Fibromyalgia syndrome
Definition, classification, clinical diagnosis and prognosis

Materials and methods
The parameters of the literature search and analysis and the preparation of the recommendations are described in the article “Methodological fundamentals used in developing the guideline”.

Results
Preliminary remarks
The following findings apply to adults. For the definition, classification, clinical diagnosis and prognosis of chronic pain in multiple areas of the body in children and adolescents, see the article titled “Definition, classification and diagnosis of chronic widespread pain in children and adolescents”.

Definition of chronic pain in multiple areas of the body
Consensus-based statement
Definition of chronic widespread pain (CWP): CWP can be defined according to the American College of Rheumatology (ACR) 1990 criteria and the modified provisional ACR 2010 criteria. EL 5, strong consensus

Comment. Pain can be categorized according to clinical criteria into monolocular pain (e.g., in one part of the body), regional pain (e.g., in one specific area of the body, such as the shoulder or arm) and pain in multiple areas of the body. Population-based studies have shown that most people with musculoskeletal pain have more than one pain location [18, 45].

The ACR classification criteria from 1990 defines CWP in multiple body regions [58] as pain >3 months of continuous pain in the following areas:
- axial skeleton (i.e., cervical spine, anterior chest, thoracic or lumbar spine)
- right and left halves of the body
- above and below the waist.

Widespread pain may also be an indication of at least 7–19 of the predefined types of pain described in the Widespread Pain Index (WPI; modified preliminary ACR 2010 criteria [20, 64]).
Widespread pain can have specific causes (e.g., inflammatory rheumatic disease and diffuse bone metastases). In most patients affected with CWP, there are no specific causes of somatic disease [45].

**Definition of FMS**

**Evidence-based statement**

FMS was defined in the ACR 1990 classification criteria by CWP and painful pressure in at least 11 out of 18 tender points. EL 2b, strong consensus

**Comment.** People with chronic pain, sleep disorders and fatigue have been described since biblical times. Smythe [51] provided a historical overview of examples of famous people, such as Florence Nightingale and Charles Darwin, who were “lifelong invalids, yet lived to a ripe old age”. In the rheumatology literature, the symptom complex is known as soft tissue rheumatism or fibrositis. According to Smythe [50], fibrositis has an imprecise symptomatology with multilocal and stiffness lasting for more than 3 months with distinctive local hyperalgesia, chronic fatigue and sleep disorders. Additionally, a depressive mood is often involved. The term fibromyalgia was first used by Hench (1976) [25]. In 1990, the ACR defined specific criteria for fibromyalgia that are distinct from inflammatory rheumatic diseases and arthritis. The ACR classification criteria of FMS represents a consensus definition based on clinicians’ descriptions of the clinical picture of the disorder. The combination of the above-mentioned criteria distinguished patients with primary (no organic disease) and secondary (co-morbidity inflammatory rheumatic disease) fibromyalgia from control patients with inflammatory rheumatic diseases and regional pain syndromes (e.g., osteoarthritis) with a sensitivity of 88% and a specificity of 81% [58]. These classification criteria were not conceptualized by the ACR authors as diagnostic criteria [61].

**Symptom complex of FMS**

**Evidence-based statement**

People with CWP are described in population-based studies and are present in facilities that treat all of the stages of clinical care. Widespread pain is associated with other physical and mental complaints. EL 2b, strong consensus

**Comment.** Patients with CWP differ from patients with local and regional pain syndromes that are caused by an increase in the severity of physical and mental symptoms (distress). According to the ACR 1990 criteria, patients with CWP and FMS are different from patients with CWP without FMS because their physical and mental symptoms are more severe [7, 19, 56], and their tender points are markers of distress [60].

In a representative German population sample of 2,504 individuals in 2009, an asymptotic distribution of pain locations and physical and mental complaints were described. In a cluster analysis, four groups of individuals were identified: pain-free individuals without physical or mental discomfort (“healthy cluster”), individuals with oligolocular pain and mild physical or psychological symptoms (“regional pain cluster”), individuals with widespread pain, mild physical pain symptoms and no mental discomfort (“CWP cluster”) and individuals with widespread pain and severe physical and mental symptoms (“FMS cluster”) [19]. On the basis of a continuum representing the severity of physical (including the number of pain locations) and psychological symptoms, individuals with CWP were located on the outer region of the continuum, and people with FMS were at the end of the continuum [60].

**Core symptoms of FMS**

**Evidence-based statement**

In addition to CWP, the other core symptoms of FMS include sleep disorders (non-restorative sleep) and fatigue or exhaustion (physical or mental). EL 3b, strong consensus

**Comment.** All of the members of a German FMS self-help organization reported numerous physical and mental complaints as a result of a symptom questionnaire developed by the organization. The primary symptoms (in >97% of those affected) were muscle pain in various locations, back pain, fatigue, joint pain in various locations, poor sleep quality, morning stiffness, exhaustion in the morning, weak concentration, lack of stimulation, reduced performance and forgetfulness [16]. These complaints were also indicated as the most common by patients with FMS from various German clinical facilities who were diagnosed based on the ACR 1990 classification criteria [17], patients with FMS who were diagnosed based on the clinical criteria from the United States (US) database for rheumatic diseases [63] and patient and expert consensuses on the “key domains of FMS” [41].

**Classification of FMS as a functional somatic syndrome**

**Consensus-based statement**

FMS can be classified as a functional somatic syndrome. EL 5, majority

**Comment.** Functional somatic syndromes are defined by a clinical complex of physical symptoms, a defined time period and the absence of the causative somatic disease factors that explain the symptoms (e.g., structural tissue damage, biochemical disorder or specific laboratory findings). The individual medical societies define functional somatic syndromes associated with their respective symptoms and do not consider additional physical and mental complaints [40] associated with other disciplines in the definition.

Fibromyalgia is described in the International Classification of Diseases in the German version of the World Health Organization (WHO) in the chapter titled “Diseases of the musculoskeletal system and connective tissue” and the subsection titled “Other soft tissue diseases not classified elsewhere” (M79.70) [8].

**Definition/overlap of FMS with persistent somatoform pain disorder (F45.40) and chronic pain disorder with psychological and somatic factors (F45.41)**

**Evidence-based statement**

The criteria for FMS (ICD-10 M79.70), persistent somatoform pain disorder (F45.40) and chronic pain disorder with psychological and somatic factors...
Fibromyalgia syndrome. Definition, classification, clinical diagnosis and prognosis

Abstract

Background. The updated German S guidelines for managing patients with fibromyalgia syndrome (FMS) published by the Association of the Scientific Medical Societies in Germany ("Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften", AWMF; registration number 041/004) was planned starting in March 2011.

Materials and methods. The development of the guidelines was coordinated by the German Interdisciplinary Association for Pain Therapy ("Deutsche Interdisziplinäre Vereinigung für Schmerztherapie", DIVS), 9 scientific medical societies and 2 patient self-help organizations. Eight working groups with a total of 50 members were evenly balanced in terms of gender, medical field, potential conflicts of interest and hierarchical position in the medical and scientific fields. Literature searches were performed using the Medline, Psycinfo, Scopus and Cochrane Library databases (until December 2010). The grading of the strength of the evidence followed the scheme of the Oxford Centre for Evidence-Based Medicine. The formulation and grading of recommendations was accomplished using a multi-step, formal consensus process. The guidelines were reviewed by the boards of the participating scientific medical societies.

Results and conclusion. The clinical diagnosis of FMS should be based on the 1990 American College of Rheumatology (ACR) classification criteria (with the examination of tender points), the modified diagnostic criteria from the ACR 2010 (without the examination of tender points) or the criteria published in the German AWMF guidelines for FMS.

The English full-text version of this article is available at SpringerLink (under "Supplemental").

Keywords
Fibromyalgia syndrome · Definition · Classification · Diagnosis · Clinical Guideline

Das Fibromyalgiesyndrom. Definition, Klassifikation, klinische Diagnose und Prognose

Zusammenfassung

Hintergrund. Die planmäßige Aktualisierung der S3-Leitlinie zum Fibromyalgiesyndrom (FMS; AWMF-Registernummer 041/004) wurde ab März 2011 vorgenommen.


Schlüsselwörter
Fibromyalgiesyndrom · Definition · Klassifikation · Klinische Diagnose · Leitlinie

Repeated presentation of physical symptoms in conjunction with persistent requests for medical examinations despite repeated negative results (dysfunctional disease behavior).

Patient resists attempts to discuss the possibility of a psychological cause,
even when the beginning and duration of the symptoms are closely related to unpleasant life events, difficulties or conflicts (somatic fixation).

- The understanding reached regarding the physical or psychological cause of the symptoms is often disappointing to the patients and doctors (dysfunctional relationship behavior).

- The attention-seeking (histrionic) behavior of patients, as listed in the “Etiology and pathophysiology of fibromyalgia syndrome” chapter [49], is not sufficiently explained by the physical symptoms of FMS through somatic disease factors. This criterion applies to most FMS patients. No studies were identified demonstrating that patients with FMS took the initiative to request another organic diagnosis by exclusion after they had been diagnosed with FMS.

Case studies from clinical facilities [15] and cohort studies by FMS self-help organizations [1] report that the majority of those affected by the question of subjective causes of the disease indicate that both physical and psychological factors are involved. A somatic fixation was determined in these samples in only a few patients with FMS. Studies on dysfunctional patient–physician behavior and attention-seeking relationship behavior in patients with FMS were not found. A multicenter German study evaluating the utilization of medical services showed that only a fraction of patients with FMS had an increased number of medical consultations compared to the entire German population [33].

Criteria for persistent somatoform pain disorder:

- **a)** severe excruciating pain >6 months,
- **b)** no sufficient evidence obtained from adequately conducted somatic testing to explain the symptoms,
- **c)** occurs in conjunction with emotional conflicts or psychosocial problems that are important causal factors due to their severity and
- **d)** exclusion of
  - psychogenic pain during the course of a depressive disorder or schizophrenia and
  - pain due to known or psychophysiological mechanisms, such as muscle tension pain or migraine.

Criteria **a** and **b** apply to patients with FMS. Criterion **c** applies to many, but not all, patients with FMS. Case studies from clinical facilities have shown that relevant psychosocial stress was temporally related to the development of or increase in CWP in 60–80% of patients with FMS [15]. Psychosocial stressors are associated with an increased risk of FMS [49]. Regarding criterion **d**, systematic review articles showed that co-morbid depressive disorders occur in 30–80% of patients with FMS [11]. The psychophysiological mechanisms of pain in FMS are described in the “Pathophysiology” chapter [49]. Longitudinal studies from the Swedish twin register have provided evidence of a common factor using path analysis (determined more by environmental factors than by genetic factors), which can affect both functional somatic disorders (e.g., FMS, irritable bowel syndrome, headaches and chronic fatigue syndrome) and psychological disorders (e.g., depression and generalized anxiety disorder) [28, 29]. A dimensional analysis of the FMS symptom complex based on physical and psychological complaints, psychosocial stressors, availability of medical services and subjective beliefs regarding of the cause of the illness is more appropriate than the categorical classification of FMS as a persistent somatoform pain disorder [24].

The criteria of a chronic pain disorder with somatic and psychological factors (F45.41) are as follows: pain that is present for at least 6 months in one or more anatomical regions, which originated due to a physiological process or a physical disorder. Although psychological factors play an important role in the severity, exacerbation or continuation of the pain, they are not the direct cause. The pain induces clinically significant distress and impairment in social, occupational or other important functional areas. Pain disorders that are specifically associated with mood, anxiety, somatization or psychotic disorders should not be considered in this context [8].

This diagnostic category can be used for patients with symptoms of CWP that originated due to inflammatory rheumatic disease or arthritis and because the current extent of their pain symptoms (i.e., number of pain sites, impairments) can be explained by psychosocial processes instead of inflammatory processes in cases of remission or mild clinical courses of the inflammatory symptoms.

Definition/overlap of FMS with depressive disorders

**Evidence-based statement**

FMS can be associated with depressive disorders (EL1b). However, FMS is not to be classified as a depressive disorder. (EL 3a), strong consensus

**Comment.** Population-based and clinical studies reveal an association between CWP, FMS and depressive disorders. However, not every patient with a depressive disorder reports pain, and not every patient with FMS is depressed [43].

The main symptoms of FMS, including pain and fatigue, are also possible symptoms of depressive disorders. Among patients with depressive disorders, 30–60% reported pain [2]. The most common physical symptom in patients with major depression disorders in pharmacological studies was fatigue [53]. Six percent of the patients in these studies reported ≥6 pain localizations [54]. The association rates of multilocular (>2) pain and mood disorders were between 2.8–19.6% in the World Mental Health Survey [13]. In a clinical study, 13% of patients with major depression fulfilled the ACR 1990 criteria for FMS [55]. In a German study, 38% of patients with depressive disorders (F32–34, F43.2) fulfilled the survey criteria for FMS (≥7/19 pain sites and fatigue ≥6/10 using the visual analogue scale) [20]. A subgroup of patients who were diagnosed as depressed also showed fibromyalgia-like symptoms.

