



## Review

# Chronic musculoskeletal pain in patients with the chronic fatigue syndrome: A systematic review

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## Abstract

**Background:** In addition to debilitating fatigue the majority of patients with chronic fatigue syndrome (CFS) experience chronic widespread pain.

**Aims:** Conducting a systematic review to critically assess the existing knowledge on chronic pain in CFS. We focussed on the definition, the prevalence and incidence, the aetiology, the relevance and the therapy strategy for chronic musculoskeletal pain and post-exertional pain in CFS.

**Methods:** To identify relevant articles, we searched eight medical search engines. The search terms “chronic fatigue syndrome” AND “pain”, “nociception”, “arthralgia” and “myalgia”, were used to identify articles concerning pain in CFS. Included articles were reviewed by two blinded researchers.

**Results:** Twenty-five articles and two abstract were identified and selected for further appraisal. Only 11 search results focussed on musculoskeletal pain in CFS patients. Regarding the standardized review of the articles, a 96% agreement between the researchers was observed. There is no consensus in defining chronic widespread pain in CFS, and although there is little or no strong proof for the exact prevalence, chronic pain is strongly disabling in CFS. Aetiological theories are proposed (sleep abnormalities, tryptophan, parovirus-B, hormonal and brain abnormalities and central sensitisation) and a reduction of pain threshold after exercise has been shown. Furthermore depression seemed not related to pain in CFS and a staphylococcus toxoid vaccine caused no significant pain reduction.

**Conclusions:** The results from the systematic review highlight the clinical importance of chronic pain in CFS, but only few studies addressing the aetiology or treatment of chronic pain in CFS are currently available.

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**Keywords:** Chronic fatigue syndrome (CFS); Musculoskeletal pain; Epidemiology; Aetiology; Treatment; Review

## 1. Introduction

Chronic fatigue syndrome (CFS) is a debilitating condition that is characterised by persistent and relapsing

fatigue, lasting at least six months, not resolved by rest, causing a marked reduction of working activity, and exacerbated by minimal physical exercise. Fatigue is accompanied by secondary symptoms including sore throat, memory and concentration impairments, headache, sleep disorders, but most often muscle and joint pain. The diagnosis of CFS is performed according to

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standardized clinical criteria established by the “Centre of Disease Control and Prevention” (CDC) in 1994 (Fukuda et al., 1994).

In addition to debilitating fatigue the majority of chronic fatigue syndrome (CFS) patients experience chronic widespread persistent pain, such as arthralgias and myalgias (Goldenberg et al., 1990; Goldenberg, 1991; Buchwald, 1996; Jason et al., 1999). A population-based study revealed that 94% of the persons diagnosed with CFS report muscle aches and pain, and 84% report joint pain (Jason et al., 1999). Nishikai et al. (2001) reported muscle pain in 85 CFS-patients of 114 patients (74.6%). Seventy-four patients (64.9%) complained of arthralgia. In another study 24 of 44 patients suffered from chronic widespread pain (Nijs et al., 2004a). Furthermore clinic-based investigations suggest that 35–70% of persons with CFS meet criteria for fibromyalgia (FM) and 20–70% of individuals with FM also suffer from CFS (Goldenberg et al., 1990; Wysenbeek et al., 1991; Norregard et al., 1993; Buchwald and Garrity, 1994; Buchwald, 1996). Following the criteria of the American College of Rheumatology (ACR) individuals with FM present with a history of widespread pain and pain in at least 11 of 18 tender point sites on digital palpation (with an appropriate force of 4 kg). Pain is considered to be “widespread” when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or lower back) must be present. Pain complaints are present for at least three months (Wolfe et al., 1990). Chronic fatigue accompanied by chronic musculoskeletal impairments, such as myalgias and arthralgias, could be considered as an important subclass of CFS (Tan et al., 2002). However it should be considered that the high frequency of pain in persons with CFS may be due, in part, to the inclusion of myalgias and arthralgias as two of the minor symptoms in the diagnostic criteria following the CDC (Fukuda et al., 1994). Besides the persistent musculoskeletal pain, CFS patients typically experience an exacerbation of their symptoms, after previously well-tolerated levels of exercise (Fukuda et al., 1994; Clapp et al., 1999). They experience muscle pain after a level of exertion that does not cause any tissue damage. The worsening of symptoms is considered to be an important reason for low compliance with graded exercise therapy (Chaudhuri, 2002).

