PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Treatment for paediatric chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) and co-morbid depression: A systematic review.
AUTHORS	Loades, Maria; Sheils, Elizabeth; Crawley, Esther

VERSION 1 - REVIEW

REVIEWER	Norman E Booth Emeritus Professorial Fellow Mansfield College, University of Oxford
REVIEW RETURNED	09-May-2016

GENERAL COMMENTS	Re check list: 11. No attempt has been made to understand the pathophysiology and effects of stress, both psychological and physical, or degree of illness and depression. 12. In view of the small amount of literature the results of any surveys (if such exist) could have been mentioned. I am not persuaded that this manuscript has a real positive value. This is mainly due to the fact that there is very little literature that specifically deals with co-morbid depression in paediatric CFS/ME. The result is that the overall conclusions are uncertain; they don't offer any practical solution as to how to treat children and adolescents with CFS/ME who also have depression. Reference 30 of this manuscript is to a 2011 paper by Kawatani, Minzuo et al. on cognitive dysfunction and mental fatigue. This Japanese collaboration has published several subsequent papers on childhood chronic fatigue syndrome, including studies of some of the pathophysiological aspects coupled with functional magnetic resonance imaging (fMRI). The authors have found effects that correlate cognition with fMRI in regions of the brain, and which correlate with cerebral energetics and oxidative stress and their cellular and subcellular consequences [1]. This type of approach leads to new understanding that will result in the use of appropriate treatments. In contrast, attempts to make progress based on the hypothetical models described in ref. 36 of the manuscript are unlikely to lead to new solutions. There are often complaints and controversy about the use of the various diagnostic criteria for CF, CFS and ME. Some of the criteria, such as the Oxford criteria are far out-of-date and should be abandoned. However, one feature that they all seem to have is chronic stress.

Stress can be due to infection or environmental contaminants or other unidentified causes, and/or it can be psychological in origin. Regardless of the source, stress is characterized by the release of stress mediators including the hormonal mediators cortisol and adrenaline, and also proinflammatory cytokines. All cells with appropriate receptors are affected, regardless of their location, anywhere in the body including the brain [2]. The stress mediators have both protective and damaging effects. At the present time detailed studies have been made only in mouse models [3]. Many of the cellular effects, including those mediated by cytokines, have been observed in people with CFS/ME. Adaptation to stress depends upon cellular energetics, and this area is potentially amenable to treatment [4].

The wide-reaching aspects of the stress response need to be included in new guidelines for CFS/ME and in the NICE guideline on depression. Exercise programmes need to be used with caution in paediatric CFS/ME.

Regarding the treatment of children and young people, it is my personal experience that there should be no pressure to return to school – this just increases the existing stress. The most important aspect is to keep in contact with friends. A young winner in an art competition a few years ago commented: “I have found that isolation from friends is the hardest part to manage, which is why I needed to portray this in my (art) work.”

When quality of life has improved, young people are almost invariably eager to get back to school. Treatment plans need to initially concentrate on minimizing stress of all forms. To proceed further we need to have cellular measurements of stress damage and adaptation.

References

1. Mizuno K, Tanaka M, Tanabe HC, Joudoi T, Kawatani J, Shigihara Y, Tomoda A, Miike T, Imai-Matsumura K, Sadato N *et al*: **Less efficient and costly processes of frontal cortex in childhood chronic fatigue syndrome**. *NeuroImage Clinical* 2015, **9**:355-368.
2. Manoli I, Alesci S, Blackman MR, Su YA, Rennert OM, Chrousos GP: **Mitochondria as key components of the stress response**. *Trends in Endocrinology & Metabolism* 2007, **18**(5):190-198.
3. Picard M, McManus MJ, Gray JD, Nasca C, Moffat C, Kopinski PK, Seifert EL, McEwen BS, Wallace DC: **Mitochondrial functions modulate neuroendocrine, metabolic, inflammatory, and transcriptional responses to acute psychological stress**. *Proceedings of the National Academy of Sciences* 2015, **112**(48):E6614-E6623.
4. Kaiser JD: **A prospective, proof-of-concept investigation of KPAX002 in chronic fatigue syndrome**. *Int J Clin Exp Med* 2015, **8**(7):11064-11074.