In a representative sample of the German population in 2009, 12.5% of individuals with FMS met the survey criteria for major depression and 12.5% met the criteria for another depression syndrome, as measured using the depression module of the health questionnaire for patients [18]. A systematic review of clinical studies showed a prevalence rate of 30–70%
for depressive disorders in patients with FMS [11]. The symptomatology of a percentage of patients diagnosed with FMS also meets the criteria for depressive disorders (e.g., major or minor depression or atypical depression).

Despite a partial overlap in the symptoms and neuroendocrine mechanisms, one review article concluded that major depressive disorders and FMS should not be regarded as variants of the same disease [44].

**Fibromyalgia versus fibromyalgia syndrome**

**Consensus-based statement**

Because symptomatology is defined by a symptom complex, the term “fibromyalgia syndrome” is more appropriate than the term “fibromyalgia”. EL 5, consensus

**Comment.** Functional somatic syndromes do not exhibit a distinctive clinical picture (such as myocardial infarction). The basis for the definition of functional somatic syndromes is a continuum of complaints. The definition of a disease pattern results from the establishment of a threshold by an expert consensus and/or by clinical studies. The same approach is used to describe pronounced continuous biological variables, such as the degree of constriction of the coronary vessels and blood sugar levels. The authors are aware that the term “syndrome” is not used consistently in the medical literature. The concept of a syndrome is understood in these guidelines as “the aggregation of symptoms, which by themselves are not characteristic of the disease, to form a characteristic disease pattern”. Other functional somatic syndromes include irritable bowel syndrome or urethra syndrome. FMS is classified as a first-order syndrome or a symptom complex with unknown or unclear etiology, heterogeneous pathogenesis and a defined phenotype (see statement “Core symptoms of FMS”). Second-order syndromes (sequences) are defined by unknown etiologies, homogeneous pathogenesis and defined phenotypes (e.g., Cushing’s syndrome). Third-order syndromes are defined by homogeneous etiologies, unknown or insignificant pathogenesis and defined phenotypes (e.g., Down syndrome and Marfan syndrome) [34].

**Progression of FMS**

**Evidence-based statement**

Different forms of FMS progression with varying severity can be distinguished based on clinical characteristics. However, a generally accepted classification of the degree of severity does not exist. EL 5, strong consensus

**Comment.** Because the conditions that define FMS are distributed in the general population and clinical populations within a continuum (see statement “Symptom complex of FMS”), any classification of severity depends on the criteria and thresholds used. There is no generally accepted classification for the degree of severity of functional disorders in general and for FMS in particular. The German Guideline “Non-specific, functional and somatof orm physical symptoms” differentiates between mild and severe manifestations ([14], Tab. 1).

In clinical populations of FMS, different clusters of patient groups or severity levels have been distinguished. An increase in physical distress and subjective disturbances were associated with increased drug consumption and physical and mental health comorbidities [6, 48]. In clinical trials, a severity level classification for FMS can be obtained using the Fibromyalgia Impact Questionnaire (FIQ) [46].

**Case study of a patient with mild FMS:**

A 37-year-old female patient reported recurring back pain starting at the age of 11 without radiation to other areas. However, the pain began to extend to her entire back and to all of her extremities 2.5 years ago. Since that time, she reported experiencing pain almost every day of the year. However, in the summer months or during vacations to Mediterranean countries, she experienced little or no pain. For 2 years, she experienced a constant pain level, with an average pain intensity of 6/10, ranging from the lowest pain intensity of 2/10 to the maximum pain intensity of 9/10 on an 11-point numerical scale (NRS). Additional physical discomforts included an increased stiff feeling in her hands and an increased cold sensitivity with no autonomic symptoms. Carrying heavy loads (such as hot boxes) was no longer possible, and the patient could walk but was unable to jog. There were no restrictions on domestic work. The patient had unobtrusive biographical amnesia. At the time of the case study, the patient was married, had a self-employed husband and did not have any children. She had no current mental complaints or emotional disorders, and there were no reports of psychiatric and psychotherapeutic treatments in her patient history.
She has increasing anxiety traceable back to her childhood, such as a fear of the dark and abandonment, and experienced panic attacks and an increase in avoidance behavior at the age of 18. She has not been able to drive alone for the past 2 years and can only shop in small stores within the vicinity of her home. The patient has experienced withdrawal from social contacts for 2 years. For the past 3 years, she has been depressed most of the time and has a lack of desire and motivation. She has received outpatient psychiatric treatment for the past 2 years and has taken several unsuccessful psychiatric drug regimens.

**Prevalence of FMS in Germany**

**Evidence-based statement**
The prevalence of FMS in Germany is approximately 3.5%. EL 2c, consensus

**Comment.** In a summary of 10 studies representing the general adult population from various countries, the prevalence of FMS was between 0.7% and 3.3%. The prevalence was between 1.0% and 4.9% in women and between 0.0% and 1.6% in men. The female-to-male ratio was between 2–21:1 [12].

In Germany, the prevalence of FMS based on the ACR criteria of 1990 in a population of 35- to 74-year-old women was 5.5% [46]. In a representative sample of the population in Germany, the point prevalence of widespread pain (backache and pain in all four extremities) was 8.6%. The point prevalence of FMS (according to the survey criteria of ≥7/19 pain locations and fatigue of ≥6/10 on the visual analog scale) was 3.8% [95% confidence interval (95% CI) 3.6–4.0]. The ratio of women to men was 1.2:1 [18]. In a European study (including Germany), the point prevalence of CWP was determined based on the pain criteria from the London Fibromyalgia Epidemiology Study Screening Questionnaire. The point prevalence of FMS was estimated based on the frequency of FMS in rheumatology practices using the CWP criterion from the London Fibromyalgia Epidemiology Study Screening Questionnaire. The point prevalence of CWP in Germany was 1%, and the point prevalence of FMS was 3.2% (95% CI 2.1–4.3). The female-to-male ratio for FMS was 1.6:1 [5].

In clinical settings, the female-to-male ratio is 8–12:1 [21]. The higher prevalence rates among men in recent epidemiolog-
Clinical studies [5, 18] compared to the rates in clinical institutions can be explained as follows:

1. Not using the tender point criteria for the clinical diagnosis of FMS in epidemiological studies leads to a more frequent diagnosis of FMS in men with CWP because the average pressure pain intensity is lower in men than in women. In the general population [58] and clinical samples, men have fewer pressure-sensitive tender points than women.

2. It is possible that FMS in men with CWP is not diagnosed because FMS is considered a “female sickness” [22].

3. Women with chronic physical discomforts demand more medical services than men with the same discomforts [14].

Clinical diagnosis

Clinical consensus point

The clinical diagnosis of FMS can be determined according to the ACR 1990 classification criteria, the symptom-based criteria of the German FMS S3 guidelines or the current modified ACR 2010 criteria. The clinical diagnosis is based on the anamnesis of a typical symptom complex, clinical examination and the exclusion of physical diseases, which could satisfactorily explain this symptom complex. Strong consensus

Comment. Although the ACR 1990 classification criteria for FMS [58] were designed as classification criteria and not as diagnostic criteria, they were subsequently used for diagnosis in daily clinical routines and studies. The use of the tender point examination was criticized due to the lack of acceptance by non-rheumatologists, lack of objectivity in implementation, missing data on the reliability of the results outside of rheumatology settings and the lack of validity [21, 61].

Based on patient surveys, comparisons between patients with arthritis and rheumatoid arthritis and expert consensus [61], the tentative diagnostic criteria for FMS were developed by a group of experts from the ACR. In the modified preliminary ACR 2010 criteria, the medical assessment of the physical symptoms was replaced by a patient self-assessment using a questionnaire [64]. In the consensus conference of the German S3 guidelines for FMS [10], the AWMF criteria were developed for the clinical diagnosis of FMS ([21], Tab. 2). The historically described symptom triad of CWP, fatigue and sleep disorders is a required diagnostic criterion, and these symptoms are considered core symptoms in the diagnosis of FMS.

Obligatory somatic diagnosis at the initial evaluation

Clinical consensus point

If the initial assessment indicates possible CWP, the following measures are recommended:

- completion of a sketch of the pain or the regional pain scale by the patient,
- targeted exploration of other core symptoms, such as fatigue or sleep disorders,
- complete medical anamnesis, including drug history,
- complete physical examination, including skin, neurological and orthopedic findings
- basic laboratory tests:
  - erythrocyte sedimentation rate, C-reactive protein and full blood count (e.g., polymyalgia rheumatica, rheumatoid arthritis),
  - creatine kinase (CK) (e.g., muscular disorders),
  - calcium (e.g., hypercalcemia),
  - basal thyroid-stimulating hormone (e.g., hypothyroidism),
- for indications of somatic causes of the symptoms, further diagnostics may be necessary depending on the suspected diagnosis.

Strong consensus

Comment. CWP and fatigue can be symptoms of several internal and neurological disorders (Tab. 3, 4). Muscle and joint pain in multiple body regions without evidence of a neuropathy or myopathy can be caused by many drugs. Statins are frequently prescribed, and 10–15% of the patients receiving statin therapy develop myalgia of varying degrees with and with-
Additional technical diagnostics

Clinical consensus point
In a typical symptom complex and the absence of clinical references to internal, orthopedic or neurological diseases (anamnesis and clinical examination without reference to other diseases as causes of pain and fatigue, including unremarkable basic laboratory test results), additional technical diagnostics, such as follow-up laboratory tests, neurophysiology or imaging are not recommended.

Strong consensus

Comment. The most common co-morbid mental disorders in FMS are depressive and anxiety disorders [11]. Screening (via a questionnaire or questions from the doctor to the patient) is possible using the German version of the patient health questionnaire (PHQ)-4 [37] (Fig. 1).

Values ≥3 are observed as the limit for possible depressive disorder (questions 1 and 2) or possible generalized anxiety disorder, panic disorder or posttraumatic stress disorder (questions 3 and 4) and correspond to a percentile rank of 93.4% (depression) and 95.2% (fear) relative to a representative German population sample [37].

Professional psychotherapeutic investigation

Clinical consensus point
A professional psychotherapeutic investigation by a specialist in psychiatry and psychotherapy, psychosomatic medicine, psychotherapy or a medical or psychological psychotherapist is recommended in the following cases:

- a) indications of increased psychological distress (e.g., anxiety or depression),
- b) anamnestic information on current severe psychosocial stressors,
- c) anamnestic information on current or previous psychiatric treatments,
- d) anamnestic information on serious biographical stress factors,
- e) maladaptive in coping with disease,
- f) subjective attributes of mental illness

Consensus

Mortality

Evidence-based statement
Mortality is not increased in FMS. EL 2b, strong consensus

Comment. In a retrospective case control study of 8,186 patients with FMS treated in rheumatology practices (US National Data Bank for Rheumatic Diseases) from 1974–2009, the death rate was not elevated compared to 12,329 patients with osteoarthritis (US National Death Index). The standardized risk of suicide was increased when compared to the US population [odds ratio (OR) 3.3, 95% CI 2.2–5.1] [65]. In a retrospective cohort study in Denmark, 1,361 patients with FMS were observed from 1984–1999. The mortality risk was not elevated, although the female patients had an increased risk of suicide (OR 10.5, 95% CI 4.5–20.7) [9].

Use of medical services

Evidence-based statement
FMS causes high direct and indirect medical expenses in Germany in terms of utilization of health care and health benefits, respectively. EL 2b, strong consensus

Comment. Only studies from Germany were considered. In “IMS Mediplus”, a database of 900 general medical practices in Germany, the use of outpatient services was compared for 4,983 patients with FMS and 4,983 age- and gender-matched controls from 2/2006–2/2007. Patients with FMS reported twice as many visits to general practitioners, transfers to specialists and sick leave compared to the control patients during the investigation period. The medical expenses for patients with FMS (e.g., doctor visits, medications, inpatient treatments and sick leave) were estimated to be $9,573 compared to $329 for the controls [3].

In a study of the former Barmer health insurance (Barmer Ersatzkasse, BEK) from 1 July 2008 to 30 June 2009 for 19,592 insured individuals (0.3% of the total insured in the population) diagnosed with FMS, the annual direct medical costs were calculated to be 3,160 € (outpatient and inpatient treatment), and the indirect medical costs were 721 € (sick pay). Data
from the control group were not reported [39].