Musculoskeletal pain complaints appeared to be more disabling than chronic fatigue in patients with CFS. Evidence supportive of the clinical importance of widespread pain in CFS has been provided: correlation coefficients between pain intensity and self-reported activity limitations and participation restrictions ( $r$  varying between 0.51 and 0.58) were stronger than those between fatigue and the functional status ( $r = 0.50$ )

(Nijs et al., 2003, 2004c). Interpreting these correlation coefficients chronic pain accounts for 26–33% of the CFS patients’ self-reported activity limitations and participation restrictions (Nijs, 2005). In general, pain complaints strongly compromise the physical (Crook et al., 1984; Becker et al., 1997), the social (Latham and Davis, 1994), psychological (Magni et al., 1993; Becker et al., 1997; Gureje et al., 1998), and the financial integrity (Kemler and Furnée, 2002) of the individual and his environment. Furthermore the professional and the socio-economic consequences should be considered.

A large body of literature concerning pain complaints in patients with FM is available, since musculoskeletal pain is the main concern in these patients. In CFS however, fatigue is rather emphasized. Therefore, we would like to make an inventory about what exactly is yet known about chronic musculoskeletal pain in CFS. This might be important to identify lacunas for future research. After all, amassing knowledge about chronic pain in CFS is essential, given the high prevalence and the relevance of this symptom.

The aim of this study was to systematically review the existing knowledge on chronic musculoskeletal pain in CFS. A systematic review is defined as “a review of the evidence on a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyse data from the studies that are included in the review.” (NHS Centre for Reviews and Dissemination, 2001). The systematic review thus aims to identify all valid answers from existing research to such focused questions. Explicit methods are used to judge the quality of the literature and (crucially) the same criteria are applied to all studies (Griffiths et al., 2005).

Concretely we aimed at answering following questions: (1) How do researchers define chronic musculoskeletal pain, (2) What is the prevalence and incidence of chronic musculoskeletal pain, (3) What is known about post-exertional pain, (4) What is known about the aetiology of (post-exertional) pain, (5) Is there evidence for the clinical relevance, and finally (6) Are there effective treatment strategies for chronic musculoskeletal pain in CFS patients?

## 2. Methods

### 2.1. Systematic literature search

We sought to identify all studies concerning chronic musculoskeletal pain in individuals with CFS. To identify relevant articles, we searched Science Direct (<http://www.sciencedirect.com>), Biomed Central (<http://www.biomedcentral.com>), PubMed (<http://www.ncbi.nlm.nih.gov/entrez>), Article Database of the Vrije Universiteit

Brussel (<http://www.vub.ac.be/BIBLIO>), CEBAM (<http://www.cebam.be>), Cochrane Central Register of Controlled Trials (<http://www.cochrane.org>), Cochrane Database of Systematic Reviews (<http://www.cochrane.org>), and Web of Science (<http://isiwebofknowledge.com>) covering the period 1972 to December 2004. The combination of the search terms “chronic fatigue syndrome” AND pain, nociception, arthralgia and myalgia, was used to identify articles concerning pain in CFS. These key words are not really specific, because we anticipated that there would not be a large body of literature concerning pain in CFS.

To be included in the review an article had to meet the following criteria: (1) subjects of the study had to be individuals diagnosed with CFS; (2) the author(s) studied the concept of musculoskeletal pain in these individuals; (3) both the words “pain”, “nociception”,

“arthralgia” or “myalgia” together with the phrase “chronic fatigue syndrome” must be presented in the title; and (4) the studies were presented in English written full texts. If any of the four inclusion were not fulfilled, then the article was excluded from the literature review.