REVIEWER	Dr. Alison C. Bested Hematological Pathologist Clinical Associate Professor Faculty of Medicine University of British Columbia 1265 Morningside Avenue, Suite 107 Toronto, Ontario Canada
REVIEW RETURNED	30-May-2016

GENERAL COMMENTS	I would encourage you to keep up the good work. Please read the enclosed review with my suggestions. This is a very helpful article for helping future researchers in this field. Having reviewed the article, I have much admiration for the authors for tackling this is very difficult complex topic. I agree that very little research is been done in this area due to lack of research funding and also due to lack of practitioners working in this particular field of medicine. I think the authors have done an amazing job of sifting through this very complex information about ME/CFS +/- depression in children. I agree with the conclusion of the paper that states that there is poor evidence of effective treatment and that there needs to be future research done on both children and adolescents with CFS/ME +/- depression. I think that the paper's intent was to look for treatment of children and adolescents with ME/CFS +/- depression in the literature and it succeeded in finding the little research available on this topic. I would suggest some areas of clarification needed in order to strengthen the article's conclusions. In the literature search the article uses three different definitions of ME/CFS including: The Fukuda definition of Chronic Fatigue Syndrome, the Oxford guidelines - which includes both the definition of Chronic Fatigue Syndrome and Post-infectious Fatigue Syndrome and the NICE guidelines. Just to be clear in my mind I printed out the 3 definitions or guidelines to clarify this information for myself and included it below in this review. It would be helpful to include this information as tables so that people reading this paper could understand the differences in the definitions and the different patient results. As result of searching the literature with the 3 different definitions or guidelines for and ME/CFS; different results and treatments were found. The Fukuda CFS definition describes post infectious illness with sore throats and tender lymph nodes. Did Henderson's research

	using the antiviral medication use the Fukuda definition? The Oxford criteria of Chronic Fatigue Syndrome excludes post viral illness. Other psychiatric illnesses are not necessarily excluded such as depression. In fact the definition describes post-viral illness as a separate entity called Post-infectious Fatigue. Is the Oxford definition of Chronic Fatigue Syndrome preselecting for depressed patients since it is not excluded in this definition? Did the articles sited include this Chronic Fatigue Syndrome definitions and thereby exclude the post-viral patients? Can this paper shed light on this? The NICE guidelines are unclear to me, having fatigue, post-exertional malaise or fatigue and only one more symptoms in a list of other symptoms. As part of the treatment suggestions NICE guidelines suggest that patients limit the length of rest periods to 30 minutes at a time. This may be harmful to patients with ME/CFS and push patients beyond their physical limits causing a relapse of their symptoms. This guideline recommends pacing but at the same time pushes patients not to rest beyond 30 minutes. I found this contradictory. Using three different guidelines for ME/CFS literature and stating the results without stating which of the different ME/CFS guideline were used in the specific research needs clarification in the article. Each research review needs to have stated specifically which guideline was used. It would be very powerful if the results of the specific research were listed using a summary table including which particular guidelines were used with the results of the measurement tools that had been used in the particular study and the results of the intervention if one was done. I think that with these suggestions this article could be very valuable to both researchers and clinicians in clarifying what the role ME/CFS guidelines play in research and why the specific treatment results are obtained. Comment: The alexithymia study by Van Putte (33). Alexithymia is the inability to recognize or describe one's emotions. Suggest defining alexithymia in the article and adding: The research was looking for alexithymia as a prognostic factor for the recovery of ME/CFS vs. those who did not have alexithymia. No differences were found.

Oxford Definition: Sharpe et al. A report - Chronic Fatigue Syndrome: Guidelines for research. J Royal Society of Medicine 1991:84(2):118-21.