Conclusion

The validation of the first version of the German S3 guidelines based on clinical consensus and symptom-based diagnostic criteria [22] and the participation of guideline group members toward the development of the modified provisional 2010 ACR diagnostic criteria [64], which provides a diagnosis of FMS without tender point examination, continues the efforts to facilitate the diagnosis of FMS by non-rheumatologists.

By comparing the recommendations of the S3 guidelines to “non-specific/functional/somatoform disorders of the body” [24] for diagnostic labeling and treatment of the symptom complex, the working group hopes to end the debate of the classification of CWP without sufficient explanatory somatic disease factors. We hope to focus toward filling in the following research gaps:

- development of reliable and internationally accepted degrees of severity for non-specific/functional/somatoform physical disorders in general and in FMS patients in particular and
- prospective cohort studies on the importance of secondary disease gain, social factors, such as unemployment and pension loss, iatrogenic chronicification and diagnostic labels for patients with FMS.

References


Corresponding address

Prof. Dr. W. Eich
Department of Internal Medicine II (General Internal and Psychosomatic Medicine), Heidelberg University Hospital
Im Neuenheimer Feld 10, 69210 Heidelberg
Germany
wolfgang.eich@med.uni-heidelberg.de

Conflict of interest. See Tab. 5 in “Methodological fundamentals used in developing the guideline” by W. Häuser, K. Bernardy, H. Wang, and I. Kopp in this issue.
Etiology and pathophysiology of fibromyalgia syndrome

Background and goals

There is extensive scientific literature on the etiology and pathophysiology of fibromyalgia syndrome (FMS) which makes it difficult for the individual practitioner to stay up-to-date. Recent review articles focus either on biological or psychological aspects. The classification of FMS (physical illness vs. mental disorder), contents of patient education, and the preferred treatment methods are closely related to the identified etiologic and pathophysiologic factors. Therefore, we decided to perform a literature review and a formal consensus process on the pathogenesis and pathophysiology of FMS and chronic widespread pain (CWP). We aimed to analyze the content and quality of published studies on these topics in order to identify possible risk factors for the development of FMS and CWP and also to identify factors that are unrelated to the two syndromes.

Methods

The methodology of the literature search and analysis, and preparation of recommendations are presented in the article "Methodological fundamentals used in developing the guideline".

Results

Preliminary note

The following findings apply to adults. For the etiology and pathophysiology of FMS and CWP in children and adolescents please refer to the chapter "Definition, diagnosis and therapy of chronic widespread pain and so-called fibromyalgia syndrome in children and adolescents".

Etiology

Risk indicators and factors

Evidence-based observation
Current evidence does not allow definite conclusions to be drawn about the etiology of CWP/FMS. It is unclear whether the risk indicators of CWP and FMS described in the following observations are risk factors. Strong consensus

Comment. Risk indicators are characteristics whose presence indicates a greater risk of illness without playing a causative role. Risk factors (etiologic factors) are characteristics that are causally associated with an increased risk of disease. Risk indicators and risk factors for disease are identified by retrospective and prospective cohort studies. The design of these studies, however, do not allow proof of a causal relationship. The following criteria increase the likelihood of a causal relationship: dose–effect relationship and experimental evidence, i.e., randomized-
controlled trials that demonstrate elimination of risk when the risk factor is eliminated.

The literature search yielded 3,107 hits. There were 6 prospective cohort studies with a follow-up duration ranging from 15 months to 45 years on biopsychosocial risk indicators for the development of CWP. There were 2 prospective cohort studies with a follow-up duration ranging from 11–24 years on biopsychosocial risk indicators for the development of FMS and 2 systematic reviews of case–control studies. There were no studies on dose–effect relationships. Experimental studies on risk factors for CWP and FMS were not found.

### Risk indicators of CWP

**Evidence-based observation**

The following biologic, mechanical, and psychosocial factors are associated with the development of CWP (risk indicators):

- **biological factors**: gene polymorphisms (\(\beta_2\)-adrenergic receptors, ACTH precursor receptor, corticosteroid binding globulin), dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis (EL 2b);
- **mechanical factors**: uncomfortable postures at work (crouching, repetitive movements of wrist), monotonous work (EL 2b);
- **psychological factors**: increased physical complaints and illness behavior; low physical health-related quality of life; sleep disorders (EL 2b); permanent threat to life (EL 2c);
- childhood: hospitalization after traffic accident; institutionalization; maternal death; financial need (EL 2b).

### Strong consensus

**Comment.** The results of prospective cohort studies are summarized in Table 1. A study from Israel [1] compared 1,024 people from a town (Sderot) that was repeatedly attacked by rocket fire with 1,006 people who lived in another town (Ofakim) with a similar socioeconomic and demographic profile, but who were not exposed to rocket fire. Trauma-related symptoms and physical complaints were more frequent and the point prevalence of CWP was higher in Sderot (11.1%) than in Ofakim [8.3%; odds ratio (OR) 1.37].

### Table 1

<table>
<thead>
<tr>
<th>Study design</th>
<th>Risk indicator (statistical predictor)</th>
<th>Risk (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective population-based cohort study of 1,658 adults between 25–65 years of age; follow-up after 36 months</td>
<td>Repetitive movements of wrists</td>
<td>OR 1.8 (1.2–2.7)</td>
<td>[25, 26, 27]</td>
</tr>
<tr>
<td></td>
<td>Increased ill health behavior</td>
<td>OR 9.0 (3.7–22.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regional pain at baseline measurement</td>
<td>OR 2.1 (1.3–3.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased physical symptoms</td>
<td>OR 3.3 (1.5–7.4)</td>
<td></td>
</tr>
<tr>
<td>Prospective cohort study of 1,081 newly employed individuals at 12 different work places; follow-up after 24 months</td>
<td>Crouching activity &gt;15 min</td>
<td>OR 2.0 (1.1–3.6)</td>
<td>[16]</td>
</tr>
<tr>
<td></td>
<td>Monotonous work</td>
<td>OR 1.9 (1.1–3.2)</td>
<td></td>
</tr>
<tr>
<td>Prospective population-based cohort study; 3,171 adults without CWP between 25–65 years of age; follow-up after 15 months</td>
<td>Increased physical symptoms</td>
<td>OR 1.8 (1.1–3.1)</td>
<td>[14]</td>
</tr>
<tr>
<td></td>
<td>Increased illness behavior</td>
<td>OR 3.3 (2.3–4.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep disorder</td>
<td>OR 2.7 (1.6–3.2)</td>
<td></td>
</tr>
<tr>
<td>Prospective cohort study of 768 individuals without CWP but with a profile indicating increased risk for CWP; out of a population-based sample of 11,000 individuals; follow-up after 15 months</td>
<td>HPA axis dysfunction</td>
<td>OR 8.5 (1.5–47.9)</td>
<td>[28]</td>
</tr>
<tr>
<td>EPIFUND: 2,509 patients from three British general practitioners between 25–65 years of age; follow-up after 15 months</td>
<td>Gene polymorphisms affecting the HPA axis</td>
<td>OR 1.61 (1.0–2.6)</td>
<td>[19]</td>
</tr>
<tr>
<td></td>
<td>ACTH-precursor-receptor</td>
<td>OR 1.2 (1.0–1.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SERPINA6, rs941601, genotype CT</td>
<td>OR 2.2 (1.1–4.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Genotype TT</td>
<td>OR 2.2 (1.2–4.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corticosteroid-binding globulin MC2R rs11661134, genotype AG and AA</td>
<td>OR 2.2 (1.2–4.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased health-related quality of life</td>
<td>RR 4.0 (2.6–6.2)</td>
<td>[33]</td>
</tr>
<tr>
<td>1958 British Cohort Study: 18,558 individuals; follow-up after 45 years</td>
<td>Teacher reports of persistent behavioral abnormalities at ages 7, 11 and 16 years of age</td>
<td>RR 2.1 (1.4–3.2)</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>(\beta_2)-adrenergic receptor (ADRB2) combinations, e.g. H2-H2</td>
<td>RR 1.8 (1.1–2.9)</td>
<td>[18]</td>
</tr>
<tr>
<td></td>
<td>Hospitalization after traffic accident</td>
<td>RR 1.5 (1.1–2.1)</td>
<td>[30, 31]</td>
</tr>
<tr>
<td></td>
<td>Institutionalization</td>
<td>RR 1.7 (1.3–2.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maternal death</td>
<td>RR 2.0 (1.1–3.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Financial need</td>
<td>RR 1.6 (1.3–1.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple physical symptoms at the age of 7 years</td>
<td>RR 1.5 (1.0–2.3)</td>
<td></td>
</tr>
</tbody>
</table>

ACTH adrenocorticotropin hormone; CI confidence interval; CWP chronic widespread pain; HPA hypothalamic–pituitary–adrenal; OR odds ratio; RR relative risk.
Risk indicators for FMS

Evidence-based observation

The following biological and psychosocial factors are associated with the development of FMS:
- biological factors: inflammatory-rheumatic diseases (EL 2b),
- gene polymorphisms of the SHT2-receptor (EL 3a),
- life style: smoking, overweight, lack of physical activity (EL 2b)
- psychological factors: physical abuse in childhood and adulthood, sexual abuse in childhood and adulthood (EL 3a), stress at the workplace (EL 3b).

Strong consensus

Comment. See Tab. 2. Genetic factors are likely present since FMS tends to cluster in families [38]. Candidate genes in the serotonergic, dopaminergic, and catecholaminergic systems may play a role. However, this is also the case in other chronic pain syndromes and therefore these findings are not specific for FMS [3, 4].

In a retrospective cohort study of 62,000 members of a U.S. health insurance association with FMS was found for rheumatoid arthritis [HR (relative risk) for women 4.5 (95% CI 3.6–5.5), RR for men 6.1 (95% CI 4.2–8.8)] and with systemic lupus erythematosus [RR for women, 5.8 (95% CI 4.2–8.0); RR for men not significant; [46]].

Out of 9,739 patients with rheumatoid arthritis without FMS (U.S. National Data Bank for Rheumatic Diseases) on average 19.8% met the criteria for FMS at least once during 4.4 years of observation; 7.4% met the criteria at the end of the observation period. Poverty [HR (hazard ratio) 1.64 (95% CI 1.47–1.82)], overweight [HR 1.60 (95% CI 1.43–1.79)], depressive symptoms [HR 2.28 (95% CI 1.97–2.64)], numerous physical comorbidities [HR 2.53 (95% CI 2.36–2.71)], and low physical activity [HR 2.53 (95% CI 2.36–2.71)] predicted FMS [47].

In a 2-year prospective observational study of 4,791 hospital employees (4,250 women, 541 men), increased bullying in the workplace, low freedom of action, and high workload increased the risk of physician-diagnosed FMS [22]. Due to problems with the study design (no detection of pain using validated instruments at the beginning and end of the study), the level of evidence was downgraded for this study.

Abstract · Zusammenfassung

Schmerz 2012 · DOI 10.1007/s00482-012-1174-0
© Deutsche Schmerzgesellschaft e.V. Published by Springer-Verlag - all rights reserved 2012

C. Sommer · W. Häuser · M. Burgmer · R. Engelhardt · K. Gerhold · F. Petzke · T. Schmidt-Wilcke · M. Späth · T. Tölle · N. Üçeyler · H. Wang · A. Winkelmann · K. Thieme

Etiology and pathophysiology of fibromyalgia syndrome

Abstract

Background. The updated schedule to the German S3 guidelines on fibromyalgia syndrome (FMS) by the Association of the Scientific Medical Societies ("Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften"; AWMF; registration number 041/004) was planned starting in March 2011.

Materials and methods. The development of the guidelines was coordinated by the German Interdisciplinary Association for Pain Therapy ("Deutsche Interdisziplinäre Vereinigung für Schmerztherapie"; DIVS), 9 scientific medical societies and 2 patient self-help organizations. Eight working groups with a total of 50 members were evenly balanced in terms of gender, medical field, potential conflicts of interest and hierarchical position in the medical and scientific fields. Literature searches were performed using the Medline, Psycinfo, Scopus and Cochrane Library databases (until December 2010). The grading of the strength of the evidence followed the scheme of the Oxford Centre for Evidence Based Medicine.

Results. Current data do not identify distinct etiologic or pathophysiological factors mediating development of FMS. The development of FMS is associated with inflammatory rheumatic diseases (EL2b), with gene polymorphisms of the 5-hydroxytryptamine (HT)2-receptor (EL3a), lifestyle factors (smoking, obesity, lack of physical activity; EL2b), physical and sexual abuse in childhood and adulthood (EL3a).

Conclusion. FMS is most likely the result of various pathogenic factors and pathophysiological mechanisms. The English full-text version of this article is available at Springer-Link (under "Supplemental").

Keywords

Fibromyalgia syndrome · Guideline · Systematic review · Etiology · Pathophysiology

Zusammenfassung

Hintergrund. Die planmäßige Aktualisierung der S3-Leitlinie zum Fibromyalgiesyndrom (FMS; AWMF-Registernummer 041/004) wurde ab März 2011 vorgenommen.


