UK, BS8 1NU; and [b] School of Physiology, Pharmacology & Neuroscience, University of Bristol, Bristol, UK, BS8 1TD; and [c]School of Psychological Science, Priory Road, Bristol, UK, BS8 1TU

Address correspondence to: Dr Caitlin Ascough, Centre for Academic Child Health, University of Bristol, Bristol, BS8 1NU. Email: caitlin.ascough@bristol.ac.uk. Telephone: 0117 42 83072

Abbreviations: CFS - chronic fatigue syndrome; ME – myalgic encephalomyelitis, RCT – randomised controlled trial

Key Words: Chronic Fatigue Syndrome, Pain

Systematic Review Registration Number: CRD42019117540

Word count: 2496

ABSTRACT

Background

Paediatric CFS/ME is common (prevalence 1-2%). Two thirds of children experience moderate or severe pain, which is associated with increased fatigue and poorer physical function. However, we do not know if treatment for CFS/ME improves pain.

Objective

Identify whether specialist treatment of paediatric CFS/ME improves pain.

Methods

We conducted a detailed search in MEDLINE, EMBASE, PsycINFO, and the Cochrane Library. Two researchers independently screened texts published between 1994 and 24th January 2019 with no language restrictions. Inclusion criteria were (1) RCTs & observational studies; (2) Participants aged <19 years with CFS/ME; (3) Measure of pain before and after an intervention.

Results

Of 1898 papers screened, 26 studies investigated treatment for paediatric CFS/ME, 19 of which did not measure pain at any time point. Only five treatment studies measured pain at baseline and follow-up and were included in this review. None of the interventions were specifically targeted at treating pain. Of the included studies, two showed no improvement in pain scores, one suggested an improvement in one subgroup, and two studies identified improvements in pain measures in 'recovered' patients compared to 'non-recovered patients'.

Conclusions

Despite the prevalence and impact of pain in children with CFS/ME surprisingly few treatment studies measured pain. In those that did measure pain, the treatments used focused on overall management of CFS/ME and we identified no treatments that were targeted specifically at managing pain. There is limited evidence that treatment helps improve pain scores. However, patients who recover, appear to have less pain than those who do not recover.

More studies are needed to determine if pain in paediatric CFS/ME requires a specific treatment approach, with a particular focus on patients who do not recover following initial treatment.

What is already known on this topic

- CFS/ME is prevalent (1-2%) in adolescents and nearly two thirds of patients report moderate or severe pain.
- Pain is associated with worse fatigue and poorer physical function in adolescents with CFS/ME.

What this study adds

- Despite the prevalence and impact of pain in children with CFS/ME few treatment studies have measured pain as an outcome and no interventions targeted pain.
- There is insufficient evidence to suggest that the treatment of fatigue also improves pain in paediatric CFS/ME.
- Patients who recover from CFS/ME appear to have less pain at follow-up than those who do not recover.

INTRODUCTION

Paediatric chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) is relatively common and causes significant suffering for children and their families.[1-3] It affects 1-2% of UK adolescents and is associated with low mood, poor quality of life, and a mean total loss of school attendance of one year.[4, 5] In addition to fatigue, children and young people experience a range of symptoms including headaches, muscle and joint pain, and sore throats.[6]

Pain is a common and disabling symptom in children with CFS/ME. Over 60% of CFS/ME children experience moderate or severe pain (as evidenced by a pain visual analogue scale >40/100) and this is associated with worse fatigue and poorer physical function.[6, 7] This is much higher than in healthy children where between 3.6% and 16.6% will describe severe pain [8]. In adult patients with CFS/ME pain is associated with worse outcomes.[7, 9]

However, the aetiology and pathophysiology of pain in this population is poorly understood and current treatment approaches do not target pain.[10, 11] This systematic review aimed to identify what interventions, if any, have been used to treat pain in children with CFS/ME, and to establish whether interventions used to treat paediatric CFS/ME change pain scores at follow-up.

METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement and the Cochrane Handbook 5.1.[12, 13] The protocol was prospectively registered on Prospero (https://www.crd.york.ac.uk/prospero) under the registration number CRD42019117540.

Search Strategy

We performed a detailed literature search in MEDLINE, EMBASE, PsycINFO, and the Cochrane library. The search strategy was developed in conjunction with a data specialist at the University of Bristol. It was adapted appropriately for each database and there were no language restrictions. We searched trial registration websites for unpublished trials and hand searched reference lists of all included studies. Full details of the search strategy can be seen in

supplementary file 1. We searched only for studies published since 1994, as this is when the CDC definition of CFS/ME was introduced[14], and included articles published until 24th January 2019.