Afterwards we focussed on the search results that fulfilled these four criteria. Two independent, blinded researchers (MM and JN) reviewed the selected manuscripts, i.e., they were not acquainted with each others evaluation of the search results. Both reviewers achieved the degree of Master of Science and concentrated on research regarding CFS for respectively three and six years. JN already obtained the degree of PhD on this matter. Articles were categorised by the reviewers following study design (clinical trial/review/meta-analysis/case report/cross-sectional/prospective/hypothetical) and study aim (aetiology/prevalence/incidence/treatment/case report/diagnosis). In case of clinical trials, the reviewers were expected to specify the used diagnostic criteria for CFS and widespread pain, and to assess the methodological quality of the trial. In order to make a clear separation between clinical trial and cross-sectional studies, following definitions were used. The US National Library of Medicine (NLM) defines a clinical trial in the Medical Subject Headings (MeSH) as a pre-planned study of the safety, efficacy, or optimum dosage schedule (if appropriate) of one or more diagnostic, therapeutic, or prophylactic drugs, devices, or techniques selected according to predetermined criteria of eligibility and observed for predefined evidence of favourable and unfavourable effects. A cross-sectional study is defined as a study in which the presence or absence of disease

Table 1  
Evaluation criteria methodological quality

Criteria
1. Comparable control group?
2. Accounted for gender as a potential confounder?
3. Blind assessment (in case of comparison of CFS patients with controls)
4. Outcome measurements clearly described?
5. Statistical methods clearly described?
6. Co-interventions avoided?
7. Intention to treat analysis?
8. Randomisation?
9. Randomisation procedure described?
10. Drop outs and reasons mentioned?
11. Double blind? Procedure?
12. Follow-up?

Table 2  
Assessment of the included articles

	Diagnostic criteria	Aim	Design	N	1	2	3	4	5	6	7	8	9	10	11	12
Van Houdenhove (2003)	–	Aetiology, diagnosis, case report	Case report	3	/	/	/	/	/	/	/	/	/	/	/	/
Kerr et al. (2002)	Fukuda et al. (1994)	Aetiology, incidence	Prospective	101	+	+	/	+	+	/	/	/	/	/	/	/
Priori et al. (1994)	Holmes et al. (1988)	Aetiology, case report	Case report	4	/	/	/	+	/	/	/	/	/	/	/	/
Bradley et al. (2000)	/	Aetiology, prevalence	Review	/	/	/	/	/	–*	/	/	/	/	/	/	/
Morriss et al. (1999)	Oxford 1991, ACR 1990	Aetiology	Cross-sectional	145	+	–	+	+	+	/	/	/	/	/	/	/
Nijs et al. (2005)	/	Aetiology	Hypothetical	/	/	/	/	/	/	/	/	/	/	/	/	/
Andersson et al. (1998)	Fukuda et al. (1994), ACR 1990	Treatment	Clinical trial	28	+	+	+	+	+	–	–	–	–	+	+	+/-
Lindal et al. (1996)	Iceland disease	Prevalence epidemiological	Cross-sectional	23	–	+	/	+	–	/	/	/	/	/	/	/
Whiteside et al. (2004)	Fukuda et al. (1994)	Aetiology	Cross-sectional	10	+	+	/	+	+/-	/	/	/	/	/	/	/
Nijs et al. (2004a)	Fukuda et al. (1994), ACR 1990	Aetiology	Cross-sectional	64	–	–	/	+	+	/	/	/	/	/	/	/
Whelton et al. (1992)	Holmes et al. (1988)	Aetiology	Cross-sectional	26	+	–	/	+	+	/	/	/	/	/	/	/

1: comparable control group?; 2: accounted for gender as a potential confounder?; 3: blind assessment?; 4: outcome measurements defined?; 5: statistical methods clearly described?; 6: co-interventions?; 7: intention to treat?; 8: randomised?; 9: randomisation procedure described?; 10: drop-out mentioned?; 11: double-blind?; 12: follow-up?; +: clearly described; –: not mentioned; /: not applicable; \*: literature search not described.

or other health-related variables are determined in each member of the study population or in a representative sample at one particular time (NLM, 2002).