Ergebnisse. Die aktuelle Studienlage erlaubt keine eindeutigen Aussagen zur Ätiologie und Pathophysiologie des FMS. Die Entwicklung eines FMS ist mit entzündlich-rheumatischen Erkrankungen (EL2b), Genpolymorphismen des 5-Hydroxytryptamin(HT)2-Rezeptors (EL3a), Lebensstilfaktoren (Rauchen, Übergewicht, mangelnde körperliche Aktivität; EL2b), körperlicher Misshandlung und sexuellem Missbrauch in Kindheit und Erwachsenenalter (EL3a) assoziiert.

Schlussfolgerung. Das FMS ist wahrschein lich die Endstrecke verschiedener ätiopathogenetischer Faktoren und pathophysiologischer Mechanismen.

Schlüsselwörter

Fibromyalgiesyndrom · Leitlinie · Systematische Übersicht · Ätiologie · Pathophysiologie

Ätiologie und Pathophysiologie des Fibromyalgiesyndroms

Zusammenfassung


Ergebnisse. Die aktuelle Studienlage erlaubt keine eindeutigen Aussagen zur Ätiologie und Pathophysiologie des FMS. Die Entwicklung eines FMS ist mit entzündlich-rheumatischen Erkrankungen (EL2b), Genpolymorphismen des 5-Hydroxytryptamin(HT)2-Rezeptors (EL3a), Lebensstilfaktoren (Rauchen, Übergewicht, mangelnde körperliche Aktivität; EL2b), körperlicher Misshandlung und sexuellem Missbrauch in Kindheit und Erwachsenenalter (EL3a) assoziiert.

Schlussfolgerung. Das FMS ist wahrschein lich die Endstrecke verschiedener ätiopathogenetischer Faktoren und pathophysiologischer Mechanismen.

Schlüsselwörter

Fibromyalgiesyndrom · Leitlinie · Systematische Übersicht · Ätiologie · Pathophysiologie
**Vitamin D deficiency, infectious diseases, and accidents**

**Evidence-based observation**
Data on the association between FMS and vitamin D deficiency, infectious diseases, and accidents is inconsistent. **EL 3b. Strong consensus**

**Comment**

*Vitamin D deficiency*: In population-based studies [29] and in case–control studies [17], an association of CWP with decreased vitamin D levels has been reported. However, in case–control studies no difference in vitamin D levels were found between patients with FMS and healthy controls [10, 42].

*Infections*: Prospective studies are not available. In case–control studies, the association of chronic hepatitis C and FMS is contradictory. The results of two case–control studies showing an increased prevalence of FMS in patients with chronic hepatitis B and HTLV-1 infection, respectively, have not been replicated [38, 39]. Case–control studies investigating the association of Lyme disease with FMS are not available. In a large single-center observational study of 287 patients, 22 patients (8%) developed FMS. Fifteen patients diagnosed with FMS participated in the 4.5-year observational study. Symptoms of Lyme disease improved in 14 of 15 patients following antibiotic therapy but FMS symptoms persisted in all patients [11]. Following Lyme disease, 5% of patients report persistent musculoskeletal pain, fatigue, and difficulties in concentrating [6].

*Accidents*: Data are contradictory. A total of 154 patients who were hospitalized after a whiplash injury were examined after 1.5 and 3 years for the presence of FMS; 53 patients with fractures served as a control group. After 3 years of follow-up, 3 of 126 patients with whiplash injury and 1 of 53 patients with fracture were diagnosed with FMS [43]. A prospective cohort study of 957 members of a health insurance who had recently suffered an automobile accident examined the occurrence of widespread pain (WP) after 12 months of follow-up; 7.8% of patients had WP. Physical symptoms after the accident (RR 2.5, 95% CI 1.2–5.1), high utilization of health care services prior to the accident (RR 3.6, 95% CI 1.6–7.9), somatization prior to the accident (RR 1.7, 95% CI 0.99–2.8), and older age (RR 3.3, 95% CI 1.5–7.1) predicted WP [48].

In a prospective cohort study of 7,462 members of a health insurance company with whiplash injuries of the cervical spine, 266 individuals had localized pain after the accident and were followed-up at 4, 6, and 12 months. The cumulative incidence of CWP was 21%. CWP was reported most commonly in the early time period after the accident. The risk of developing CWP was greater in individuals with depressive symptoms at baseline measurement (OR 3.2, 95% CI 1.6–6.3) [20]. CWP at 12 months was rare [49].

The examination of 53 of 153 survivors 3.5 years after a major train accident demonstrated that 15% fulfilled FMS criteria [5].

**Pathophysiology**

*Altered central pain processing, dysfunction of the HPA axis, peripheral pain generators*

**Evidence-based observation**
It is possible that the following pathophysiological mechanisms play a pathogenic role in FMS: altered central pain processing (EL 3b), dysfunction of the HPA axis (EL 2b), and peripheral pain generators (EL 3b).

**Strong consensus**

**Comment**

The literature search yielded 763 hits. These included a systematic review of biomarkers [9], no other systematic reviews of other pathophysiological mechanisms, and numerous narrative review articles (e.g., [2, 3, 13, 35, 37, 38, 40]). Systematic reviews completed by members of the working group regarding cytokines [44] and central nervous system im-
The best evidence for the role of a disturbed HPA axis derives from a prospective population-based study. Out of 11,000 individuals, 768 were chosen because their psychosocial profile indicated an increased risk for the development of CWP. Then, 463 subjects were randomly selected and 267 (58%) eventually agreed to participate in the study, of whom 241 completed the study. After 15 months, 12% of these individuals had newly developed CWP. A lack of suppression in the dexamethasone suppression test (OR 3.53, 95% CI 1.17–10.65), low morning serum cortisol levels, and high evening salivary cortisol levels were associated with the development of CWP [28].

Neurotransmitter: The neurotransmitter substance P is increased in the cerebrospinal fluid (CSF) of patients with FMS, but also in other chronic pain syndromes, so that substance P is more of a marker for chronic pain than for FMS specifically. Serotonin levels in CSF and serum are decreased. The CSF levels of the neurotrophic factors nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are increased, but the significance of these findings is unclear. Data for other neuropeptides and neurotransmitters are inconsistent [39].

Peripheral nervous system and muscle: It was hypothesized that peripheral pain generators contribute significantly to the initiation or maintenance of FMS [41]. In a subgroup of patients with FMS, polyneuropathy was present [7]. Modulation of muscle afferent fibers may play a role [38].

Altered central pain processing: The studies on central pain processing in FMS cannot be reliably interpreted due to the use of different methods (e.g., PET, IMRI, EEG), different study designs (e.g., measurement while resting or during stimulation), the lack of longitudinal studies, and the low quality of the methods used and of data analysis. Augmentation of pain processing and a tendency for altered structure and functions of brain areas that are important for the cognitive–emotional processing of pain and descending pain inhibition have been reported. However, due to the general lack of patients with other chronic pain syndromes in the control groups, these findings cannot be interpreted as being FMS specific [35].

Disorders of the thyroid hormone system, disorders of the female sex hormones, disorders of the renin–angiotensin–aldosterone system, structural muscle changes, cosmetic breast implants

Evidence-based observation
The following statements from the first version of the guidelines still apply: there is no evidence of a link between FMS and —
- disorders of the thyroid hormone system,
- disorders of the female sex hormones,
- disorders of the renin–angiotensin–aldosterone system,
- structural muscle changes, and
- cosmetic breast implants.

EL 2c, strong consensus

Mechanisms of learning

Evidence-based observation
The following statements from the first version of the guidelines still apply: learning mechanisms such as operant conditioning, and sensitization play a role in the chronicity of FMS.

EL 2b, strong consensus

Comment. See [39]
Biopsychosocial model

Evidence-based observation
A biopsychosocial model with respect to predisposition, initiation, and chronicity of FMS is postulated. Physical and/or biological and/or psychosocial stressors in the context of an appropriate genetic predisposition and learning history produce autonomic, endocrine, and central nervous system reactions that result in the symptoms of FMS, such as pain, fatigue, and sleep disorders, autonomic and psychological symptoms. There is heterogeneity in the genetic predisposition, learning history, and in the autonomic, endocrine, and central nervous system reactions. FMS is a final pathway of various pathogenetic factors and pathophysiological mechanisms. Strong consensus

Comment. See [39]

Discussion

It is difficult to summarize the evidence on the etiology and pathophysiology of CWP and FMS due to several factors. There is an extensive literature on individual factors that are related to CWP or FMS and which may play a role in the etiology or pathophysiology of these conditions. Since the publication of the first version of these guidelines, multiple other factors have been examined, including gene polymorphisms, smoking, overweight and nutrition, vitamins, neuroendocrine factors, immunologic factors, mitochondrial function, different infections, central pain processing, and individual biographical aspects.

Unfortunately, for the majority of these studies, due to limitations in methodology and design, it remains unclear whether the findings indicate random associations, factors inherent to the conditions studied, consequences of disease, or if they indeed represent relevant factors in etiology or pathophysiology.

As was mentioned in the first version of these guidelines, there are some factors for which there is definitely no relationship with FMS. These conclusions are still accurate and apply to the thyroid hormone system, the renin–angiotensin–aldosterone system, female sex hormones, structural muscle changes, Lyme disease, and cosmetic breast implants.

The best evidence for positive correlations of causative factors with the development of CWP or FMS has been obtained from prospective cohort studies. Several biologic factors could be identified, including the presence of inflammatory–rheumatic diseases, genetic factors, lifestyle factors such as smoking, overweight, and decreased physical activity, and psychological factors, such as physical abuse or sexual abuse. Additional prospective, population-based studies with an analysis of dose–effect relationships, and interactions of presumed risk factors are required.

Conclusion for clinical practice

Several factors reduce the meaningfulness of many studies on pathophysiology, such as their sectional design, the lack of consideration of confounding comorbidities, the small number of study subjects, and the use of very heterogeneous methods. The pathophysiological factors that are probably associated with FMS have been listed above. However, because of the aforementioned limitations, it is difficult to assess a causal relationship. There is an urgent need for further research. Future research should employ standardized methods, control for current medication use and psychological comorbidities, and include adequate control groups consisting of healthy individuals and individuals with other chronic pain syndromes. In addition, studies with larger sample sizes are required to simultaneously examine different potential neuroimmunological and neurobiological factors, and their reciprocal relationships.

Corresponding address

C. Sommer
Neurologische Klinik, Universitätssklinikum Würzburg Josef-Schneider-Str. 11, 97080 Würzburg Germany sommer@uni-wuerzburg.de

Conflict of interest. See Tab. 5 in “Methodological fundamentals used in developing the guideline” by W. Häuser, K. Bernardy, H. Wang, and I. Kopp in this issue.

References

7. Caro XJ, Winter EF, Dumas AJ (2008) A subset of fibromyalgia patients have findings suggestive of chronic inflammatory demyelinating polyneuropathy and appear to respond to IV Ig, Rheumatology (Oxford) 47:208–211
Due to its usually chronic course and the highly subjective suffering and functional limitations of many patients, fibromyalgia syndrome (FMS) presents physicians from all fields with complex care and cooperative tasks.

The following key questions were formulated by the supervisory team for the update of this guidelines chapter:

1. Should the diagnosis of FMS be explicitly communicated to the affected individual?
2. Which information concerning symptoms, treatment goals and options should be given at the initial diagnosis?
3. Is patient education worthwhile?
4. Which specialties should coordinate the treatment of FMS?
5. Does a graded treatment approach make sense?
6. When is a stationary, multimodal therapy indicated?
7. How should "therapeutically refractory" courses continue to be treated?

**Materials and methods**

The methods for the literature research and analysis, as well as for the preparation of recommendations, are presented in the article “Methodological fundamentals used in developing the guideline”.

**Results**

**Preliminary note**

The following findings and recommendations apply to adults. The general principles of treatment and coordination of care for children and adolescents are covered in the article “Definition, diagnosis and therapy of chronic widespread pain and so-called fibromyalgia syndrome in children and adolescents”. The key recommendations are italicized.

**Initial diagnosis**

**Information at the initial diagnosis**

**Evidence-based recommendation**

The patients with chronic pain in multiple body regions who meet the criteria of FMS should be informed of the FMS diagnosis. EL 4, strong recommendation, strong consensus

**Comment.** In the case of an initial diagnosis of a disease/disorder, releasing the diagnosis is an ethical medical obligation. This measure is highly feasible and carries little risk. Therefore, an upgrade of the recommendation level by two levels was performed.