Eligibility Criteria

We included randomised controlled trials and observational studies that investigated a treatment or intervention in patients <19 years of age with CFS/ME. A diagnosis of CFS/ME was determined according to NICE (2007)[11], CDC (Fukuda 1994, 2004)[14] or Oxford (1991)[15] criteria. Studies were eligible if they described a measure of pain (quantitative, qualitative, or mixed methods) before and after an intervention. Studies that described self-reported symptoms such as 'abdominal discomfort' and 'muscle aches' were excluded unless they also included an objective or subjective measure of pain.

Study Selection

Two researchers independently screened the abstracts of all studies generated from the literature search. Any discrepancies were discussed and resolved, if necessary, with a third reviewer. The researchers then independently reviewed the full texts of all potentially eligible studies. To identify all available evidence, we reviewed the full text of all studies that described interventions in paediatric CFS/ME. Any studies involving patients both above and below 19 years of age were also reviewed at full text to establish if there was separate data for patients under 19 years.

Data Extraction

Two researchers extracted the data from all studies that met the inclusion criteria using a purpose-designed data extraction form. We collected data on study characteristics (study type, country, sample size), intervention characteristics (type, length of course), pain characteristics (type, severity, pain measure used) and change in pain measure from baseline to follow-up.

Assessment of Risk of Bias

The risk of bias was evaluated in all studies for outcomes relating to pain. The four RCTs were evaluated using the Revised Cochrane risk of bias tool for randomised trials (RoB 2).[16] One study reported pain and assessment in a longitudinal cohort derived from a randomised controlled trial. We chose to evaluate this using the Risk of Bias In

Non-Randomized Studies of Interventions (ROBINS-I) tool.[17] Assessment was conducted by two independent assessors, who resolved disagreements by discussion.

Data Synthesis

We performed a descriptive analysis of the results, taking into account the methodological quality of the evidence. There was substantial heterogeneity between studies, and we were therefore unable to perform a meta-analysis.

RESULTS

Summary of Included Studies

Figure 1 describes the search results and study selection process. The search identified 1898 studies of which, we reviewed 107 full text papers for eligibility. Six papers were eligible for inclusion with data from five studies.[18-23] Papers were considered to be ineligible because: they did not include CFS/ME patients <19 years of age (n=65); measure pain (n=19); measure pain at both time points (n=1); describe an intervention (n=2); or because they were not published papers of RCTs/observational studies (n=14).

Table 1 details the characteristics of the included studies. Of these studies, four were randomised controlled trials and one was an observational study. The total sample size consisted of 414 adolescents aged between 10 and 18 years with a diagnosis of CFS/ME.

Table 1: Study Characteristics

Author, Year	Country	Study Design	Intervention	Sample at baseline (n)	Sample at follow-up (n, % baseline)	Mean age (range)	Follow-up
Crawley, 2013 2018	UK	RCT	Specialist care and Lightning Process vs specialist care alone	100	61 (61%) 59 (59%)	14	6 months 12 months
Knoop, 2007 [Analysis of data from Stulemeijer, 2005]	Netherlands	RCT	CBT vs. waiting list	69	66 (96%)	15.6 (10-17.2)	5 months
Nijhof, 2013	Netherlands	Cohort Study	CBT (internet-delivered or face-to-face)	83	72 (87%)	15.8 (12-18)	12 months
Sulheim, 2013	Norway	RCT	Low dose clonidine vs. placebo	120	103 (86%)	15.4 (12-18)	8 weeks 30 weeks
Van Geelen, 2011	Netherlands	RCT	6 sessions self-confrontation method vs. 12 sessions self-confrontation method	42	35 (83%)	16.5 (N/A)	4 months 14 months

RCT, randomised controlled trial; CBT, cognitive behavioural therapy

Figure 2 describes the risk of bias in the RCTs. One was deemed low risk of bias and one was deemed moderate risk of bias. The remaining two were at high risk of bias following assessment. The ROBINS-I tool suggested the longitudinal cohort study following an RCT was at high risk of bias. Due to the paucity of studies that measured pain outcomes in paediatric CFS/ME all studies were included in the review and the risk of bias was taken into account when evaluating study findings.

Pain Measurement in Treatment Studies of Paediatric CFS/ME

In total, we identified 26 randomised controlled trials or observational studies that investigated treatment interventions in paediatric CFS/ME. However, 19 of these studies did not measure pain at any timepoint,[24-43] and two studies measured pain at a single timepoint only.[10, 44] They were therefore excluded from this review. Four of the studies included the prevalence of self-reported symptoms e.g. muscle aches, abdominal discomfort, and tender lymph nodes, but did not include measures of pain severity.[24, 25, 31, 41] The remaining studies did not discuss pain at all.