Methodological quality factors were derived from a general knowledge of the literature on bias (for example, importance of comparable groups). The “check-list”, used to categorise and to assess the search results, is shown in Table 1. After reviewing the selected articles, the results of both researchers were compared and differences were analysed. In case of disagreement, the reviewers screened the manuscript a second time and the point of difference was discussed. Both reviewers got the opportunity to argue and to convince the other in order to obtain a consensus. A consensus means the same answers since the possible answers were rather limited as mentioned in an earlier paragraph (study design and study aim) and as shown in Table 2 (yes, no, not applicable). When a consensus was impossible, both views were recorded.

Finally the results were analysed and the existing knowledge off chronic pain in CFS was summarised.

### 3. Results

#### 3.1. Study selection

Twenty-five articles and two abstracts were identified by the literature search and selected for further appraisal. Eleven of the 27 search results were considered after screening following the already mentioned selection criteria. Afterwards the 11 manuscripts were screened and reviewed by the two independent researchers. In most cases (96% or 184 of the 192 items) the two researchers agreed. After a second review and a comparison of the eight differences, the reviewers reached a consensus for six items. Only twice, the two assessors could not agree. The properties of the 11 studies that fulfilled the four inclusion criteria are presented in Table 2.

#### 3.2. Study characteristics

Two of the 11 remaining articles were case reports. One manuscript was a hypothetical article. Furthermore the remainders included one clinical trial and one review, and finally one prospective and five cross-sectional studies.

Focussing on the study aim of the manuscripts, 10 of them concerned the aetiology of pain, of which the review also described the prevalence and two other articles were completed by the incidence and by diagnostic considerations. Besides those 10 articles, one focussed on a possible treatment and the last one targeted the prevalence and epidemiology of pain in CFS.

Another point of interest were the diagnostic criteria used to define CFS patients and widespread pain. In

four cases the 1994 CDC criteria (Fukuda et al., 1994) were used (see Section 1). In two articles the older 1988 CDC criteria were applied (Holmes et al., 1988). Morriss et al. (1999) used the Oxford criteria (Sharpe et al., 1991). In the review, the hypothetical article and the case report by Van Houdenhove (2003), diagnostic criteria were not applicable. Only three research groups defined widespread pain, following the American College of Rheumatology (ACR) classification (Wolfe et al., 1990). Andersson et al. (1998) and Morriss et al. (1999) did not only use the criteria for widespread pain, as defined by ACR. Patients included in their investigations had to meet the criteria for FM (see Section 1: widespread pain and 11 of the 18 tender point), described by ACR (Wolfe et al., 1990). Study criteria are thus even more strict, because in order to fulfil the FM criteria tender point have to be controlled.

#### 3.3. Methodological quality

The evaluation of the methodological quality was not applicable for all the manuscripts (i.e., the review and the hypothetical article). The two case reports included three and four subjects. The number of subjects included in the prospective study, the cross-sectional studies, and the clinical trial varied between 13 and 145. Evaluation points one to five of Table 2 (1: comparable control group?; 2: accounted for gender as a potential confounder?; 3: blind assessment?; 4: outcome measurements defined?; 5: statistical methods clearly described?) could be applied to the cross-sectional and the prospective study. The clinical trial could be subjected to the entire assessment. A score, dependent on the applicable evaluation points, was given to these studies. The results are shown in Table 3. Only one study (Kerr et al., 2002) was given a maximum score (4/4).

Besides listing the different search results and their characteristics, this review attempts to answer, as presented below, the six key questions asked in Section 1. Table 4 will clarify the current findings concerning these six questions, based on the included manuscripts.

Table 3  
Score obtained following the methodological evaluation

	N	Score	Lacuna
Kerr et al. (2002)	101	4/4	/
Morriss et al. (1999)	145	4/5	♀/♂
Andersson et al. (1998)	28	7/12	Co-interventions?, intention to treat?, no randomisation, follow-up?
Lindal et al. (1996)	23	2/4	Controls, statistics?
Whiteside et al. (2004)	26	3/4	♀/♂
Nijs et al. (2004a)	64	2/4	Controls, ♀/♂

♀/♂: not accounted for gender as a potential confounder.