No randomized control trials (RCTs) have been conducted on the issue of whether an FMS diagnosis positively or negatively affects the health and functioning of those affected. From the perspective of those affected, the diagnostic labeling of a complex complaint, which may have led to lengthy, frustrating medical diagnostics and therapy, may provide psycholog-
ical relief and a more adequate basis for their treatment. A Canadian study showed greater patient satisfaction with their state of health and a lower incidence of symptoms 18 months after diagnosis [38]. The data regarding the impact of an FMS diagnosis on the further use of medical services are inconsistent, and there are no studies from Germany on this topic. Recent studies from the general medical sector in Great Britain and France indicate a possible reduction in direct medical costs as a result of an earlier diagnosis of FMS [3, 18].

Clinical point of consensus
After an initial diagnosis of FMS, the patient should be informed regarding recommended and non-recommended FMS treatment measures. Strong consensus

Clinical point of consensus
The patient should be advised that their complaint is not an organic disease (fibromyalgia, in the sense of a rheumatic disease) but is instead based on a functional disorder. The legitimacy of the ailment should be assured. The patient's symptoms should be explained in a clear manner with the aid of a biopsychosocial disease model, which builds on the subjective disease theory of the patient, e.g., by means of psychophysiological relationships (stress, vicious circle model). Information regarding the harmlessness of the ailment should be given. The possibilities for the patient to alleviate these symptoms through their own activities should be emphasized. Strong consensus

Comment. The recommendations of the FMS guidelines on the basic measures were adapted based on the recommendations for the German ("Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften", AWMF) S3 guideline recommendations for the management of patients with "non-specific, functional and somatoform physical complaints" [15].

Initial therapy after the initial diagnosis

Criteria for recommending therapeutic procedures

Clinical consensus point
For the selection of therapeutic measures, the preferences and comorbidities of the patient, within the guideline recommendations, should be considered. Strong consensus

Comment. Regarding treatment recommendations, the consideration of patient preferences (e.g., possible weight gain under antidepressant therapy) and comorbidities (e.g., aqua jogging instead of walking with comorbid knee arthritis) is a medical ethical obligation.

Comorbidities

Clinical point of consensus
Comorbid mental disorders and physical illnesses should be treated according to the current guidelines. EL 2a (indirect evidence), strong consensus

Comment. For the treatment of common comorbid disorders other than FMS (e.g., back pain, arthritis and depression), the evidence and recommendation grades for individual therapeutic procedures are found in the relevant guidelines [9, 11, 22].

Therapy evaluation

Clinical point of consensus
The benefits (symptom reduction and performance improvement versus side effects and cost) should be regularly evaluated by patients and clinicians. Therapy should only be continued in the case of a positive benefit. Strong consensus

Comment. The time frame of the evaluation may be different for drug and non-drug therapies. In the first 2 weeks of drug therapy, the compatibility (collection of subjective side effects) of the medication is especially important. The assessment of the effectiveness of the treatment is usually possible after 4 weeks [32]. If benefits (the positive effects that outweigh the side effects) are not determined after 4 weeks, the medication should be stopped. The assessment of the benefits of exercise therapy and psychotherapeutic procedures is recommended after 3 months.

Mild forms of FMS

Clinical point of consensus
For mild forms of FMS, the patient should be encouraged to perform adequate physical and psychosocial activity. Strong consensus

Comment. The distinction between mild and severe cases can be found in the chapter "Definition, classification and diagnosis of fibromyalgia syndrome" [12]. The recommendations for the FMS guidelines on basic measures were adapted based on the German S3 guideline "Recommendations for the management of patients with non-specific, functional and somatoform physical complaints" [15].

Psychosocial activity involves mental activity and the maintenance of hobbies and social contact.

Severe cases

Clinical point of consensus
In severe cases, physical therapy, temporary drug therapy and multimodal therapy should be discussed with the patient.

Consensus
Note: "multimodal" — at least one physically activity with at least one psychotherapeutic procedure

Comment. The distinction between mild and severe cases can be found in the chapter "Definition, classification and diagnosis of fibromyalgia syndrome" [12]. The recommendation for initial therapy is based on the recommendation degree of the therapies mentioned (strong recommendation). The recommendations of the FMS guidelines on basic measures were adapted based on the German (AWMF) S3 guideline "Recommendations for the management of patients with non-specific, functional and somatoform physical complaints" [15].
Lack of response to multimodal therapy in severe cases

Clinical point of consensus
The patients with severe cases who do not respond adequately to the above-mentioned measures should be treated with multimodal programs following the German Operations and Procedures Code ("Operationen- und Prozedürenschlüssel", OPS) and using disorder-specific psychological and/or drug therapy for physical comorbidities. Strong consensus

Comment. According to the German OPS, multimodal therapy is performed in the context of multimodal complex treatments, e.g., (semi-)inpatient multimodal pain therapy (OPS paragraphs 8-91c and 8-918.x), multimodal rheumatological complex treatment (OPS paragraph 8-983.01/2) or an inpatient psychosomatic–psychotherapeutic hospital treatment (OPS paragraph 9-60.x to 9-64.x).

Multimodal pain management requires an interdisciplinary diagnosis in at least two disciplines (compulsory psychiatric, psychosomatic or psychological discipline) and is characterized by the concomitant use of at least three of the following active therapy procedures under medical supervision: psychotherapy, special physiotherapy, relaxation treatment, occupational therapy, medical training therapy, sensorimotor training, workplace training, art or music therapy or other exercise therapies. Multimodal pain management also includes a review of the treatment process through a standardized therapeutic assessment with interdisciplinary team discussion [4].

The intensity of multimodal pain therapy for patients with severe cases of chronic pain syndromes should be >100 h (>25 h of psychotherapy) [26]. The integration of specific modules for mental disorders (e.g., major depression) in multimodal programs is recommended [17]. Regarding disorder-specific psychological and/or drug therapy for unipolar depression, refer to the national guidelines [11].

Abstract
Background. The scheduled update to the German S3 guidelines on fibromyalgia syndrome (FMS) by the Association of the Scientific Medical Societies ("Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften", AWMF; registration number 041/004) was planned starting in March 2011.

Materials and methods. The development of the guidelines was coordinated by the German Interdisciplinary Association for Pain Therapy ("Deutsche Interdisziplinäre Vereinigung für Schmerztherapie", DIVS), 9 scientific medical societies and 2 patient self-help organizations. Eight working groups with a total of 50 members were evenly balanced in terms of gender, medical field, potential conflicts of interest and hierarchical position in the medical and scientific fields. Literature searches were performed using the Medline, PsychINFO, Scopus and Cochrane Library databases (until December 2010). The grading of the strength of the evidence followed the scheme of the Oxford Centre for Evidence-Based Medicine. The formulation and grading of recommendations was accomplished using a multi-step, formal consensus process. The guidelines were reviewed by the boards of the participating scientific medical societies.

Results and conclusion. A diagnosis of FMS should be explicitly communicated with the afflicted individual. A step-wise treatment, depending on the severity of FMS and the responses to therapeutic measures, is recommended. Therapy should only be continued if the positive effects outweigh the side effects. The English full-text version of this article is available at SpringerLink (under "Supplemental").

Keywords
Fibromyalgia syndrome · Review, systematic · Meta-analysis · Guidelines · Coordination of care · Patient education

Das Fibromyalgiesyndrom. Allgemeine Behandlungsgrund­sätze, Versorgungs­koordination und Patientenschulung

Zusammenfassung
Hintergrund. Die planmäßige Aktualisierung der S3-Leitlinie zum Fibromyalgiesyndrom (FMS; AWMF-Registernummer 041/004) wurde ab März 2011 vorgenommen.


Schlüsselwörter
Fibromyalgiesyndrom · Systematische Übersicht · Metaanalyse · Leitlinie · Versorgungs­koordination · Patientenschulung
**Schwerpunkt**

**Duration of drug therapy**

**Evidence-based recommendation**
In the case of a response to drug therapy, after a treatment duration of at least 6 months, a drug cessation trial should be considered for the patient. EL 2a (indirect evidence), recommendation, consensus

**Comment.** For this consensus point, procedures that have a proven efficacy for their temporary use have been recommended. The long-term use of these measures can be implemented to a large extent and carries little risk.

**Coordination of care**

**Long-term therapy**

**Clinical point of consensus**
Treatment coordination should, if possible, be performed by a doctor who has the necessary knowledge and experience in the treatment of FMS. Consensus

**Comment.** The maximum duration of the RCT study with amitriptyline, duloxetine and pregabalin was 6 months [31]. The results of subsequent open RCT studies conducted for up to 6 months showed a sustained reduction in symptoms for only a subset of patients.

**Duration of endurance training**

**Evidence-based recommendation**
The patients who experience an improvement with aerobic endurance training should continue this training permanently. EL 1a, strong recommendation, strong consensus

**Comment.** Only for aerobic training was it shown through RCTs that the positive effects at the initiation of training disappear after some time, yet persist with continuous exercise [35, 36]. At the beginning of endurance training, instruction by trainers/physical therapists experienced in the care of chronically ill people may be useful to match the intensity level to individual performance, which is necessary to achieve symptom reduction, e.g., in the form of formulated functional training. The purpose of this guide is to enable afflicted individuals to have independent endurance training (either alone or in a sports group) [28].

**Patient education**

**Evidence-based recommendation**
Patient and psychological education can be considered a basic measure. EL 1a, open recommendation, strong consensus

**Comment.** The boundaries between patient education, psychoeducation and cognitive behavioral therapy are fluid. The various education methods have been distinguished as follows:

- education (patient education): information regarding the disease and course of treatment in a group and/or in writing and/or on the Internet by a qualified person, fostering discussion and emotional exchange within a group;
- psychoeducation: patient education and information/motivation for self-management (e.g., physical activity and stress reduction) in group lectures and/or in writing and/or on the Internet by a qualified person; and cognitive behavioral therapy: patient education, psychoeducation and exercises/homework on behavioral change with individual feedback by a psychotherapist (direct personal contact or Internet contact).

For the analysis, the two methods of education and psychoeducation were combined. Studies with cognitive behavioral therapy are referenced in the psychotherapy paper [34]. The literature search yielded 934 hits. The results of two studies were published twice [6, 7, 25, 37]. One study was excluded from the meta-analysis because patient education was combined with other methods [21]. One study was excluded because the results for the FMS subgroup were not reported [30]. Fourteen studies (of which four were with psychoeducation) with 1,053 patients and an average treatment duration of 10 (6–20) weeks were qualitatively analyzed (Evidence report, Tab. 1) [5, 7, 8, 10, 13, 14, 16, 19, 20, 24, 27, 29, 33, 39].

The quality of evidence was moderate (moderate methodological quality; moderate external validity; Evidence report, Tab. 2). Patient education was inferior in the control groups with respect to the selected target variables (Evidence report, Tab. 3 and Fig. 1). The standardized mean differences (SMDs; patient education group versus control group) were not very useful for determining effectiveness because in some studies, patient education served as the control group and a higher therapeutic dose was used in the active treatment group. The results of self-efficacy for pain were inconsistent; three studies showed no improvement in self-efficacy (at the beginning and the end of therapy) in the education group [8, 16, 20], and three studies showed an improvement [19, 26, 28]. Education was superior to pain self-efficacy with respect to pain improvement in one study of a wait-list control group [29]. In one study, aerobic training and multimodal therapy were superior to education with respect to the improvement in pain self-efficacy [27].

The acceptance was low (38% dropout rate) and did not differ significantly from that of the control group (Evidence report, Fig. 1). The side effects were not systematically collected or reported. The side ef-
fects of patient education are very rare and minor.

Patient education sessions are offered by FMS self-help organizations on an outpatient basis and are part of (semi-)inpatient treatment programs. Informing patients regarding the diagnosis and treatment possibilities is an ethical obligation. Due to the high feasibility, low risks and ethical obligation, an upgrade of the recommendation level by two levels was recommended. Psychoeducation is essential as a preparation for active therapy.

**Patient-centered communication**

**Evidence-based recommendation**

Patient-centered communication can be used. EL 3a, open recommendation, strong consensus

**Comment.** This analysis included studies in which the doctors received special training in patient communication, such as shared decision-making [6] and communication skills (e.g., information exchange, conversational structure and empathy) [23].

The literature search yielded 20 hits. Two studies with 148 patients and treatment durations of 1 and 52 weeks were used in the analysis [2, 5, 6, 23]. In one study, a follow-up examination was conducted after 52 weeks (Evidence report, Tab. 4). Due to the small sample size, gradation of the evidence was decreased by 2°.

Quantitative data synthesis was not possible due to the different time measurement points. Patient-centered communication was not effective based on the specified endpoints. Patient-centered communication and shared decision making improved the quality of the doctor–patient relationship from both the patient and physician points of view [6]. The patients appreciated the communication skills of doctors who had received training in patient-centered communication more than those of doctors in the control group (typical medical communication). The acceptance was moderate. The dropout rate was 25/107 (23.4%) and did not differ significantly from that of the control group. Side effects were not detected and were not expected. Patient-centered communication can be provided within psychosomatic primary care. Including patients in the decision-making process is an ethical obligation. Due to the lack of risks, the high feasibility and ethical obligations, an upgrade of the recommendation by 2° was made.