Syndromes
Two broad syndromes can be defined:

Chronic fatigue syndrome (CFS)
(a) A syndrome characterized by fatigue as the principal symptom.
(b) A syndrome of definite onset that is not life long.
(c) The fatigue is severe, disabling, and affects physical and mental functioning.
(d) The symptom of fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time.
(e) Other symptoms may be present, particularly myalgia, mood and sleep disturbance.
(f) Certain patients should be excluded from the definition. They include:
(i) Patients with established medical conditions known to produce chronic fatigue (eg severe anaemia). Such patients should be excluded whether the medical condition is diagnosed at presentation or only subsequently. All patients should have a history and physical examination performed by a competent physician.
(ii) Patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease. Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not necessarily reasons for exclusion.

Post-infectious fatigue syndrome (PIFS)
This is a subtype of CFS which either follows an infection or is associated with a current infection (although whether such associated infection is of aetiological significance is a topic for research). To meet research criteria for PIFS patients must (i) fulfil criteria for CFS as defined above, and (ii) should also fulfil the following additional criteria:
(a) There is definite evidence of infection at onset or presentation (a patient's self-report is unlikely to be sufficiently reliable).
(b) The syndrome is present for a minimum of 6 months after onset of infection.
(c) The infection has been corroborated by laboratory evidence.

In reporting studies it should be clearly stated which of these two syndromes is being studied. The degree of disability should be measured and stated. The criteria and method used to exclude subjects from study must be clearly described and the degree of examination and investigation specified. All patients should be assessed for associated psychiatric disorder

Table: CFS definition: Fukuda et al. *Ann Intern Med* 1994; 121(12): 953-9.

CHRONIC FATIGUE SYNDROME
1. clinically evaluated, unexplained, persistent or relapsing chronic fatigue
that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities; and
2. the concurrent occurrence of four or more of the following symptoms,
all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue:
□ **impairment in short-term memory or concentration** severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities
□ **sore throat**
□ **tender cervical or axillary lymph nodes**
□ **muscle pain**
□ **multijoint pain without joint swelling or redness**
□ **headaches of a new type, pattern, or severity**
□ **unrefreshing sleep**
□ **postexertional malaise lasting more than 24 hours**

Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy): diagnosis and management

NICE guidelines [CG53] Published date: August 2007

1.3 Diagnosis

	1.3.1 Making a diagnosis
	
	1.3.1.1 A diagnosis should be made after other possible diagnoses have been excluded and the symptoms have persisted for:
	
	• 4 months in an adult
	• 3 months in a child or young person; the diagnosis should be made or confirmed by a paediatrician.
	
	1.3.1.2 When a diagnosis of CFS/ME is made, healthcare professionals should provide honest, realistic information about CFS/ME and encourage cautious optimism.
	
	• **Most people with CFS/ME will improve over time and some people will recover and be able to resume work and normal activities.**
	• However, others will continue to experience symptoms or relapse and some people with severe CFS/ME may remain housebound.
	• The prognosis in children and young people is more optimistic.
	
	1.3.1.3 The diagnosis of CFS/ME should be reconsidered if none of the following key features are present:
	
	• post-exertional fatigue or malaise
	• cognitive difficulties
	• sleep disturbance
	• chronic pain.
	
	Specialist CFS/ME care
	
	• Any decision to refer a person to specialist CFS/ME care should be based on their needs, the type, duration, complexity and severity of their symptoms, and the presence of comorbidities. The decision should be made jointly by the person with CFS/ME and the healthcare professional.
	• An individualised, person-centred programme should be offered to people with CFS/ME. The objectives of the programme should be to:
	  ○ **sustain or gradually extend, if possible, the person's physical, emotional and cognitive capacity**
	  ○ manage the physical and emotional impact of their symptoms.
	• Cognitive behavioural therapy and/or graded exercise therapy should be offered to people with mild or moderate CFS/ME and provided to those who choose these approaches, because currently these are the interventions for which there is the clearest research evidence of benefit.