Table 4  
Present knowledge based on search results

	Define pain	Prevalence-incidence	Post-exertional pain	Aetiology	Relevance	Treatment
Van Houdenhove (2003)	Pain	/	/	/	/	/
Kerr et al. (2002)	Arthralgia	/	/	Parovirus B19	/	/
Priori et al. (1994)	Myalgia	/	/	L-tryptophan	/	/
Bradley et al. (2000)	Pain	84% arthralgia and 94% myalgia (Jason et al., 1999)	/	↓CRH, brainstem activity	/	/
Morriss et al. (1999)	ACR 1990	/	/	No relation with depression, but relation tender points-anxiety?	/	Depression no influence on pain, but + for perception of health and social functioning
Nijs et al. (2004a)	ACR 1990	/	/	/	/	/
Andersson et al. (1998)	ACR 1990	/	/	/	/	Staphylococcus toxoid vaccine → overall clinical improvement, and trend for ↓ pain reduction
Lindal et al. (1996)	Pain	Localisation: neck and right buttock, upper chest, left calf and lower back	/	/	/	/
Whiteside et al. (2004)	(Post-exertional) pain	/	Reduction pain threshold after exercise	/	/	/
Nijs et al. (2005)	Chronic widespread pain	/	/	Central sensitisation by NO and by behavioural changes	Pain 33.6% variance of functioning	/
Whelton et al. (1992)	Musculoskeletal pain	/	/	Sleep abnormalities	/	/

Overview of the answers found in the included articles on the six key question.

### 3.4. How do researchers define chronic musculoskeletal pain?

As already mentioned only three research applied the ACR criteria for widespread pain (Wolfe et al., 1990). In the other investigations the term “chronic musculoskeletal pain” is not used or not defined, as for example in the review, the case report of Van Houdenhove (2003), the hypothetical article and the study of Lindal et al. (1996), Whelton et al. (1992) and Whiteside et al. (2004). They talk about (musculoskeletal) pain complaints in general. Others simply talk about arthralgias (Kerr et al., 2002) and myalgias (Priori et al., 1994).

### 3.5. Prevalence

The review of Bradley et al. (2000) mentions that widespread pain is indeed quite common in patients with CFS and refers even so to the study of Jason et al. (1999), in which 94% of the CFS patients reported muscle aches and 84% reported joint pain. Also the overlap between CFS and FM is described in the review. Arthralgias, myalgias, and other pain complaints show the greatest overlap between sufferers with FM and CFS (Bradley et al., 2000). Van Houdenhove (2003) even concluded that there is preliminary evidence for a relationship between CFS/FM and complex regional pain syndrome type I, based on many clinical features similar with CFS and FM, such as a predominance in women, frequent traumatic onset and allodynia or hyperalgesia.

Most frequent experiences of pain in CFS, reported in the study of Lindal et al. (1996) were localised in the neck and right buttock (11 out of 23 patients, or 44%), upper parts of the chest, left calf and lower back (10 out of 23 patients, or 40%). The investigators used a picture of a human body, divided into grids, as described by Lindal (1993). Patients had to mark the grids where they experienced pain.

### 3.6. Clinical relevance

Nijs et al. (2005) describe the high disabling character of the chronic musculoskeletal pain in patients with CFS. Chronic pain accounts for up to 33.6% of the CFS patients' self-reported activity limitations and participation restrictions. Chronic pain would even be more disabling than chronic fatigue.

### 3.7. Post-exertional pain

Following the 1994 CDC criteria patients with CFS typically experience worsening of symptoms after previously well-tolerated levels of exercise (Fukuda et al., 1994). Whiteside et al. (2004) reported that healthy volunteers presented with a mean increase of the pressure pain threshold (PPT) of 2.7 Newton, measured on the

skin fold between thumb and the second finger. CFS patients, in contrary, showed a mean reduction of the PPT of 4.7 Newton. Increased perception of pain/fatigue after exercise may be indicative of a dysfunction associated with the central anti-nociceptive mechanism. Post-exertional myalgia and chronic muscle pain have implications for successful rehabilitation programmes in CFS. However Nijs et al. (2004b) found no associations between pain-related fear of movement, measured with the Tampa Scale for Kinesiophobia-Dutch version, and exercise capacity and activities limitations and participation restrictions in CFS patients experiencing widespread pain.

