PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pain and Pressure Pain Thresholds in Adolescents with Chronic Fatigue Syndrome and Healthy Controls; a cross sectional study
AUTHORS	Winger, Anette; Kvarstein, Gunnvald; Wyller, Vegard; Sulheim, Dag; Fagermoen, Even; Småstuen, Milada; Helseth, Sølvi

VERSION 1 - REVIEW

REVIEWER	Elise van de Putte University Medical Center Utrecht The Netherlands
REVIEW RETURNED	29-Jun-2014

GENERAL COMMENTS	The research question is not original but has been subject of research in more studies, which are neither mentioned nor discussed (e.g. van de Putte, Pediatrics 2005; Nijhof, Lancet 2012; Nijhof Pain Medicine 2013). Regarding etiology one of the most impressive papers is the one writteh by Nijs, Pain Physician 2012, which is not mentioned. See my report. I do not recommend publishing this article and it's beyond repair, I'm afraid, because: 1. the classification of patients to the diagnosis CFS is not according to international guidelines 2. this concept of pain and fatigue has already been studied and published several times, also in adolescents. But they seem to have overlooked these studies. **Introduction** Why do you want to know more about pain adolescents with CFS? 1. Because 'pain' is insufficiently addressed in treatment of CFS adolescents? 2. Because you want to understand the aetiology of CFS and the co-occurrence of pain? 3. Because you want to know the overlap between chronic pain syndromes and CFS? Please elaborate on one of these questions in the introduction. In all 3 questions you need a straight definition of CFS and that's my

	first point of worry. The researchers do not adhere to international diagnostic guidelines for CFS (neither the CDC criteria nor the ME criteria for youth in the UK). That means that their patient group will be a mix of CFS patients and patients with chronic unexplained pain. In the introduction they state that hypersensitivity is not investigated in youth with CFS. I did not perform a thorough search, but I know at least from 2 studies performing almost the same research question, but in a well defined patient population and with a clear question: van de Putte, Pediatrics 2005; Nijhof, Lancet 2012; Nijhof Pain Medicine 2013 **Material and methods** CFS patients: how do we know if these are really CFS patients? Perhaps these are patients with chronic unexplained pain and fatigue? Or patients with a school fobia? I think it's necessary to adhere to clear diagnostic criteria. The fact that exercise intolerance is not part of the diagnostic criteria, and that fatigue is not necessarily the main symptom, means that this is not a homogenic population of CFS patients. Only 12% of the patients fulfilled Fukuda criteria! (table 2) *Measures* Is the BPI validated for youth? The fact that the questionnaire had to be changed (from 'work' to 'school') implies that this questionnaire is not validated for patients and controls Pressure pain threshold: what is the intrarater and interrater validity of this method? I need to know to rates to check the validity of the results. Were the researchers blinded for the diagnosis (CFS or not) Pain may be confounded by anxiety and depression. Did the researchers consider this? **Discussion** There is a lot of repetition of results in the discussion. Please remove all sentences with repeated results. There is a lot of speculation about the possible hypersensitivity in CFS patients. The data do not support these (speculated) theories. I

	am quite convinced (but not by this study, but by other studies) about the difference in pressure pain thresholds and interference scores and frequency of pain episodes in this patient group. But, my worries are: - are these CFS patients or do they have another diagnosis (see before) - is the method for measuring pain and pain interference validated? - is this result confounded by mood states? (anxiety, depression) Regarding CFS adolescents, we already know that there is hypersensitivity and lowered pain thresholds, reversible after successful treatment. These new data do not add to this knowledge. page 13 line 21: the study of Nijhof et al examines the pain in relation to increased sensitivity throughout the process of illness page 13 line 24/40: this is all said in the results section. Please skip here. Pain severity and … You can not conclude from this cross sectional study that pain influenced school attendance, general activity and mood etc. It might be the other way around. This study is cross sectional and you can not conclude anything about cause or effect. page 14: fatigue can not be a confounding factor in the relationship between daily interference and pain, because fatigue is the main symptom of the illness. And you should not view pain as a complete different symptom from fatigue. There are more reasons to believe that it is one symptom complex of fatigue AND pain. Strength and limitations This is NOT the first study Limitation is: the imprecise definition of Chronic Fatigue Syndrome

REVIEWER	Prof.dr. Raoul Engelbert dept Rehabilitation, university hospital amsterdam, the Netherlands

	education of physical therapy amsterdam the netherlands
REVIEW RETURNED	06-Jul-2014