**The following recommendations of the first guideline remain valid**

**Transfer to the hospital by general practitioner/specialist**

Clinical point of consensus

Treatment of FMS is usually on an outpatient basis. In the following situations, admission to a hospital is recommended:

- inpatient treatment needs for comorbid physical and mental disorders and (semi-)inpatient multimodal pain therapy.

The indication for (semi-)inpatient treatment from the hospital doctor is based on the inclusion-indication lists of medical societies such as the inclusion indicator list (“Aufnahmeindikationsliste”, AIL) of the German Society for the Study of Pain [1].

**Strong consensus**

**Cause for (semi-)inpatient rehabilitation measurements**

Clinical point of consensus

Instigation of (semi-)inpatient rehabilitation measures is recommended, based on the criteria of the International Classification of Functioning (ICF), when

- participation in the labor force is at risk,
- participation in social life or ability for self-sufficiency is at risk, and
- strongly recommended outpatient therapeutic measures are unavailable or insufficiently effective.

**Strong consensus**

**Discussion**

Given the different interests of the people involved in establishing the guidelines (patients, clinicians, doctors, psychologists, general practitioners, specialists, established doctors, hospitals and physicians in acute care hospitals and rehabilitation facilities), the strong consensus that was reached for all recommendations is emphasized. The recommendations for treatment and coordination of care were adapted to the existing health care structure in Germany.

In addition to the first guideline, step-wise care (depending on the response to recommended therapies) graded according to the severity of FMS treatment was included.

The following care and research requirements exist:

- Further development of care structures and processes:
  - cooperation and networking across fields,
  - avoidance of overcare, underage care and lack of care, and
  - advancement of existing care structures, including a comprehensive offering of high quality care near the patient’s home.

- Therapy:
  - definition of responder criteria (a combination of several core symptoms of FMS),
  - identification of predictors for a positive and negative treatment outcome,
  - studies on “optimal dose finding” for non-drug therapies,
  - evaluation of graded treatment models, and
  - studies on the indication for and effectiveness of rehabilitation.

**Corresponding address**

**Prof. Dr. W. Eich**
Department of General Internal and Psychosomatic Medicine, Heidelberg Medical University Hospital Im Neuenheimer Feld 10, 69210 Heidelberg Germany wolfgang.eich@med.uni-heidelberg.de

**Conflict of interest.** See Tab. 5 in “Methodological fundamentals used in developing the guideline” by W. Häuser, K. Bernardy, H. Wang, and I. Kopp in this issue.
References


Physiotherapy and physical agent therapies for fibromyalgia syndrome

Systematic review, meta-analysis and guidelines

The board of the working groups proposed following questions for the planned revision of the guidelines:
1. Do physiotherapy and therapy agent treatments provide short- and long-term effect for the treatment of fibromyalgia syndrome (FMS)?
2. Which risks are associated with the use of physiotherapy and therapy agents (i.e., passive treatment modalities such as hot/cold packs, massage, electrotherapy, laser and ultrasound) for the treatment of FMS?
3. Which physiotherapy and therapy agent treatments are not recommended for the treatment of FMS?

Materials and methods

The methods used for the literature search and analysis, and for the compilation of the recommendations are reported in the article “Methodological fundamentals used in developing the guidelines”.

Results

Preliminary note: the following statements and recommendations are aimed at adults. For the general treatment objectives and treatment coordination for children and teenagers, please refer to the article “Definition, diagnosis and therapy for chronic pain and so-called fibromyalgia syndrome in children and adolescents”. Key recommendations are italicized.

Strong recommendation

Aerobic training

Evidence-based recommendation

Aerobic training with low to moderate intensity (e.g. faster walking, Nordic walking, cycling or ergometer training, dancing, aqua jogging) should be implemented 2–3 times per week for at least 30 continuous minutes. EL1a, strong recommendation, strong consensus

Comment. For the analysis, studies with physical training, in which at least 60% of the therapy time was spent on aerobic training, were included. Studies, in which aerobic training was combined with psychological therapies, are included and listed in the article “Multicomponent therapy for fibromyalgia syndrome”. For the classification of the intensity of the aerobic training, following criteria were used:
- low intensity: 50–70% Hfmax (maximal heart rate),
- moderate intensity: 70–85% Hfmax and
- high intensity: 85–100% Hfmax.

The literature search produced 285 results. Two studies were excluded from the analysis, as the reported clinical end stage did not meet our inclusion criteria [102, 112]. Forty two studies [1, 4, 10, 15, 19, 22, 27, 28, 29, 33, 36, 40, 44, 45, 49, 53, 55, 58, 60, 66, 67, 70, 72, 74, 76, 77, 81, 82, 84, 87, 89, 90, 91, 93, 95, 100, 101, 105, 109, 111, 112, 116], with a total of 2,071 patients and an average duration time of the study of 12 (3–24) weeks, were included in the qualitative analysis. A total of 16 studies carried out a follow-up at an average of 41 (4–208) weeks (Evidence Report, Tab. 6).
The quality of the evidence was moderate (moderate methodological quality, moderate external validity) (Evidence Report, Tab. 7).

The efficacy was high. The standard mean differences (SMDs; aerobic training—controls) at the end of the therapy on pain, fatigue and quality of life were low. The SMDs (aerobic training—controls) at follow-up for pain and quality of life were low (Evidence Report, Tab. 8 and Fig. 2).

The subgroup analysis showed no difference between land-based and water-based, or a combination of both, aerobic training. Studies in which the patients continued to implement the aerobic training program showed long-term (>3 months) effectiveness at follow-up. Most of the studies implemented an aerobic training program with low to moderate intensity for 30 min at least twice a week. The acceptance was moderate (dropout rate 223/932=24%) and was not greatly different from that of the controls (Evidence Report, Fig. 2). Side effects were not systematically recorded. Relevant side effects, such as stress fractures, high blood pressure and cardiac dysrhythmia were reported as individual cases.

Aerobic training can be done independently or as a part of a sports group, if necessary with guidance as part of the physiotherapy treatment or sport therapy group.

**Strength training**

**Evidence-based recommendation**

Low to moderate intensity strength training should be employed. There is evidence for a training frequency of 60 min twice a week. EL1a, strong recommendation, strong consensus.

**Comment.** The literature search produced 57 studies. Three studies were excluded from the analysis, as they did not meet the inclusion criteria; one study was excluded, as it did not have an appropriate control group [51, 78, 107, 108]. Six randomised, controlled trials (RCTs) with 246 patients and average study duration of 17 (12–21) weeks were analysed [5, 50, 57, 61, 87, 109]. A follow-up was only carried out in one study after 12 weeks (Evidence Report, Tab. 9). The quality of the evidence was moderate (moderate methodological quality, moderate external validity; Evidence Report, Tab. 10).

The efficacy was moderate. The effect size in comparison to the controls (usual care, stretching) on pain, sleep and fatigue at the end of the therapy was moderate (Evidence Report, Tab. 11 and Fig. 3).

Side effects were not systematically recorded. The dropout rate in the studies was 18.6% and not greatly different than that of the control groups (Evidence Report, Fig. 3).

Strength training is available as part of the physiotherapy treatment paid for by the social health insurance and/or can be performed independently following initial guidance by the physiotherapist or sport instructor.

**Functional training**

**Evidence-based recommendation**

Functional training (land- and water-based callisthenics) should be carried out twice a week, for at least 30 min each. EL 2a, strong evidence, strong consensus.

**Comment.** Functional training (land- and water-based callisthenics) under the guidance of a physiotherapist is a benefit offered by the social health insurance and pension insurance and can be prescribed for FMS for a duration of 2–3 weeks. EL1a, recommendation, strong consensus.

Thermal baths

**Evidence-based recommendation**

Thermal baths should be used. There is evidence available, which supports thermal baths 5 times a week over a period of 2–3 weeks. EL 1a, recommendation, strong consensus.

**Comment.** The literature search found 142 studies. Studies which included physical exercise (aerobic training, stretching, breathing exercises) in warm water are included in the section “Aerobic training” and “Stretching”. In this section studies regarding balneo therapy (moor bath, steam bath, sand bath and sauna), hydrotherapy (warm water including whirlpool), spa therapy (bathing in mineralised water) and thalasso therapy (bathing in salt water) are summarised. Studies, which included hydrogalvanic baths, were analysed separately.

One study, which included sauna treatment, was excluded due to missing randomisation [80]. One study, which used moor packs as treatment, was also excluded, as an additional therapy with trazadone was included [14]. Two studies were

1 Functional training and rehabilitation sport were devised by the pension insurance and the rheumatic league in Germany to encourage patients with pain and chronic mobility limitation to move (again) as well as improve social interaction in a group setting.

2 In Germany, the prescription of physiotherapy treatment and related therapy agents is regulated by a healthcare modalities budget (“Heilmittel Budget”). This budget determines the number and modalities of treatment that can be prescribed and must be strictly adhered to by the medical practitioner.
Physiotherapy and physical agent therapies for fibromyalgia syndrome. Systematic review, meta-analysis and guidelines

Abstract

Background. The scheduled update to the German S3 guidelines on fibromyalgia syndrome (FMS) by the Association of the Scientific Medical Societies (“Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften”; AWMF; registration number 041/004) was planned starting in March 2011.

Materials and methods. The development of the guidelines was coordinated by the German Interdisciplinary Association for Pain Therapy (“Deutsche Interdisziplinären Vereinigung für Schmerztherapie”, DIVS), 9 scientific medical societies and 2 patient self-help organizations. Eight working groups with a total of 50 members were evenly balanced in terms of gender, medical field, potential conflicts of interest and hierarchical position in the medical and scientific fields. Literature searches were performed using the Medline, PsyCINFO, Scopus and Cochrane Library databases (until December 2010). The grading of the strength of the evidence followed the scheme of the Oxford Centre for Evidence-Based Medicine. The formulation and grading of recommendations was accomplished using a multi-step, formal consensus process. The guidelines were reviewed by the boards of the participating scientific medical societies.

Results and conclusion. Low to moderate intensity aerobic exercise and strength training are strongly recommended. Chiropractic, laser therapy, magnetic field therapy, massage and transcranial current stimulation are not recommended. The English full-text version of this article is available at SpringerLink (under “Supplemental”).

Keywords

Fibromyalgia syndrome · Review, systematic · Meta analysis · Guideline · Aerobic exercise

Physiotherapie und physikalische Verfahren beim Fibromyalgiesyndrom. Systematische Übersicht, Metaanalyse und Leitlinie

Zusammenfassung

Hintergrund. Die planmäßige Aktualisierung der S3-Leitlinie zum Fibromyalgiesyndrom (FMS; AWMF-Registernummer 041/004) wurde ab März 2011 vorgenommen.


Schlüsselwörter

Fibromyalgiesyndrom · Systematische Übersicht · Metaanalyse · Leitlinie · Aerobes Training

Open recommendations

Stretching

Evidence-based recommendation

Stretching and flexibility training can be considered. There is evidence available for a training frequency of 2–3 times 60 min/week. EI za, recommendation open, strong consensus

Comment. The literature search found 85 studies. Seven studies with eight treatment arms and a total of 322 patients and 69 weeks were included in the analysis [5, 21, 69, 70, 105]. Three studies included a follow-up after 12 weeks (Evidence Report, Tab. 15).

The quality of evidence was moderate (minimal methodological quality, high external validity) (Evidence Report, Tab. 16). The low methodological quality meant that the level of evidence was adjusted down.

1 In Germany a so-called health care catalogue (“Heilmittel Katalog”) governs what can be prescribed for which diseases and diagnoses. It also governs the total amount of treatments that can be prescribed and is closely related to the health care budget.

excluded from the meta-analysis, as these studies included a combination of multimodal treatment [63, 118]. One study was excluded, as the results of the FMS patients were not recorded separately [96]. The results from one study was published twice [20, 75]. Seven studies with 396 patients and average treatment duration of 4 (1.2–12) weeks were included in the analyses [4, 6, 7, 20, 31, 32, 39, 63]. Five studies included follow-ups after an average of 20 (6–36) weeks (Evidence Report, Tab. 12).

A quantitative analysis of five studies, which included thermal baths as treatment, was possible. The quality of the evidence was moderate (moderate methodological quality, moderate external validity) (Evidence Report, Tab. 13).

The efficacy was low. The SMD (thermal bath—controls) on pain at the end of the therapy was high (Evidence Report, Tab. 14 and Fig. 4).