### 3.8. Possible causes

Bradley et al. (2000) list several possible causes for the pain complaints seen in CFS. They suggest that abnormally low hypothalamic levels of CRH may disrupt the function of several biologic systems involved in pain modulation.

Secondly, brain abnormalities are put forward. Pain experiences of patients with CFS may be related to low resting state levels of functional activity in the brain stem (Bradley et al., 2000).

The high prevalence of psychiatric comorbidity, and in particular depression, often leads to suggestions that CFS is merely a somatic presentation of depression. Morriss et al. (1999) found that CFS-patients with depressive disorder and CFS-patients without depressive disorder did not differ from each other, but experienced significantly more widespread bodily pain (defined by the ACR criteria), self-rated pain, tension headaches and lifetime medically unexplained symptoms than the patients with only a primary unipolar depressive illness. In contrary, CFS patients scoring 11 or more on the anxiety subscale of the HAD (Hospital Anxiety and Depression Scale) had significantly more tender points on examination than CFS patients scoring below 11 on this scale (Morriss et al., 1999).

Sleep patterns in patients with CFS has been studied by Whelton et al. (1992). They showed greater difficulty falling asleep, reduced sleep efficiency and rapid eye movement (REM) sleep in patients with CFS, compared to healthy subjects. Patients showed also more alpha electroencephalographic (EEG) activity during non-REM sleep. Their altered sleep physiology and symptoms are similar to those observed in FM (Whelton et al., 1992).

Priori et al. (1994) described four adolescents who developed a syndrome indistinguishable from CFS as defined by Holmes et al. (1988) after therapeutic ingestion of L-tryptophan and subsequent to the development of a transient rise in eosinophil count and severe myalgia. Following parovirus B 19 infection, 13% (5 of the 39 cases) of the patients developed CFS, as defined by

Fukuda et al. (1994) associated with severe arthralgia (80% or 4 of the 5 patients) (Kerr et al., 2002).

Finally, it is hypothesised by Nijs et al. (2005) that sensitisation of central pain processing pathways explains chronic widespread pain in patients with CFS and that nitric oxide (NO)-levels are related to central pain processing in subjects with CFS experiencing chronic widespread pain. Their hypothetical explanation is based on the current understanding of the pathoimmunity of CFS, together with the observations by Vikman et al. (2003), concerning the NO-dependent reduction of inhibitory activity of the central nervous system and consequent central sensitisation. In addition to the immunological contribution, behavioural changes, such as somatisation, catastrophising and activity-avoidance may induce central sensitisation (Nijs et al., 2005). This link is founded on the findings that these cognitive styles and personality traits may result in sensitisation of dorsal horn spinal cord neurons (through inhibition of descending tracks in the central nervous system) (Zusman, 2002).

### 3.9. Possible treatment

The current knowledge about possible treatment strategies for pain complaints in CFS, is scarce. Treatment of depression per se is likely to make little clinical impact on reported pain, psychophysiological disorders such as tension headache and irritable bowel syndrome or other medically unexplained symptoms in CFS patients but may improve their perception of their health and social function (Morriss et al., 1999).

One study addressed to the effect of staphylococcus toxoid vaccine on pain (Andersson et al., 1998). The same research group performed further studies on this matter (Zachrisson et al., 2002). This approach is based on the potential link between infectious illnesses and CFS (Wilson et al., 1994) and on the personal experiences of the authors that prolonged *Staphylococcus* vaccination, aiming at stimulating the immune system, resulted in clinical improvement. The randomised and double-blind study included 28 women, fulfilling the criteria for FM established by the ACR and the CDC-criteria for CFS. They were randomly allocated to the placebo treatment (injection of sterile water) or to the vaccination treatment (injection of *Staphylococcus* toxoid). The vaccine group showed a significant overall clinical improvement, compared with the pre-treatment results and compared to the improvement in the placebo group. Pain severity was reduced, without intergroup differences. The intergroup differences concerning Comprehensive Psychopathological Rating Scale “pain” bordered on significance ( $p > 0.1$ ). The increase in PPT, both in placebo group and in treatment group, bordered on significance in the vaccine group ( $p > 0.1$ ).