GENERAL COMMENTS	the manuscript is well written regarding a relevant topic in adolescence. We recently wrote a manuscript on pain in EDS in adults which focusses on the same topic. We advise this article to be mentioned in the discussion Clin Rheumatol. 2014 Feb 4. [Epub ahead of print] Chronic pain in patients with the hypermobility type of Ehlers-Danlos syndrome: evidence for generalized hyperalgesia. Rombaut L1, Scheper M, De Wandele I, De Vries J, Meeus M, Malfait F, Engelbert R, Calders P manuscript is well written and embedded in relevant literature. the sample of patients is large enough to analyse and generalise well. the topic is relevant in adolescence. the topic is relevant in detecting and describing pain and generalisation of pain in a lot of morbidities, thus now in CFS. The research group is known for extensive research in CFS questions: 1. why is PPT only performed in upper extremity, why is no information provided of non-muscular structures in the lower extremity? 2. is the investigator blinded for patients and controls 3. figure 1: legends and title? 4. discussion: discuss more in detail the relationship between chronic fatigue, pain and functional status which mechanism would be present regarding inactivity in relation to fatigue and pain 5. could the data provide information regarding the interaction fatique, pain and functional inactivity corrected for possible confounders. 6. CFS: time since diagnosis

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

The research question is not original but has been subject of research in more studies, which are neither mentioned nor discussed (e.g. van de Putte, Pediatrics 2005; Nijhof, Lancet 2012; Nijhof Pain Medicine 2013). Regarding etiology one of the most impressive papers is the one written by Nijs, Pain Physician 2012, which is not mentioned.

A)

We agree that some relevant references were not included in the first submission, although one of the requested studies actually was cited (Nijs et al. 2012).

One of the papers (Nijhof et al. 2012) is an intervention study and does not specifically address pain. This was the reason for not including it originally.

*Unfortunately, we did not include the study by van the Putte et al., investigating if constitutional laxity of the connective tissues is more frequently present in adolescents with CFS than in healthy controls (Van De Putte et al. 2005) showing that mean pain thresholds among adolescents with CFS differ considerably from healthy controls. The finding, however, was not further discussed; the authors just stated that the underlying processes of pain sensation were not understood. With this large CFS population, we do strengthens earlier findings and confirm the low PPT in adolescents with CFS and the big difference in PPT between healthy and controls. The relatively large sample of patients together with few missing data make it possible to generalize the results.

**We, unfortunately, overlooked the recent Editorial letter by Nijhof et al (2013) assessing pressure pain threshold in adolescents with CFS. The study showed that that adolescents, recovering from CFS after CBT, had improved PPT compared to those that did not recover, and they concluded that there is a relationship between CFS and pain (Nijhof et al. 2013). The study, however, had no healthy control group, as is the case in our paper, and can therefore not conclude on differences to healthy adolescents. Nevertheless, we have now included this paper in our reference list.
***After performing new searches of the literature, we could not find other studies on pressure pain thresholds in adolescents with CFS. With our large sample of patients, we therefore find our study highly relevant in a field, which still is insufficiently explored.

I do not recommend publishing this article and it's beyond repair, I'm afraid, because:
1. the classification of patients to the diagnosis CFS is not according to international guidelines
2. this concept of pain and fatigue has already been studied and published several times, also in adolescents. But they seem to have overlooked these studies.

B)
*Response to point 1: It seems as if important information in our paper has not come through. The classification of patients is according to international guidelines. There is so far no general agreement of the diagnostic criteria of CFS. However, we have followed recommendations from the literature and used a broad set of criteria for children and adolescents. In addition, our sample has been tested against the Fukuda-criteria. Reviewer 1 claims that only 12.5% of our CFS patients fulfill the Fukuda criteria for CFS. This must be a misunderstanding. The present paper (Table 2) shows that 75% fulfilled the Fukuda criteria. To prevent misunderstanding of the table (Table 2), we have made some adjustments.
**In the NorCAPITAL study (Sulheim et al. 2014) the patients were diagnosed with CFS by a pediatrician or a general practitioner ahead of inclusion. The Norwegian clinical guidelines are in accordance with The Royal College of Peadiatric and Child Health (Royal College of Paediatrics and Child Health) and the National Institute for Health and Clinical Health (National Institute of Helath and Care Exelence 2007). In addition, to confirm the diagnoses and to exclude patients with other conditions that could explain the fatigue, patients were thoroughly examined by a pediatrician in our research team ahead of inclusion. For exclusion criteria see Table 1. Special attention was directed toward excluding patients with depression as a primary cause of fatigue. We hope that this is a sufficient clarification concerning the study population.