Within the included studies, the pain measures used were heterogenous. Three of the five studies used validated pain questionnaires: a pain Visual Analogue Scale,[45] CHQ-87 Bodily Pain Subscale,[46] and Brief Pain Inventory.[47] The remaining two studies, conducted at the same centre, used a mean Daily Observed Pain (DOP) score calculated from a Likert scale of 1 (no pain) to 4 (severe pain) recorded four times a day for twelve consecutive days. Only one study attempted to measure pain using algometry.[21]

Interventions Used to Treat Pain in Paediatric CFS/ME

The included studies described a range of interventions used to treat children with CFS/ME (Table 2). However, none of the interventions were specifically targeted at treating pain.

All treatments were delivered in the outpatient setting. One of the studies investigated a pharmacological intervention (low dose clonidine)[22] and four studies described behavioural interventions.[19-21, 23] Behavioural interventions used were heterogenous. Two of the trials used cognitive behavioural therapy (CBT), however the

structure of the treatment varied. CBT was delivered as both a face-to-face intervention and an online intervention, and the number of sessions ranged from 10 to 22. One trial investigated the Lightning Process which is developed from life coaching and neurolinguistics programming, and another used a programme of self-confrontation, a method used to 'assess and change individual life stories through narrative self-investigation'[23].

Table 2: Study Results

Author, Year	Description of intervention	Intervention targeted at treating pain?	Pain measure used	Change in pain score following intervention
Crawley, 2013 2018	Lightning process course of 3x 4-hour sessions on consecutive days in small groups.	No	Pain visual analogue scale	Intervention group vs. control group -9.3 (-21.1 to 2.6) p=0.124 at 6 months -6.5 (-19.4 to 6.5) p=0.321 at 12 months
Knoop, 2007 [Analysis of data from Stulemeijer, 2005]	CBT 10 sessions in 5 months Two CBT protocols were used. One was for patients with a passive physical activity pattern and another for relatively active patients.	No	Mean daily observed pain score (DOP) calculated from a Likert scale of 1 (no pain) to 4 (very severe pain) done 4x per day for 12 days. % of patients with pain level within range of healthy controls defined as DOP score <2.3	Change in DOP score of CBT group vs waiting list control -2.21 (SD = 3.85) vs -0.36 (SD = 2.19) T=-2.44 p=0.04 % of participants with DOP score within range of healthy controls in CBT group vs waiting list group 56% vs 29% (χ^2 4.38, d.f. = 1, p=0.04)
Nijhof, 2013	CBT 6-month course of either internet-based (FITNET) or face-to-face CBT	No	Mean daily observed pain score (DOP) calculated from a Likert scale of 1 (no pain) to 4 (very severe pain) done 4x per day for 12 days Average pressure pain threshold (kg)	Recovered group vs non-recovered group Average DOP -2.9 (-4.2 to -1.6) p=<0.001 Average pain threshold +1.1 (0.2 to 2.2) p=0.019
Sulheim, 2013	9 weeks daily oral clonidine hydrochloride	No	Brief Pain Inventory average pain score	Clonidine group vs placebo group 0.5 (-0.16 to 1.16), p=0.14 at week 8 0.4 (-0.4 to 1.1), p=0.32 at week 30
Van Geelen, 2011	Self-confrontation method 6 or 12 sessions	No	Bodily pain subscale of CHQ-87	Change in bodily pain score at 4 months 6 sessions 11.8 (SD 28.1) p= >0.05 12 sessions 22.7 (SD 22.5) p= <0.05 Healthy controls 4.0 (SD 13.5) p= >0.05

CBT, cognitive behavioural therapy; DOP, daily observed pain score

Change in Pain Scores Following Treatment

The results of each study are presented in Table 2. Two RCTs showed no improvement in pain scores following treatment.[19, 22] One of these trials, conducted in a sample of 100 patients from the UK, investigated the effectiveness of the Lightning Process in addition to specialist medical care compared to specialist medical care alone. In this trial, fatigue, anxiety, depression, and school attendance improved. Pain, measured on a visual analogue scale (0 – 100) was similar between assessment and follow up at 6-months (adjusted difference in means -9.3 (95% CI (-21.1 – 2.6), p 0.124).[19] The second trial investigated treatment with low dose clonidine and found no change in scores on a Brief Pain Inventory compared to a placebo.[22] These studies were at a moderate and low risk of bias respectively.