## 4. Discussion

Summarising the actual knowledge concerning chronic musculoskeletal pain in CFS is difficult given the dearth of appropriate studies of good methodological quality. In practicing Evidence Based Medicine (EBM), physicians require relevant studies, with appropriate strength. Several rankings of the strength of evidence generated by different types of clinical research designs have been presented. In addressing a particular clinical issue, clinicians or policy-makers can base their decision making on the types of clinical reports that have been published along with an assessment of the strengths and weaknesses of each study. Table 5 presents the hierarchy of scientific evidence following Sackett (1989). Interpreting this table in relation to the present search results, we still have a lot of work on hand. Search results of this literature study are chiefly situated in the lowest levels of the hierarchy. However, as interpreted by Green and Byar (1984), proceeding down the list, there is a broader and broader base on which to establish one's conclusions. All of the types of studies have played a role in the development of medical science. All of them are useful, and they all have a role in EBM. However, the basic issue is which type of evidence one should rely on the most. Thus, a foundation towards research on musculoskeletal pain in patients with CFS has been laid, but more investigations of good quality are indispensable, aspiring to EBM in CFS.

In addition, although reviews are quite high classified in Table 5, it is not always appropriate to include reviews (and even meta-analyses) in a new review. In the current systematic review we included the review of Bradley et al. (2000), but one must be careful in using Bradley's findings and in drawing conclusions, given the

Table 5  
Hierarchy of evidence (Sackett, 1989)

Level 1	(1a) RCTs that are sufficiently large to be either: positive, with a small risk of being falsely positive or negative, with a small risk of being falsely negative (1b) Meta-analyses of individual patient data (ie, analyses of raw, unprocessed data on individual patients enrolled in previously conducted RCT s)
Level 2	(2a) RCTs that are not sufficiently large to confidently detect (or rule out) a treatment effect (2b) Meta-analyses of the literature (i.e., systematic reviews integrating the processed findings of previously published RCTs)
Level 3	Cohort observational studies comparing treated patients with concurrent, nonrandomised controls
Level 4	Cohort observational studies comparing treated patients with historical controls
Level 5	(5a) Case-series describing the experience of treated patients and using no controls (5b) Expert opinion

different search methods and the different selection criteria. We focussed on conducting a systematic review, in order to supervise the sources and in order to execute a reproducible investigation, therefore information extracted [in the current review, e.g., the prevalence and possible aetiological theories traced in the review of Bradley et al. (2000)] from other reviews should be handled with caution.

Furthermore, the number of investigations about a certain aspect of the chronic pain is too small to give a useful overview about incidence, consequences, possible causes or treatment strategies for musculoskeletal pain complaints in CFS patients. Anno 2005 it is known that an important subgroup of patients diagnosed with CFS suffers from chronic widespread pain, especially myalgias and arthralgias. Furthermore studies provided preliminary evidence for the huge impact of pain complaints. Despite these facts, neither an appropriate explanation nor an appropriate therapy is yet available. The current literature has led to the development of a small number of models of the development of pain in CFS. However, relatively little work has been performed to test hypotheses based on these models. Consequently, possible therapies are withheld.

The methodological problems associated with the study of this disorder may account for the lack of experimental proofs. The literature reviewed previously shows that the recruitment of the patients is the first point of discussion. It is required to recruit only patients who meet criteria for CFS. The 1994 CDC criteria for CFS are most often frequented. Unfortunately not all investigators used these criteria. In the study of Lindal et al. (1996) for example, the subjects were diagnosed with an illness like CFS in an epidemic nearly 50 years ago in Iceland. Morriss et al. (1999) included patients with CFS defined by operationalised Oxford consensus research criteria (Sharpe et al., 1991). Secondly, subjects of different studies must be comparable and representative for the population of CFS patients. That is not the case in the investigation where pain complaints were localised (Lindal et al., 1996). The mean age of the 23 women included, was 62.9 years (SD = 9.1) and all had symptoms for more than 50 years. Given the non-representative sample such results can not be generalised to the CFS population. In addition, when studying pain results should be accounted for gender as a potential confounder. Females often have lower thresholds, greater ability to discriminate, higher pain ratings, and less tolerance of noxious stimuli than males (Berkley, 1997). Women report also greater levels of pain catastrophising (Edwards et al., 2004). Finally studying CFS patients with generalised pain complaints, it is proposed that researchers around the world utilise the criteria for widespread pain of the American College of Rheumatology (Wolfe et al., 1990). This definition was used in only three investigations. The varying results