The acceptance was high (drop-out rate of 5%) and did not differ greatly from the controls (Evidence Report, Fig. 4). The risks were presumably moderate: side effects were not systematically recorded. Individual cases of skin changes and cardiac dysrhythmia were described.

Thermal baths as a treatment of choice for chronic pain syndromes are not listed in the health care catalogue1. The availability is reduced (costs for self payment, not available in all rehabilitation centers).

Average treatment duration of 14 (5–20) weeks were included in the analysis [5, 21, 69, 70, 105]. Three studies included a follow-up after 12 weeks (Evidence Report, Tab. 15).
At the end of treatment, the effect of stretching on the reduction of pain and restrictions on the quality of life was inferior to the active control groups (Evidence Report, Tab. 7 and Fig. 4).

The acceptance was moderate (dropout rate of 15%) and did not differ greatly from the controls (Evidence Report, Fig. 5).

The practical applicability is high: within the treatment scope for physiotherapy, stretching is included in the health care catalogue and/or can be accomplished by the patients on their own following supervision by the physiotherapist. Based on the minimal risks and the practicality of stretching, the recommendation level is upgraded by one level.

Strong negative recommendations

Massage

Evidence-based recommendation
Massage should not be used. EL 2a, EG strong negative recommendation, strong consensus

Comment. The literature search found 228 studies. One study with self-massage and stretching was excluded [36]. One study was excluded, as the clinical endpoints did not meet the inclusion criteria [63]. Six RCTs with 213 patients and average treatment duration of 8 (3–20) weeks were analysed [3, 17, 25, 34, 37, 97]. Three studies included a follow-up after 25 (24–26) weeks (Evidence Report, Tab. 18).

The quality of evidence was low (Evidence Report, Tab. 9). Due to the low quality of the evidence, a downgrade of the evidence level was made. Massage was not effective (Evidence Report, Tab. 20 and Fig. 6). The acceptance was high (dropout <10%) and did not differ significantly from the controls (internet evidence report illustration 6). Side effects were not systematically recorded or reported. The availability is complete. Massage for chronic pain syndromes (including FMS) is listed in the health care catalogue.

Quadrant intervention

Evidence-based observation
An operative quadrant operation should not be performed. EL 4, strong negative recommendation, strong consensus

Comment. The literature search found three studies. In contrast to current knowledge of the etiopathogenesis and pathophysiology for FMS, Bauer [11, 12] assumes that FMS can be traced to the compression of vascular-neural bundles at acupuncture points. The efficacy of this is not clearly established. A microsurgical release of the ‘adhesion’ (so called quadrant intervention) in a case study of 118 patients lead to freedom from pain in 60% of the patients [11, 12]. The results of the follow-ups (up to 12 months later) of 700 patients, who were operated on between 2003 and 2005, have only been published on Bauer’s homepage on the internet. The for spring 2009 announced data for the three year follow-up, have to date not been published [13]. This treatment method has as yet not been tested by other authors or in other studies. Neither has the author of the quadrant intervention compared this treatment method with effective treatment methods such as medication and aerobic training. The potential risks of the operation (e.g., wound infection, adhesion) are high.

The applicability is minimal. The costs of the operation are not covered by the social health insurance or by the private health insurance.

Based on the potential risks, the lack of applicability, and the ethical obligations (preservation of the patient from physical and financial damages), the level of recommendation has been downgraded by 2 levels.

Negative recommendations

Chiropractic

Evidence-based recommendation
Chiropractic should not be implemented. EL 3a, negative recommendation, strong consensus

Comment. Studies with craniosacral therapy are listed in a separate heading. The literature search found 25 studies. One study was published as a poster for a study protocol [115]. Three RCTs with 100 patients were analysed (Evidence Report, Tab. 21). As the methodological quality of the studies was low (Evidence Report, Tab. 22) and the number of studies analysed also low, the level of evidence was downgraded by two levels. A quantitative data analysis could not be carried out, as the predetermined variables were not recorded or reported. The qualitative data analysis did not result in a consistent indication of the efficacy of treatment. In one study, chiropractic was no more effective than being on the waiting list in regards to pain reduction [16]. In another study, chiropractic in combination with electrotherapy resulted in a reduction in pain in some patients [102]. In a further study, strength training alone and in combination with chiropractic treatment lead to an improvement in the quality of life [78]. None of the studies reported side effects to the treatment. The dropout rate was between 0 and 10%. Rare and grave complications (e.g., dissection of the carotid artery) have been reported in the literature [43]. Chiropractic is not listed as a prescribed treatment for chronic pain syndromes in the health care catalogue.

Hyperbaric oxygen therapy

Evidence-based statement
Hyperbaric oxygen therapy should not be used. EL 3a, negative recommendation, strong consensus

Comment. The literature search found nine studies. In one RCT 26 patients, who had 15 sessions of hyperbaric oxygen therapy, were compared with 24 patients in the control group (usual care). At the end of the treatment series, there was a greater reduction in the level of pain in the patients in the hyperbaric oxygen therapy group compared with the control group. Side effects were not reported [117]. The quality of evidence in the study was low.

Hyperbaric oxygen therapy for the treatment of FMS is not included in the health care catalogue. Serious complications are reported in the literature [71, 85]. Thus a negative recommendation was made.
Cold (chamber) therapy

Evidence-based recommendation
Cold chamber therapy should not be used as a treatment of choice. EL 3b, negative recommendation, strong consensus

Comment. The literature search found 36 studies. The results of a nonrandomised crossover study were not included, as the clinical end point was reached after 24 h after the treatment [88].

In a case study with 120 patients (41% with FMS) the short-term effects of full body cold treatment (cold chamber) were examined. A separate analysis of the FMS patients was not published. A short-term reduction in pain, (average of 1.5 h) by half of the initial pain level, was reported. At the end of the 4-week treatment period, an average pain reduction of 13% was reported, which most likely is due to the treatments, which were carried out along side the cold chamber treatment. A total of 55 of 120 patients, mainly with FMS, discontinued the cold chamber treatment [73]. In regards to side effects, 7% of the participants reported burns, headaches, shortness of breath, dizziness, increase in pain intensity and anxiety.

In one RCT 28 patients were treated with infrared light and 38 patients with cold chamber. The dropout rate for the cold chamber was 47%, for the infrared light treatment 0%. The patients, who discontinued the cold chamber treatment, did not differentiate in the level of pain reduction from the group receiving the infrared light treatment (both groups showed significant improvement in the level of pain reduction) [63]. The methodological quality of the studies was low. The quality of evidence for cold therapy is low. Efficacy (continued pain reduction) is not shown. The level of acceptance is low, the potential risks high. Thus the recommendation level is reduced by one level.

Dissenting opinion from the patient self-help groups: The experience of individual patients is very positive.

Laser therapy

Evidence-based recommendation
Laser therapy should not be used. EL 3a, negative recommendation, strong consensus

Comment. The literature search found 46 studies. Two studies were excluded from the analyses as laser therapy was combined with other physical therapy modalities [62, 69].

Three studies with 122 patients, and average treatment duration of 2 weeks, were analysed [8, 47, 48] (Evidence Report, Tab. 23). The quality of evidence was low (Evidence Report, Tab. 24). Due to the small number of cases and the low quality level of evidence, a downgrade of 2 levels of evidence was made.

The level of efficacy was moderate. The SMDs (laser—sham laser) at the end of the treatment were high for pain and moderate for tiredness and sleep (Evidence Report, Tab. 25 and Fig. 7).

The level of acceptance was high (dropout rate 0%) (Evidence Report, Fig. 7). Side effects were not reported.

In the studies, laser therapy was applied at a low level of energy. At higher levels of energy, e.g., 7-W Laser, improper use can not only lead to heat reaction, but also to tissue damage. The practicality is low. Laser therapy for FMS is not listed in the health care catalogue. This treatment method is not offered in routine clinical practice. Due to the potential risks and the lack of availability, a downgrade of the recommendation level followed.

Magnetic field therapy

Evidence-based recommendation: Magnetic field therapy should not be used. EL 2a, negative recommendation, strong consensus

Comment. The literature search found 31 studies. One study was excluded, as TENS was combined with other physical agents interventions [62]. Three RCTs with 82 patients and average study duration of 5 (3–5) weeks were analysed (Evidence Report, Tab. 29; [30, 64, 97]). The quality of evidence was moderate (low methodological quality, moderate external validity) (Evidence Report, Tab. 27).

The efficacy of magnetic field therapy was moderate. The SMDs (magnetic field therapy—sham magnetic field therapy) on pain and the quality of life at the end of the intervention period were high (Evidence Report, Tab. 28 and Fig. 8).

The acceptance was moderate (dropout rate 16%) and did not differ greatly from the controls (Evidence Report, Fig. 8). Three quarters of the studies reported side effects.

The practicality is minimal. Magnetic field therapy for FMS is not listed in the health care catalogue. There are not enough medicinal and patient reports available about the efficacy of this system in Germany. Thus a downgrade of the evidence level followed.

Based on the formal criteria, an open recommendation would be possible. This is however not in line with the preferences of the involved company representatives and patient groups. This resulted in a further downgrading in the recommendation of the level of evidence.

Transcutaneous nerve stimulation

Evidence-based recommendation
Transcutaneous nerve stimulation (TENS) should not be used. EL 3a, negative recommendation, consensus

Comment. The literature search found 31 studies. One study was excluded, as TENS was combined with other physical agents interventions [62]. Three RCTs with 82 patients and average study duration of 5 (3–5) weeks were analysed (Evidence Report, Tab. 29; [30, 64, 97]). The quality of evidence was moderate (low methodological quality, moderate external validity) (Evidence Report, Tab. 30). The clinical end points of the studies were published incompletely. Due to the low number of studies and the low methodological quality, the evidence was downgraded by two levels.

A quantitative analysis was completed despite incomplete data presentation. TENS was not effective (Evidence Re-
Port, Tab. 31 and Fig. 9). Even the pre- and post comparisons showed no significant SMDs. The acceptance was high (dropout rate 4%) and did not differ greatly from the controls. Side effects were not reported. Relevant side effects are not described in the literature. TENS as treatment option is provided in the health care catalogue.

**Transcranial direct current stimulation**

**Evidence-based recommendation**

Transcranial direct current stimulation should not be used. EL 2a, negative recommendation, strong consensus

**Comment.** The literature search found 45 studies. The results of one of the studies was published twice [41, 110].

Four studies with six treatment arms and 129 patients and average treatment duration of 15 (5–20) treatments were analysed [23, 41, 79, 110]. All studies carried out a follow up after an average of 4 (3–8) weeks (Evidence Report, Tab. 32). The low number of study participants (<200) resulted in a downgrading of the evidence level.

The quality of the evidence was moderate (high methodological quality, moderate external validity) (Evidence Report, Tab. 33).

The efficacy was low. The SMD (transcranial direct current stimulation vs sham transcranial direct current stimulation) on sleep was low at the end of the studies (Evidence Report, Tab. 34 and Fig. 10).

The acceptance was high (dropout rate of 5%; Evidence Report, Fig. 10). The side effects rate was high: head and neck pain was 10% greater than in the control group. This treatment is an experimental treatment method for chronic pain, which, as yet, is not part of the routine clinical treatment.

As a result of the high risks and low availability, the level of recommendation was downgraded by two levels.

**Neither positive nor negative recommendation possible**

**Full body heat treatment with water-filtered mild infrared-A radiation and hot full body packs**

**Evidence-based statement**

Due to the limited availability of studies, no negative or positive statement is possible. Strong consensus

**Comment.** Here RCTs are summarised, in which full body heat treatment was induced by other methods than described in the section “Thermal baths” (balneo, spa and thalassa therapy). The literature search found 11 studies. No placebo-controlled studies were found for the full body heat treatment with water-filtered mild infrared-A-radiation (6×15 min in 3 weeks). In one RCT full body heat therapy was combined with a 3-week multimodal in-patient treatment (69 patients). Here the therapy group was superior to the multimodal only in-patient (70 patients) treatment in regards to pain reduction and improvement in the quality of life. The positive effects on pain and quality of life were maintained at follow-up at 3 and 6 months. One patient dropped out due to intolerance to the heat treatment [18]. This procedure is not part of the routine clinical intervention.

In one RCT 7 patients received full body hot packs (no details were reported), 8 patients received aerobic training and 11 patients received general exercises. None of the groups showed a significant change in pain, fatigue, insomnia and quality of life [77].

**Hydrogalvanic bath**

**Evidence-based statement**

It is not possible to make either a positive or negative statement due to the limited data level. Strong consensus

**Comment.** The literature search found seven studies. In one RCT 25 patients received connective tissue massage and 25 patients received manual lymphatic drainage over a period of 3 weeks. At the end of the treatment period, lymphatic drainage resulted in a significant reduction in pain, insomnia, tiredness and restrictions in the quality of life and was superior to the connective tissue massage in regards to improvement of the quality of life [34].