The remaining three studies reported some improvement in pain measures.[20, 21, 23] Two of the studies compared DOP scores in patients that were deemed to have 'recovered' from CFS/ME with those that had 'not recovered'.[20, 21] Different definitions of recovery were used in each study. One of the largest trials to date enrolled a subgroup of patients from the FITNET study in the Netherlands and reported an association between "recovery" from CFS/ME and improved pressure pain thresholds and DOP scores. All participants were treated with 6 months of internet-based or face-to-face CBT and follow-up measures were obtained at 12 months. After the trial was reported, the authors submitted an additional, peer reviewed, letter to the editor evaluating pain. Here, they compared pain levels in those who had recovered to those who had not recovered. Within this, they described higher mean pressure pain thresholds and lower mean DOP scores in 'recovered' patients (39 of 72 patients) compared to 'non recovered' patients. However, due to a relatively small sample size, confidence intervals were large, the study was not controlled, and the risk of bias was high.[21]

Another study, with a moderate risk of bias, presented a post-hoc analysis of data that had not previously been reported in an original RCT, comparing CBT to a 'waiting list' control. Following 10 sessions of CBT 21/32 patients were classed as 'recovered' and had lower mean DOP scores than 'non-recovered' patients. This finding was replicated when comparing patients receiving CBT with the waiting list control group. However, the mean DOP score in adolescents, who had completed the course of CBT but were not classed as 'recovered', increased at 6-month follow-up.[20]

The final study assessed a 'self-confrontation method' of behavioural therapy that is not used in the NHS. Patients who received 12 sessions of self-confrontation exhibited improved scores on a Bodily Pain Subscale at 4 months, whereas patients who received 6 sessions had no significant change. Sample sizes in each group were small, confidence intervals were large, and the risk of bias was high [23].

DISCUSSION

This is the first systematic review investigating interventions used to treat pain in paediatric CFS/ME and whether they change pain scores at follow-up. We did not identify any interventions that specifically targeted pain. Surprisingly few of the CFS/ME intervention studies (<20%) identified measured pain despite the fact that pain is one of the most common and important Patient Reported Outcomes experienced by children with CFS/ME. In those studies that did measure pain, there is limited evidence that specialist CFS/ME treatment improves pain scores. However, in those that do recover, pain appears to be less compared to those that do not recover.

Strengths and limitations

Strengths of this study include its comprehensive search strategy and rigorous study selection process. We ran a detailed search in four databases, hand searched reference lists for additional papers and, in order to reduce the risk of publication bias, hand searched trial registration websites to identify unpublished studies. We included papers that were not written in the English language. During screening two independent researchers reviewed the full texts of all treatment studies in children with CFS/ME to ensure that we identified any studies in which pain was measured as a secondary outcome but not discussed in the abstract.

This review has a number of limitations. Substantial heterogeneity in the pain measures used and intervention types made comparison between studies challenging and we were unable to carry out a meta-analysis. Four studies were excluded because the secondary outcomes measured were ambiguous and it was not possible to confirm the presence or degree of pain. This included self-reported symptoms such as 'abdominal discomfort', 'muscle aches', and 'tender lymph nodes'.

In addition to this, none of the studies reported data on the use of pain medications by participants. It is therefore unclear to what extent pain medications may be responsible for improvements in pain scores. Further, one of the studies involved clonidine as an intervention. While this was employed to attenuate sympathetic and adrenocortical hyperactivity, it is also known to have an analgesic action.

One study compared different durations of the same intervention (self-confrontation method). Improved pain scores cited following 12 self-confrontation sessions could be a consequence of an increased numbers of sessions or represent the natural time course of the pain.

Almost all the studies were conducted outside of the UK and therefore the findings may not be applicable to the NHS. All patients were referred from secondary care and therefore the results may not be generalisable to patients looked after in a primary care setting. The generalisability of the findings is also limited by the fact that two of the studies excluded patients with psychiatric comorbidities and another study only included patients with mild or moderate CFS/ME.

We were also unable to locate one full text paper despite contacting the author directly, and at the time of publication there are two ongoing randomised controlled treatment trials in paediatric CFS/ME [48, 49] for which results are not yet available.

CONCLUSION

Despite the prevalence and impact of pain in children with CFS/ME, it is surprising how few treatment studies have measured pain. There is limited evidence that current treatments improve pain in paediatric CFS/ME, especially in patients who do not recover following initial treatment. Future research should investigate appropriate methods to measure pain in children with CFS/ME. This will enable large, well-powered RCTs investigating different treatment approaches to pain in this population.

FUNDING

This work was supported by the UKFPO Academic Foundation Programme.