for prevalence, as outlined in Section 1, are likely due to the different definitions of musculoskeletal pain used in the different investigations. Several investigators reported the quantity of patients that simply suffer from muscle pain or joint pain. Therefore these frequencies are higher. To talk about chronic widespread pain, it is considered to use the ACR criteria of 1990. In addition, several study protocols require a washout of psychoactive and pain-modulating medications (Bradley et al., 2000).

In contrary, a large body of scientific literature regarding the etiology of chronic pain complaints in fibromyalgia (FM) is currently available. This may be surprising given the similarities in both diseases. Is there even any good evidence that chronic pain mechanisms are different between FM and CFS? However, there is evidence for other abnormalities in CFS, like immunological abnormalities, the dysregulation of RNase L (Suhadolnik et al., 1994, 1999), and autonomic abnormalities (Naschitz et al., 2001) typically seen in patients with CFS and not in patients with FM. Also on pain processing there is evidence for differences between the two syndromes, e.g., the brain abnormalities. Patterns of functional brain activity in patients with FM are quite different from those in patients with CFS. Patients with CFS, relative to controls, showed significantly lower blood perfusion in the brain stem (Costa et al., 1995; Tirrelli et al., 1998). Patients with FM exhibited significant lower rCBF levels, during rest, in the thalamus and the caudate nucleus (Mountz et al., 1995). Furthermore Substance P has found to be elevated in CSF of FM patients (Russell et al., 1994) and not in patients with CFS (Even-gard et al., 1998). Furthermore, some peculiarities have been proofed in FM and not yet in CFS; such as increased temporal summation (Sorensen et al., 1998; Staud et al., 2001; Price et al., 2002) and spatial summation, dysregulated descending pain inhibitory control (Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997; Vierck et al., 2001; Julien et al., 2005), hypersensitization of spinal cord neurons (Banic et al., 2004), etc. Thus, as well differences as similarities between the two diseases has been shown. In order to distinguish between FM and CFS, investigations should only include patients who only fulfill the criteria of one syndrome and that would be, clinically, rather unimportant, knowing that the majority of patients present with a combination of the diseases. In future research it would be more interesting, in our opinion, to apply protocols similar to those used for FM patients on CFS patients, for example the protocols addressing spatial and temporal summation or inhibitory pain control as described by the previous mentioned investigators. Those more advanced protocols, could be preceded by more basic research, given the lack of elementary knowledge on chronic pain in CFS. For example, until now there is not much information on specific pain characteristics in CFS (intensity,

variation, course, etc.). In addition, we do not know if this widespread pain was preceded by more localized pain and there is not really certainty about the existence of hyperalgesia or allodynia in CFS. Is the chronic pain in CFS accompanied by other symptoms or complaints, like a dysregulated stress-system or decreased muscle endurance as the result of muscle pain? Based on those elementary findings in order to describe or classify the pain in CFS, further research could even so focus on the different hypothetical causes of pain in CFS and the possible treatment strategies for these complaints. For example, to test the hypothesis of the central sensitisation (as a cause of the pain) in an indirect manner, by comparing PPT of healthy controls and CFS patients in relation to painful spots indicated by the subjects on a picture of the human body. Normally, PPT on pain free spots should be similar in controls and in patients, if not the results would provide preliminary and indirect evidence for central sensitisation in patients with CFS.

To conclude, the preceding review shows that progress has been made towards understanding chronic widespread pain in patients diagnosed with CFS. Several hypotheses have been proposed, but until the present they are not yet experimentally tested. The proposed models should be used to further research focussed on possible causes and treatment strategies of pain complaints in CFS, in order to produce sustained improvements in these patients' pain experiences.

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