VERSION 1 – AUTHOR RESPONSE

Responses to Reviewer 1's comments:

We are very grateful to Norman Booth for his review of this paper. His comments were difficult to untangle from the commentary but we have done our best to respond to them as follows:

Reviewer 2 comments	*Amendments*
I am not persuaded that this manuscript has a real positive value. This is mainly due to the fact that there is very little literature that specifically deals with co-morbid depression in paediatric CFS/ME. The result is that the overall conclusions are uncertain; they don't offer any practical solution as to how to treat children and adolescents with CFS/ME who also have depression.	We agree this is a null finding. However, we believe that null findings are important in developing our understanding of the gaps in the current literature and future research questions.
Reference 30 of this manuscript is to a 2011 paper by Kawatani, Minzuo et al. on cognitive dysfunction and mental fatigue. This Japanese collaboration has published several subsequent papers on childhood chronic fatigue syndrome, including studies of some of the pathophysiological aspects coupled with functional magnetic resonance imaging (fMRI). The authors have found effects that correlate cognition with fMRI in regions of the brain, and which correlate with cerebral energetics and oxidative stress and their cellular and subcellular consequences [1]. This type of approach leads to new understanding that will result in the use of appropriate treatments. In contrast, attempts to make progress based on the hypothetical models described in ref. 36 of the manuscript are unlikely to lead to new solutions.	We have not altered the paper in response to this comment as models such as those proposed by Browne & Chalder (ref 36) are of value to both patients and clinicians in working with CFS/ME as they describe the cognitive and behavioural maintenance of CFS/ME. This provides an increased understanding of symptom maintenance which enables the development of better management/treatment strategies Empirical evidence continues to emerge for the components of the model (e.g. Knoop et al, 2010; Wiborg et al, 2011; Heins et al, 2013).
There are often complaints and controversy about the use of the various diagnostic criteria for CF, CFS and ME. Some of the criteria, such as the Oxford criteria are far out-of-date and should be abandoned. However, one feature that they all seem to have is chronic stress.	The diagnostic criteria used in each study included in the review has been included in table 2, and table 1 details the diagnostic criteria.
Stress can be due to infection or environmental contaminants or other unidentified causes, and/or it can be psychological in origin. Regardless of the source, stress is	We appreciate the interesting comments in this regard. This particular paper is not guidance, and does not describe exercises programmes.

characterized by the release of stress mediators including the hormonal mediators cortisol and adrenaline, and also proinflammatory cytokines. All cells with appropriate receptors are affected, regardless of their location, anywhere in the body including the brain [2]. The stress mediators have both protective and damaging effects. At the present time detailed studies have been made only in mouse models [3]. Many of the cellular effects, including those mediated by cytokines, have been observed in people with CFS/ME. Adaptation to stress depends upon cellular energetics, and this area is potentially amenable to treatment [4]. The wide-reaching aspects of the stress response need to be included in new guidelines for CFS/ME and in the NICE guideline on depression. Exercise programmes need to be used with caution in paediatric CFS/ME.	
Regarding the treatment of children and young people, it is my personal experience that there should be no pressure to return to school – this just increases the existing stress. The most important aspect is to keep in contact with friends. A young winner in an art competition a few years ago commented: "I have found that isolation from friends is the hardest part to manage, which is why I needed to portray this in my (art) work." When quality of life has improved, young people are almost invariably eager to get back to school. Treatment plans need to initially concentrate on minimizing stress of all forms. To proceed further we need to have cellular measurements of stress damage and adaptation.	This is personal anecdotal experience. Whilst interesting, we are not convinced that this should inform the conclusion in our paper and have therefore not made further changes.

Responses to Reviewer 2's comments:

We very much appreciate Alison Bested's comments and suggestions.