PATIENT AND PUBLIC INVOLVEMENT

A young person's CFS/ME patient advisory group identified pain in fatigue as an important topic for further research.

CONFLICTS OF INTEREST

One of the authors of this systematic review (EC) was also an author of one of the included papers. However, to avoid a conflict of interest, EC was not involved in the study selection, data extraction, or assessment of risk of bias.

AUTHORS CONTRIBUTIONS

CA conducted the review and wrote the first draft of the paper. CA, HK, LB and SJ reviewed titles and abstracts and extracted data. TS and LB completed the risk of bias assessments. TP and JB advised on the interpretation of pain scores. The idea for the study was ECs. All the authors reviewed drafts of the paper and all approved the final submitted version.

REFERENCES

1. Rangel L, Garralda ME, Levin M, Roberts H. The course of severe chronic fatigue syndrome in childhood. JRSocMed. 2000;93(3):129-34.
2. Crawley E. The epidemiology of chronic fatigue syndrome/myalgic encephalitis in children. Arch Dis Child. 2014;99(2):171-4.
3. Parslow R, Patel A, Beasant L, Haywood K, Johnson D, Crawley E. What matters to children with CFS/ME? A conceptual model as the first stage in developing a PROM. Archives of disease in childhood. 2015;100(12):1141-7.
4. Crawley E, Sterne JA. Association between school absence and physical function in paediatric chronic fatigue syndrome/myalgic encephalopathy. Arch Dis Child. 2009;94(10):752-6.
5. Crawley EM, Emond AM, Sterne JA. Unidentified Chronic Fatigue Syndrome/myalgic encephalomyelitis (CFS/ME) is a major cause of school absence: surveillance outcomes from school-based clinics. BMJ Open. 2011;1(2):e000252.
6. May M, Emond A, Crawley E. Phenotypes of chronic fatigue syndrome in children and young people. Arch Dis Child. 2010;95(4):245-9.
7. Collin SM, Nuevo R, van de Putte EM, Nijhof SL, Crawley E. Chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) is different in children compared to in adults: a study of UK and Dutch clinical cohorts. BMJ open. 2015;5(10):e008830.
8. Perquin CW, Hazebroek-Kampschreur AA, Hunfeld JA, Bohnen AM, van Suijlekom-Smit LW, Passchier J, et al. Pain in children and adolescents: a common experience. Pain. 2000;87(1):51-8.
9. Crawley E, Collin SM, White PD, Rimes K, Sterne JA, May MT, et al. Treatment outcome in adults with chronic fatigue syndrome: a prospective study in England based on the CFS/ME National Outcomes Database. QJM. 2013;106(6):555-65.
10. Winger A, Kvarstein G, Wyller VB, Sulheim D, Fagermoen E, Smastuen MC, et al. Pain and pressure pain thresholds in adolescents with chronic fatigue syndrome and healthy controls: A cross-sectional study. 2014;4(10):e005920.
11. NICE. Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): Diagnosis and management of CFS/ME in adults and children (NICE guidelines CG53). London; 2007 2007. Report No.: CG53.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, Grp P. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7).
13. Handbook for Systematic Reviews of Interventions, (2011).
14. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994;121(12):953-9.
15. Sharpe MC, Archard LC, Banatvala JE, Borysiewicz LK, Clare AW, David A, et al. A report--chronic fatigue syndrome: guidelines for research. J R Soc Med. 1991;84(2):118-21.
16. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj-Brit Med J. 2019;366.
17. Sterne JAC, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. Bmj-Brit Med J. 2016;355.
18. Crawley E, Mills N, Hollingworth W, Deans Z, Sterne JA, Donovan JL, et al. Comparing specialist medical care with specialist medical care plus the Lightning Process for chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME): study protocol for a randomised controlled trial (SMILE Trial). Trials. 2013;14:444.
19. Crawley EM, Gaunt DM, Garfield K, Hollingworth W, Sterne JAC, Beasant L, et al. Clinical and cost-effectiveness of the Lightning Process in addition to specialist medical care for paediatric chronic fatigue syndrome: randomised controlled trial. Arch Dis Child. 2017.