Response to point 2: Please see comment marked A *, ** and *** in the section above. Regarding PPT, these two studies are the only ones that have measured PPT in adolescents with CFS and both are different from our study.

Introduction
Why do you want to know more about pain adolescents with CFS?

1. Because ‘pain’ is insufficiently addressed in treatment of CFS adolescents?
2. Because you want to understand the aetiology of CFS and the co-occurrence of pain?
3. Because you want to know the overlap between chronic pain syndromes and CFS?

Please elaborate on one of these questions in the introduction.

In all 3 questions you need a straight definition of CFS and that’s my first point of worry. The researchers do not adhere to international diagnostic guidelines for CFS (neither the CDC criteria nor the ME criteria for youth in the UK). That means that their patient group will be a mix of CFS patients and patients with chronic unexplained pain.

We hope that we have been clear about the aim and reasons for this study, but it seems as if some important information have not come through. We have revised the title of our paper, and we hope this response letter (comment A*, A**, A***) explains the difference between our paper and previous research.

In the introduction they state that hypersensitivity is not investigated in youth with CFS. I did not perform a thorough search, but I know at least from 2 studies performing almost the same research question, but in a well defined patient population and with a clear question:
van de Putte, Pediatrics 2005; Nijhof, Lancet 2012; Nijhof Pain Medicine 2013

We find hypersensitivity to pressure insufficiently investigated in youths with CFS, although a few studies have reported this phenomenon in this group. In the paper by van De Putte et al. (2005), PPTs in adolescents with CFS were compared to healthy controls, but as stated above, the differences in sensitivity were not discussed. We, unfortunately, overlooked the publication (Editorial letter) on PPT in adolescents but after performing new database searches, we could not find other studies on pressure pain thresholds in adolescents with CFS. We will therefore claim that this phenomenon still is insufficiently investigated in youths with CFS, but have modified the statement in the current submission.

Material and methods
CFS patients: how do we know if these are really CFS patients? Perhaps these are patients with chronic unexplained pain and fatigue? Or patients with a school fobia? I think it's necessary to adhere to clear diagnostic criteria. The fact that exercise intolerance is not part of the diagnostic criteria, and that fatigue is not necessarily the main symptom, means that this is not a homogenic population of CFS patients. Only 12% of the patients fulfilled Fukuda criteria! (table 2)

Please see earlier comment (B* and B**).

Measures
Is the BPI validated for youth? The fact that the questionnaire had to be changed (from 'work' to 'school') implies that this questionnaire is not validated for patients and controls

We have explained the changes we made in the BPI, and we tested the internal consistency of the instrument, which had an acceptable Cronbach's Alpha. The numeric rating scales have also been shown appropriate for use with children from 5 years of age (Gaffney 2003). Modified versions of the BPI interference score was used in studies by Engel et.al (Engel et al. 2012, Engel et al. 2005) with participants aged between 8 and 20.

Pressure pain threshold: what is the intrarater and interrater validity of this method? I need to know to rates to check the validity of the results. Were the researchers blinded for the diagnosis (CFS or not)

Regarding validity, we have added a sentence and a citation.
Regarding testing PPT among patients vs controls, the researcher was not blinded. We have added information under "measures" and in limitations.

Pain may be confounded by anxiety and depression. Did the researchers consider this?

In the paper (below the heading Participants), we have made a thorough explanation about the criteria for inclusion taking into consideration the awareness mood disorders. The thorough examination is also specified in this reply (B**). In addition, we have made some comments in

limitations. We have added information in the limitations.

Discussion
There is a lot of repetition of results in the discussion. Please remove all sentences with repeated results.

We have re-written the text in question

There is a lot of speculation about the possible hypersensitivity in CFS patients. The data do not support these (speculated) theories. I am quite convinced (but not by this study, but by other studies) about the difference in pressure pain thresholds and interference scores and frequency of pain episodes in this patient group. But, my worries are:
- are these CFS patients or do they have another diagnosis (see before)
- is the method for measuring pain and pain interference validated?
- is this result confounded by mood states? (anxiety, depression)

Our study cannot explain the mechanisms for hypersensitivity, but it does show that they are hypersensitive regarding pressure and that there is a difference between cases and controls. Further, our study confirms and strengthens the limited research regarding this topic. We aim to discuss our findings in relation to other findings and suggest possible explanations and theories, which could contribute to further development in this field. We do not find this to be speculations.