Reviewer 2 comments	*Amendments*
In the literature search the article uses three different definitions of ME/CFS including: The Fukuda definition of Chronic Fatigue Syndrome, the Oxford guidelines - which includes both the definition of Chronic Fatigue Syndrome and Post-infectious Fatigue Syndrome and the NICE guidelines. Just to be clear in my mind I printed out the 3 definitions or guidelines to clarify this information for myself and included it below in	The definitions of CFS/ME have been included in a table, table 1, for clarity and ease of reference/comparison.

this review. It would be helpful to include this information as tables so that people reading this paper could understand the differences in the definitions and the different patient results. As result of searching the literature with the 3 different definitions or guidelines for and ME/CFS; different results and treatments were found.	
The Fukuda CFS definition describes post infectious illness with sore throats and tender lymph nodes. Did Henderson's research using the antiviral medication use the Fukuda definition? The Oxford criteria of Chronic Fatigue Syndrome excludes post viral illness. Other psychiatric illnesses are not necessarily excluded such as depression. In fact the definition describes post-viral illness as a separate entity called Post-infectious Fatigue. Is the Oxford definition of Chronic Fatigue Syndrome preselecting for depressed patients since it is not excluded in this definition? Did the articles sited include this Chronic Fatigue Syndrome definitions and thereby exclude the post-viral patients? Can this paper shed light on this?	This has been clarified in table 3. A sentence has also been added to indicate that the Kawatani et al study utilised the Jason et al (2006) diagnostic criteria, in which depressive disorders are an exclusionary criterion.
Using three different guidelines for ME/CFS literature and stating the results without stating which of the different ME/CFS guideline were used in the specific research needs clarification in the article. Each research review needs to have stated specifically which guideline was used. It would be very powerful if the results of the specific research were listed using a summary table including which particular guidelines were used with the results of the measurement tools that had been used in the particular study and the results of the intervention if one was done.	Table 3 (methodology) now includes a column showing which definition of CFS/ME was utilised by each study.
The alexithymia study by Van Putte (33). Alexithymia is the inability to recognize or describe one's emotions. Suggest defining alexithymia in the article and adding: The research was looking for alexithymia as a prognostic factor for the recovery of ME/CFS vs. those who did not have alexithymia. No	This has been added as suggested.

differences were found.	

In addition, a justification has been included for why the quality of observational studies was not formally assessed. This has been acknowledged in the limitations of the study, and we have clarified that we would have undertaken a quality assessment of the observational studies had the evidence from those studies contributed significantly to answering the review questions. This can be found in the second paragraph of the discussion as follows:
'However, a formal review of the quality of the observational studies was not undertaken. This would have been undertaken had those studies provided significant evidence to inform the review questions.'

We hope that this addresses the comments sufficiently. We look forward to hearing from you, and very much hope that this study will be published in your journal.

VERSION 2 – REVIEW

REVIEWER	Norman E. Booth Emeritus Professorial Fellow Mansfield College, University of Oxford
REVIEW RETURNED	07-Jul-2016

GENERAL COMMENTS	I am not persuaded that this manuscript has a real positive value. This is mainly due to the fact that there is very little literature that specifically deals with co-morbid depression in paediatric CFS/ME. The result is that the overall conclusions are uncertain; they don't offer any practical solution as to how to treat children and adolescents with CFS/ME who also have depression. Reference 30 of this manuscript is to a 2011 paper by Kawatani, Minzuo et al. on cognitive dysfunction and mental fatigue. This Japanese collaboration has published several subsequent papers on childhood chronic fatigue syndrome, including studies of some of the pathophysiological aspects coupled with functional magnetic resonance imaging (fMRI). The authors have found effects that correlate cognition with fMRI in regions of the brain, and which correlate with cerebral energetics and oxidative stress and their cellular and subcellular consequences [1]. This type of approach leads to new understanding that will result in the use of appropriate treatments. In contrast, attempts to make progress based on the hypothetical models described in ref. 37 of the manuscript are unlikely to lead to new solutions. There are often complaints and controversy about the use of the various diagnostic criteria for CF, CFS and ME. Some of the criteria, such as the Oxford criteria are far out-of-date and should be abandoned. The revised version of the manuscript contains a reference (ref. 35) on the Canadian diagnostic criteria for paediatric cases, and this is included in Table 1. This is welcome. All sets of diagnostic criteria contain the malaise and other features of chronic stress. Stress can be due to infection or environmental contaminants or other unidentified causes, and/or it can be psychological in origin. Regardless of the source, stress is characterized by the release of stress mediators including the hormonal mediators cortisol and adrenaline, and also proinflammatory cytokines. All cells with