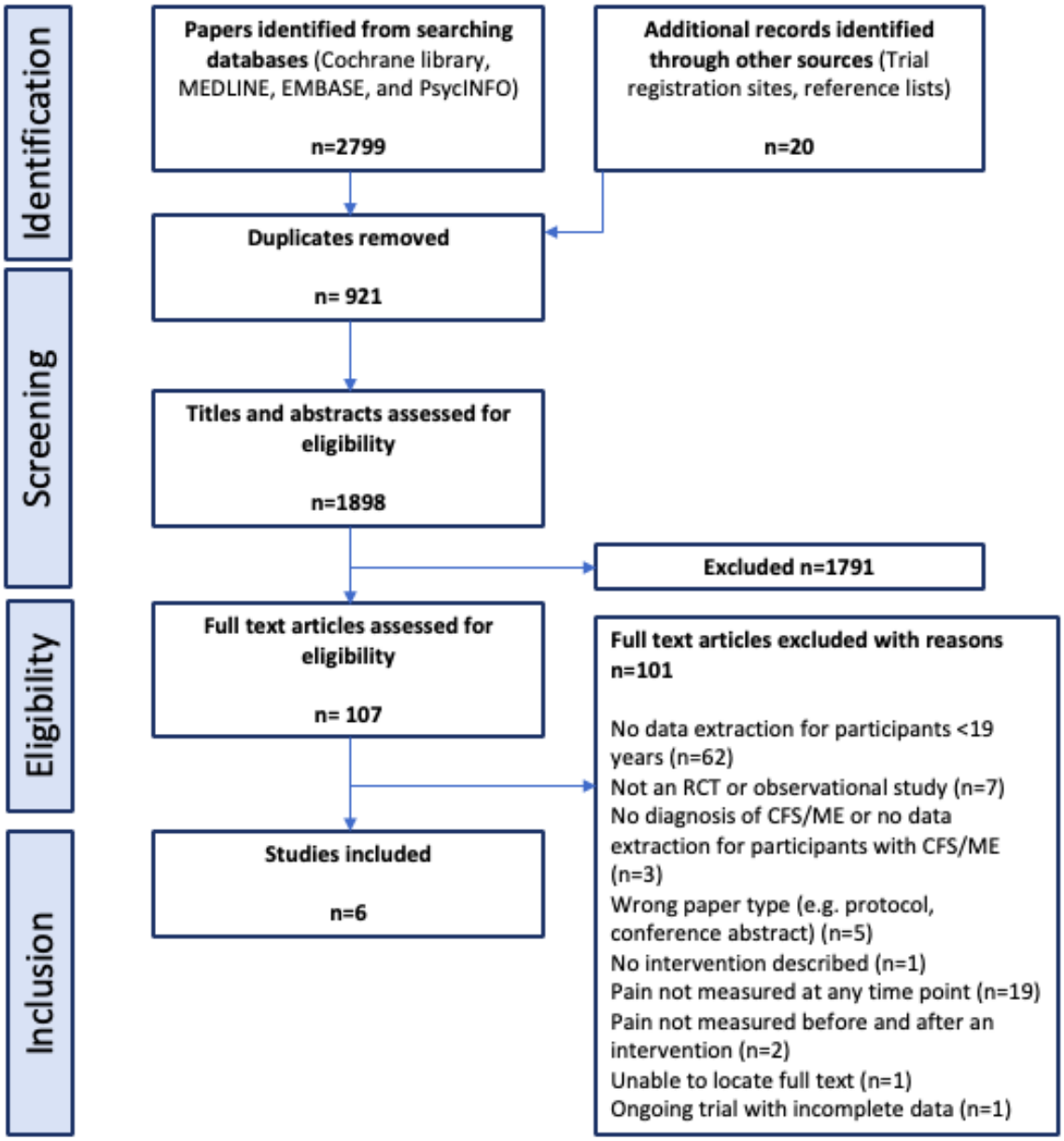
20. Knoop H, Stulemeijer M, Prins JB, van der Meer JW, Bleijenberg G. Is cognitive behaviour therapy for chronic fatigue syndrome also effective for pain symptoms? Behav Res Ther. 2007;45(9):2034-43.
21. Nijhof SL, Priesterbach LP, Bleijenberg G, Engelbert RH, van de Putte EM. Functional improvement is accompanied by reduced pain in adolescent chronic fatigue syndrome. Pain Med. 2013;14(9):1435-8.
22. Sulheim D, Fagermoen E, Winger A, Andersen AM, Godang K, Muller F, et al. Disease mechanisms and clonidine treatment in adolescent chronic fatigue syndrome: a combined cross-sectional and randomized clinical trial. JAMA Pediatr. 2014;168(4):351-60.
23. van Geelen SM, Fuchs CE, Sinnema G, van de Putte EM, van GR, Hermans HJ, et al. Self-investigation in adolescent chronic fatigue syndrome: narrative changes and health improvement. PatientEduc Couns. 2011;83(2):227-33.
24. Al-Haggar M S, Al-Naggar Z A, Abdel-Salam M A. Biofeedback and cognitive behavioural therapy for Egypian adolescents suffering from chronic fatigue syndrome. . J Paediatric Neurol. 2006;4:8.
25. Ashby B, Wright B, Jordan J. Chronic Fatigue Syndrome: An Evaluation of a Community Based Management Programme for Adolescents and their Families. Child and Adolescent Mental Health. 2006;11(1):13-8.
26. Chalder T, Tong J, Deary V. Family cognitive behaviour therapy for chronic fatigue syndrome: an uncontrolled study. Arch Dis Child. 2002;86(2):95-7.
27. Chalder T, Deary V, Husain K, Walwyn R. Family-focused cognitive behaviour therapy versus psycho-education for chronic fatigue syndrome in 11- to 18-year-olds: a randomized controlled treatment trial. Psychol Med. 2010;40(8):1269-79.
28. Gordon B, Lubitz L. Promising outcomes of an adolescent chronic fatigue syndrome inpatient programme. JPaediatrChild Health. 2009;45(5):286-90.
29. Gordon BA, Knapman LM, Lubitz L. Graduated exercise training and progressive resistance training in adolescents with chronic fatigue syndrome: a randomized controlled pilot study. Clin Rehabil. 2010;24(12):1072-9.
30. Khawaja S, Van Boxel P. Chronic fatigue syndrome in childhood: seven-year follow-up study. Psychiatric Bulletin. 1998;22(4):198-202.
31. Knoop H, Stulemeijer M, de Jong LW, Fiselier TJ, Bleijenberg G. Efficacy of cognitive behavioral therapy for adolescents with chronic fatigue syndrome: long-term follow-up of a randomized, controlled trial. Pediatrics. 2008;121(3):e619-e25.
32. Lim A, Lubitz L. Chronic fatigue syndrome: successful outcome of an intensive inpatient programme. J Paediatr Child Health. 2002;38(3):295-9.
33. Lloyd S, Chalder T, Rimes KA. Family-focused cognitive behaviour therapy versus psycho-education for adolescents with chronic fatigue syndrome: Long-term follow-up of an RCT. BehavResTher. 2012;50(11):719-25.
34. Lloyd S, Chalder T, Sallis HM, Rimes KA. Telephone-based guided self-help for adolescents with chronic fatigue syndrome: A non-randomised cohort study. BehavResTher. 2012;50(1):304-12.
35. Loades ME, Chalder T. Same, Same But Different? Cognitive Behavioural Treatment Approaches for Paediatric CFS/ME and Depression - CORRIGENDUM. Behav Cogn Psychother. 2017;45(4):432.
36. Nijhof SL, Bleijenberg G, Uiterwaal CS, Kimpen JL, van de Putte EM. Effectiveness of internet-based cognitive behavioural treatment for adolescents with chronic fatigue syndrome (FITNET): a randomised controlled trial. Lancet. 2012;379(9824):1412-8.
37. Nijhof SL, Priesterbach LP, Uiterwaal CS, Bleijenberg G, Kimpen JL, van de Putte EM. Internet-based therapy for adolescents with chronic fatigue syndrome: long-term follow-up. Pediatrics. 2013;131(6):e1788-95.
38. Rimes KA, Papadopoulos AS, Cleare AJ, Chalder T. Cortisol output in adolescents with chronic fatigue syndrome: Pilot study on the comparison with healthy adolescents and change after cognitive behavioural guided self-help treatment. J Psychosom Res. 2014;77(5):409-14.