- Please see our previous explanation regarding diagnosis (B* and B**)
- The method for pain and pain interference are used in other studies with children and adolescents. Additional information is provided in the “measures” section above as well as in the paper.
- The present study has not looked at anxiety and depression as confounding factors. Additional information is added in limitations.

Regarding CFS adolescents, we already know that there is hypersensitivity and lowered pain thresholds, reversible after successful treatment. These new data do not add to this knowledge.

We believe our study supports and strengthens earlier findings by the large population.
Please see A*, A** and A***

page 13 line 21: the study of Nijhof et al examines the pain in relation to increased sensitivity throughout the process of illness

We don’t quite understand this comment. To our understanding, Nijhof et. al. did not examine pain and pressure pain threshold ahead off (which was our point) - and throughout the whole process of illness. Nevertheless, we have added a sentence and cited the editorial letter (Nijhof et.al, 2013).

page 13 line 24/40: this is all said in the results section. Please skip here.
We have re-written this section.

Pain severity and …
You can not conclude from this cross sectional study that pain influenced school attendance, general activity and mood etc. It might be the other way around. This study is cross sectional and you can not conclude anything about cause or effect.

We agree that we cannot conclude about cause and effect. However, we have measured pain interference with function. At this point we have made changes in the text saying that “adolescents

reported that pain interfered …..". Also, we have included your comment about cause and effect.

page 14: fatigue can not be a confounding factor in the relationship between daily interference and pain, because fatigue is the main symptom of the illness. And you should not view pain as a complete different symptom from fatigue. There are more reasons to believe that it is one symptom complex of fatigue AND pain.

We fully agree at this point. When the participants were asked about pain and filled in the questionnaire, a few patients thought it was difficult to focus on pain and not the fatigue at the same time. We have made changes in the text to prevent misunderstanding.

Strength and limitations
This is NOT the first study
We have modified this statement, both in the introduction and in the section about strength and limitations

Limitation is: the imprecise definition of Chronic Fatigue Syndrome

The study population is already commented (B* and B**) in the review letter and in the limitation section of the Discussion.

Reviewer 2:

The manuscript is well written regarding a relevant topic in adolescence. We recently wrote a manuscript on pain in EDS in adults, which focusses on the same topic.
We advise this article to be mentioned in the discussion Clin Rheumatol. 2014 Feb 4. [Epub ahead of print]
Chronic pain in patients with the hypermobility type of Ehlers-Danlos syndrome: evidence for generalized hyperalgesia.
Rombaut L1, Scheper M, De Wandele I, De Vries J, Meeus M, Malfait F, Engelbert R, Calders P

As suggested, we have included the paper in the discussion section, as well as in the chapter; pressure pain threshold.

Manuscript is well written and embedded in relevant literature. the sample of patients is large enough to analyse and generalise well.
the topic is relevant in adolescence. the topic is relevant in detecting and describing pain and generalisation of pain in a lot of morbidities, thus now in CFS. The research group is known for extensive research in CFS
questions:
1. why is PPT only performed in upper extremity, why is no information provided of non-muscular structures in the lower extremity?

We agree that measurements from other body sites would have been interesting. However, the adolescents went through multiple tests and examinations and we had to limit the examination. From a pragmatic perspective, we decided to limit PPT measurements to symptomatic and asymptomatic areas of the upper extremity.

2. is the investigator blinded for patients and controls

The investigator was not blinded for patients and controls. This has been added as a limitation.

3. figure 1: legends and title?

Table 5 has replaced the bar charts in Figure 1

4. discussion: discuss more in detail the relationship between chronic fatigue, pain and functional status which mechanism would be present regarding inactivity in relation to fatigue and pain

We have added a couple of sentences.

5. could the data provide information regarding the interaction fatique, pain and functional inactivity corrected for possible confounders.

In this study we do not have data regarding activity and inactivity, and it is beyond the focus for this paper. We do agree that this would be interesting to look into, and we will have this comment in mind for future papers.

6. CFS: time since diagnosis

Table 2 only provides information regarding disease duration and unfortunately, we do not have information regarding time since diagnosis.

VERSION 2 – REVIEW

REVIEWER	Prof.dr. Raoul Engelbert university hospital amsterdam (AMC), department of rehabilitation, Amsterdam, the Netherlands
REVIEW RETURNED	14-Aug-2014

GENERAL COMMENTS	all my remarks have been discussed thoroughly. the paper is acceptable for publication i am curious who the second and perhaps third reviewers were