	appropriate receptors are affected, regardless of their location, anywhere in the body including the brain [2]. The stress mediators have both protective and damaging effects. At the present time detailed studies have been made only in mouse models [3]. Many of the cellular effects, including those mediated by cytokines, have been observed in people with CFS/ME. Adaptation to stress depends upon cellular energetics, and this area is potentially amenable to treatment [4]. The wide-reaching aspects of the stress response need to be included in new guidelines for CFS/ME and in the NICE guideline on depression. Exercise programmes need to be used with caution in paediatric CFS/ME. Regarding the treatment of children and young people, it is my personal experience that there should be no pressure to return to school – this just increases the existing stress. The most important aspect is to keep in contact with friends. A young winner in an art competition a few years ago commented: "I have found that isolation from friends is the hardest part to manage, which is why I needed to portray this in my (art) work." When quality of life has improved, young people are almost invariably eager to get back to school. Treatment plans need to initially concentrate on minimizing stress of all forms. To proceed further we need to have cellular measurements of stress damage and adaptation. References 1. Mizuno K, Tanaka M, Tanabe HC, Joudoi T, Kawatani J, Shigihara Y, Tomoda A, Miike T, Imai-Matsumura K, Sadato N *et al*: **Less efficient and costly processes of frontal cortex in childhood chronic fatigue syndrome**. *NeuroImage Clinical* 2015, **9**:355-368. 2. Manoli I, Alesci S, Blackman MR, Su YA, Rennert OM, Chrousos GP: **Mitochondria as key components of the stress response**. *Trends in Endocrinology & Metabolism* 2007, **18**(5):190-198. 3. Picard M, McManus MJ, Gray JD, Nasca C, Moffat C, Kopinski PK, Seifert EL, McEwen BS, Wallace DC: **Mitochondrial functions modulate neuroendocrine, metabolic, inflammatory, and transcriptional responses to acute psychological stress**. *Proceedings of the National Academy of Sciences* 2015, **112**(48):E6614-E6623. 4. Kaiser JD: **A prospective, proof-of-concept investigation of KPAX002 in chronic fatigue syndrome**. *Int J Clin Exp Med* 2015, **8**(7):11064-11074.

REVIEWER	Dr. Alison Bested Faculty of Medicine University of British Columbia Vancouver, BC Canada
REVIEW RETURNED	27-Jul-2016

GENERAL COMMENTS	I think the table of the different ME/CFS criteria was helpful to illustrate the difficulties in comparing different studies about patients with ME/CFS. Do you know if when the Oxford criteria were used if the patient population was (1) Chronic fatigue syndrome (CFS) or (2) Post-infectious fatigue syndrome (PIFS)? If you know this information and could add it, the information would clarify which population was used and possible results from the studies done. If you can't add this information, it would be useful to add a comment that it was not clear in the studies reviewed which subgroup was studied.

VERSION 2 – AUTHOR RESPONSE

Responses to Reviewer 1's comments:

Once again, we appreciate Norman Booth's review of this revised paper. From our reading of his comments, no further amendments seem to be suggested.

Responses to Reviewer 2's comments:

We also very much value Alison Bested's comments and suggestions.

Reviewer 2 comments	*Amendments*
I think the table of the different ME/CFS criteria was helpful to illustrate the difficulties in comparing different studies about patients with ME/CFS. Do you know if when the Oxford criteria were used if the patient population was (1) Chronic fatigue syndrome (CFS) or (2) Post-infectious fatigue syndrome (PIFS)? If you know this information and could add it, the information would clarify which population was used and possible results from the studies done. If you can't add this information, it would be useful to add a comment that it was not clear in the studies reviewed which subgroup was studied.	The following statement has been added to table 3 which describes the design of the studies, including the diagnostic criteria used: 'in the studies using the Oxford criteria (Sharpe et al, 1991) it is unclear if the criteria for CFS or post-infectious fatigue syndrome (PIFS) were applied.'