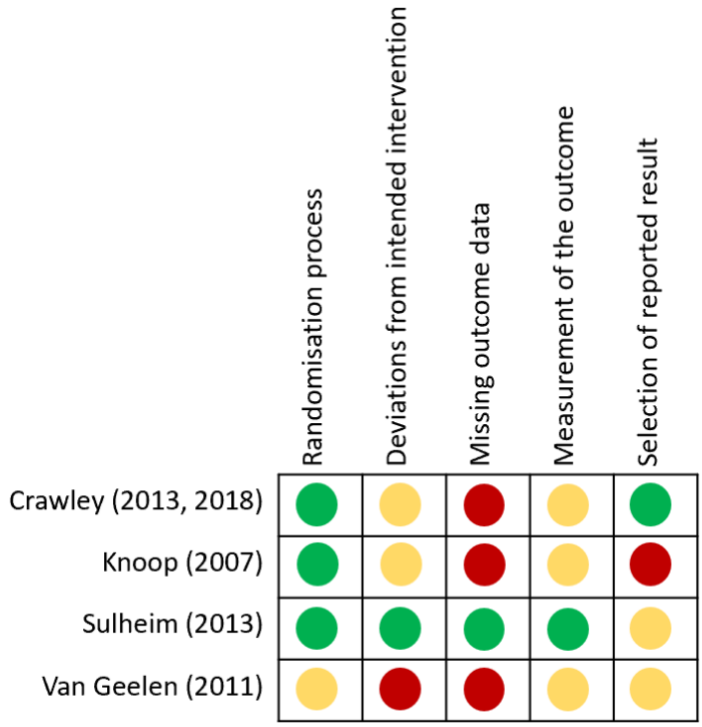
39. Rowe KS. Double-blind randomized controlled trial to assess the efficacy of intravenous gammaglobulin for the management of chronic fatigue syndrome in adolescents. J PsychiatrRes. 1997;31(1):133-47.
40. Rowe KSJJoCFS. Five-year follow-up of young people with chronic fatigue syndrome following the double blind randomised controlled intravenous gammaglobulin trial. 1999;5(3-4):97-107.
41. Stulemeijer M, de Jong LW, Fiselier TJ, Hoogveld SW, Bleijenberg G. Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial. BMJ. 2005;330(7481):14.
42. Viner R, Gregorowski A, Wine C, Bladen M, Fisher D, Miller M, et al. Outpatient rehabilitative treatment of chronic fatigue syndrome (CFS/ME). ArchDisChild. 2004;89(7):615-9.
43. Wright B, Ashby B, Beverley D, Calvert E, Jordan J, Miles J, et al. A feasibility study comparing two treatment approaches for chronic fatigue syndrome in adolescents. Arch Dis Child. 2005;90(4):369-72.
44. van Geelen SM, Bakker RJ, Kuis W, van de Putte EM. Adolescent chronic fatigue syndrome: a follow-up study. Arch Pediatr Adolesc Med. 2010;164(9):810-4.
45. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain. 1983;17(1):45-56.
46. Witherspoon D, Drotar D, Greenley R, Zebracki K, Palermo T, Burant C. Exploratory and confirmatory factor analyses of the Child Health Questionnaire-Child Form 87 (CHQ-CF87) with children chronic conditions and healthy children. J Dev Behav Pediatr. 2006;27(5):448-.
47. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore. 1994;23(2):129-38.
48. Nijhof SL, Bleijenberg G, Uiterwaal CSPM, Kimpen JLL, van de Putte EM. Fatigue In Teenagers on the interNET - The FITNET Trial. A randomized clinical trial of web-based cognitive behavioural therapy for adolescents with chronic fatigue syndrome: study protocol. [ISRCTN59878666]. BMC Neurol. 2011;11:23.
49. Brigden A, Beasant L, Hollingworth W, Metcalfe C, Gaunt D, Mills N, et al. Managed Activity Graded Exercise iN Teenagers and pre-Adolescents (MAGENTA) feasibility randomised controlled trial: study protocol. BMJ open. 2016;6(e011255).

FIGURE LEGENDS

Figure 1. PRISMA flow diagram detailing the study selection process.

Figure 2. Assessment of risk of bias using the Revised Cochrane Risk of Bias Tool for Randomised Trials (RoB 2).[16]





Appendix 1: Search Strategy

MEDLINE/EMBASE

Paediatric

#1 exp Adolescent/
#2 exp Child/
#3 exp Child, Preschool/
#4 exp Infant/
#5 exp Minors/
#6 exp Pediatric/
#7 (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.

CFS/ME

#8 exp Fatigue Syndrome, Chronic/
#9 Chronic Fatigue Syndrome.tw
#10 myalgic encephal*.tw.
#11 CFS.tw
#12 fatigue syndrome*.mp.
#13 chronic fatigue syndrome*.mp.
#14 myalgic encephal*.mp.

Randomised control trial/observational

#15 Clinical Trial/
#16 Controlled Clinical Trial/
#17 Randomized Controlled Trial/
#18 controlled clinical trial.mp
#19 randomi?ed control* trial.mp
#20 (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).mp
#21 placebo*.mp
#22 trial.mp
#23 (control* adj3 (trial* or study or studies)).mp
#24 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp
#25 ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).mp
#26 Clinical Study/
#27 Feasibility Studies/
#28 Observational study/
#29 study.mp

#30 (#1 or #2 or #3 or #4 or #5 or #6 or #7)
#31 (#8 or #9 or #10 or #11 or #12 or #13 or #14)
#32 (#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29)
#33 (#30 and #31 and #32)
#34 (Limit #32 to yr=’1994-current)