In a case study, 17 patients were treated for 12 sessions (60 min each) over a period of 4 weeks. At the end of the treat-
ment, pain, tiredness and insomnia were reduced and the quality of life had improved. At a follow-up after 5 months, pain and tiredness were reduced [9]. The dropout rate was between 0 and 4%. Side effects were not recorded. Relevant side effects are not reported in the literature.

Lymphatic drainage for FMS is not specifically contained in the health care catalogue.

**Physiotherapy (combined active and passive intervention)**

**Evidence-based statement**

It is not possible to make either a positive or negative statement due to the limited number of studies. Strong consensus

**Comment.** Individual content of physiotherapy treatment are analysed in the sections “Strength training” and “Stretching” as well as in the article “Complementary and alternative therapies in fibromyalgia syndrome” under the section “Meditative movement therapies”.

Physiotherapy uses passive—for example movement carried out by the therapist—and active—Independently carried out—movements and interventions as well as the inclusion of physical agents for the treatment and prevention of diseases. For the inclusion in this analysis it was required that passive and active movements were combined. The combination with physical agents was optional. Studies, which included active movements only (with and without physiotherapy guidance) are analysed in the sections “Stretching” and “Strength training”. Studies, which included active movements only (with and without physiotherapy guidance) in combination with movement, breathing exercises and relaxation or meditation are described in the article “Complementary and alternative therapies in fibromyalgia syndrome” under the section “Meditative movement therapies”.

The literature search found 442 studies. One study was excluded, as it did not include randomisation and the physiotherapy program was not described adequately [56]. One study was excluded, as the as “Physiotherapy” described program did not include passive movement [114]. Two RCTs with the above-described criteria were found. In one RCT, 34 patients served as a control group receiving a kinesiotherapy treatment to the cervical spine and ultrasound to pain points over a period of 3 weeks on 5 days for a total of 15 treatments. The experimental group received 50 mg of sertraline per day over a period of 6 months. In the physiotherapy group no significant reduction in pain and insomnia was ascertained, but in the sertraline theses were attained [42]. In one RCT 2 physiotherapy programs were compared: 10 patients received kinesiotherapy and active muscle stretching, and 10 patients received myofascial release according to Mézières twice a week for 75 min each over a duration of 12 weeks. At the end of the treatment period both groups showed a significant improvement in the quality of life. This was not maintained at follow-up 12 weeks later [104].

**Discussion**

In comparison to the first version of the guidelines [91], a stronger recommendation could be given by the quantitative data analysis for aerobic training. The indirect evidence for the efficacy of functional training resulted in a stronger recommendation in the current version of the guidelines. The new version of the guidelines provides a stronger recommendation for strength training. In the first version this intervention was not dealt with. The evidence for the lack of efficacy of massage resulted in a strong negative recommendation. The quantitative data synthesis with absent proof of efficacy resulted in a negative recommendation for TENS and transcranial direct current stimulation, the consideration of limited availability and risks in a negative recommendation for chiropractic, full body cold treatment, laser and magnetic field therapy. Changed criteria for a positive recommendation (presence of at least two studies) resulted in, after an open recommendation for physiotherapy, lymphatic drainage and ultrasound in the first version of the guidelines, the statement that neither a positive nor a negative recommendation is possible due to the restricted current level of data available (Tab. 1).

Further research, in the form of randomised clinical trials, is required for functional training, physiotherapy, lymphatic drainage, magnetic field thera-

---

<table>
<thead>
<tr>
<th>Tab. 1 Changes in the recommendation levels for physical agents and physiotherapy in the first and second version of the guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>Chiropractic</td>
</tr>
<tr>
<td>Functional training</td>
</tr>
<tr>
<td>Strength training</td>
</tr>
<tr>
<td>Full body heat treatment with water filtered mild infrared-A radiation</td>
</tr>
<tr>
<td>Full body cold therapy</td>
</tr>
<tr>
<td>Exercise therapy</td>
</tr>
<tr>
<td>Laser</td>
</tr>
<tr>
<td>Lymphatic drainage</td>
</tr>
<tr>
<td>Magnetic field therapy</td>
</tr>
<tr>
<td>Massage</td>
</tr>
<tr>
<td>Osteopathy</td>
</tr>
<tr>
<td>Physiotherapy</td>
</tr>
<tr>
<td>Transcranial direct current stimulation</td>
</tr>
<tr>
<td>Ultrasound/electrotherapy</td>
</tr>
</tbody>
</table>

---
py, TENS (with adequate stimulation) as well as long-term studies looking into self-management with infrared cabins and bio sauna.

**Conclusion for clinical practice**

It is strongly recommended that aerobic training (e.g., faster walking, Nordic walking, cycling or ergometer training, dancing, aqua jogging) and strength training should be performed on a regular basis at least 2–3 times a week. Recommended is functional training, as well as from the therapy agents, the thermal baths.

Stretching can be considered. The current state of research means that no recommendation can be given for physiotherapy (defined as the implementation of active and passive treatment interventions), craniosacral therapy, hydrogalvanic bath, lymphatic drainage and full body heat treatment with water-filtered mild infrared-A radiation. Not recommended are chiropractic, hyperbaric oxygen therapy, cold chamber treatment, laser therapy, TENS and tran- rapid current direct stimulation. Strong negative recommendations are issued for operative quadrant intervention and massage.

**Corresponding address**

Dr. A. Winkelmann  
Klinik und Poliklinik für Physikalische Medizin und Rehabilitation,  
Klinikum der Universität München, Munich  
Ziemssenstr. 1, 80336 Munich  
Germany  
Andreas.Winkelmann@med.uni-muenchen.de

**Conflict of interest.** See Tab. S in “Methodological fundamentals used in developing the guidelines” by W. Hauser, K. Bernardy, H. Wang, and I. Kopp in this issue.

**References**

Scherpunkt


For the planned revision of the guideline, the steering group of the workgroup posed the following questions:
1. Is multicomponent therapy in FMS effective short-term and long-term?
2. What study duration is needed for a multicomponent therapy to be effective?
3. Which patients should be offered a multicomponent therapy?
4. What are the crucial components in multicomponent therapy?

Materials and methods
Details on literature search and analysis as well as on the development process of the recommendations are listed in the article “Methodological fundamentals used in developing the guideline” in this issue.

Results
The following conclusions are valid for adult patients. For multicomponent therapy of chronic pain in several body parts of children and adolescents, see article “Definition, diagnosis and therapy of chronic widespread pain and so-called fibromyalgia syndrome in children and adolescents”. Key recommendations are italicized.

Multicomponent therapy
Evidence-based recommendation Multicomponent therapy should be applied. EL1a, strong recommendation, strong consensus

Duration of multicomponent therapy
Evidence-based recommendation Duration of therapy should be at least 24 h. EL1a, strong recommendation, strong consensus

Comment to the two recommendations above. In the German Operation and Procedure Code (“Operationen- und Prozeduren schlüssel”, OPS), multicomponent therapy is applicable in the context of a multicomponent complex treatment such as inpatient/outpatient multicomponent pain therapy (OPS items 8-91c and 8-918.x, respectively) or an inpatient psychosomatic–psychotherapeutic clinical treatment (OPS items 9-60.x to 9-64.x).

According to OPS item 8-918.x, a multicomponent pain therapy requires inter-
disciplinary diagnostics by at least 2 distinct disciplines (obligatory one psychiatric, psychosomatic or psychological discipline) and is defined by the simultaneous application of at least 3 of the following therapies under medical administration: psychotherapy, special psychotherapy, relaxation techniques, ergotherapy, medical training therapy, sensomotoric training, employment training, art or music therapy or other practicing therapies. Furthermore, multicomponent pain therapy involves monitoring of the treatment progress via a standardized therapeutic assessment through interdisciplinary team meetings [7]. In the literature, “multidisciplinary approaches” in FMS are defined as the combination of at least one activating procedure (endurance, strength or flexibility training) with at least one psychotherapeutic procedure (patient education and/or cognitive behavioral therapy) [4]. Accordingly, studies combining at least one activating with at least one psychotherapeutic procedure were classified as “multicomponent studies” and therefore included into the analysis. Literature search obtained 760 such studies. One study was excluded as the clinical endpoints did not meet the criteria for inclusion [21]. A second study was excluded because multicomponent therapy was combined with amitriptyline treatment [22]. The outcomes of one study were published twice [17, 18]. All studies that were included in the analysis met the criteria of a multidisciplinary therapy. Whether these studies meet the criteria of a multicomponent therapy (monitoring of the treatment progress via a standardized therapeutic assessment through interdisciplinary team meetings) could not be investigated based on the published study descriptions.

Seventeen studies with 18 study arms, 1,572 patients and an average study duration of 11 weeks (3–26 weeks) were analyzed [2, 3, 4, 6, 8, 9, 10, 12, 13, 14, 15, 16, 18, 19, 21, 23, 24]. In 8 studies, follow-ups after an average of 8 months (range 4–24 months) were conducted (Evidence Report Tab. 35).

The quality of evidence was moderate (high quality of methods, moderate external validity) (Evidence Report, Tab. 36).

Multicomponent therapy was highly effective. The standardized mean differences (SMDs) of multicomponent therapy vs. controls at the end of therapy were low for pain and fatigue and moderate for quality of life. The SMDs for multicomponent therapy vs. controls at follow-up were low for fatigue and quality of life (Evidence Report, Tab. 37 and Fig. 11). Subgroup analysis showed that significant effects on pain, fatigue and quality of life were obtained only at a study duration of 24 h or more (the maximum within the included studies was 64 h) [10]. The acceptance was moderate [dropout rate 107/712 (12%)] and was not significantly different compared to controls (Evidence Report Fig. 11). Side effects were not systematically determined (or reported, respectively). According to clinical experience, multicomponent therapy has no significant side effects.

As in the majority of the analyzed studies patients with comorbid depression or anxiety disorder were excluded, multicomponent therapy in more severe cases is not sufficiently represented. For treatment in cases of more severe disease progression, more intensive multicomponent programs are recommended (see recommendation in the article “Fibromyalgia syndrome: general principles of and coordination of clinical care and patient education”).

Discussion
Quantitative data analysis confirmed the outcome of the first version of this guideline [1] where multicomponent therapy (MT) was strongly recommended.

The following recommendations should be considered to avoid methodological constraints in future studies of MT in FMS:
1. medication and concomitant treatment should be documented along the study progress and should be taken account of as covariates,
2. comorbidity of mental conditions, psychosocial stress and coping with stress should be determined at the beginning, the end, and at follow-up of therapy and should also be included as covariates,
3. predefined dichotomous parameters of the outcome (return to employment, number of patients with defined reduction of pain etc.) allow for the determination of prognostic parameters to MT,
4. identification of predictors of positive as well as negative outcomes of therapy,
5. randomized comparative clinical trials to identify the crucial components in MT,
6. randomized comparative clinical trials on the efficiency of MT dependent on therapy intensity including the documentation of long-term effects, and
7. randomized comparative clinical trials to identify the needed duration of therapy in a multicomponent program dependent on the severity of disease.

Conclusion for clinical practice
The review of more recent literature confirmed the strong recommendation of multicomponent therapy as given in the first version of this guideline. In the analyzed studies, multicomponent therapy was defined as a combination of one somatically activating therapy with one psychological procedure and was implemented in an outpatient setting. The studies included in the analysis did not meet the high quality standards of an inpatient/outpatient multicomponent therapy as specified in the German OPS. There are no studies at hand which could validate the recommendation of a scaling of the intensity of treatment based on case severity. Therefore, the recommendation of the application of more intensive multicomponent programs in cases of more severe disease progressions relies on clinical consensus.

Corresponding address
Dr. B. Arnold
Abteilung Schmerztherapie, Klinikum Dachau
Krankenhausstr. 15, 85221 Dachau
Germany
bernhard.arnold@amperkliniken.de

Conflict of interest. See Tab. 5 in “Methodological
Multicomponent therapy of fibromyalgia syndrome. Systematic review, meta-analysis and guideline

Abstract

Background. The scheduled update to the German S3 guidelines on fibromyalgia syndrome (FMS) by the Association of the Scientific Medical Societies (“Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften”; AWMF; registration number 041/004) was planned starting in March 2011.

Materials and methods. The development of the guidelines was coordinated by the German Interdisciplinary Association for Pain Therapy (“Deutsche Interdisziplinären Vereinigung für Schmerztherapie”, DIVS), 9 scientific medical societies and 2 patient self-help organizations. Eight working groups with a total of 50 members were evenly balanced in terms of gender, medical field, potential conflicts of interest and hierarchical position in the medical and scientific fields. Literature searches were performed using the Medline, PsycINFO, Scopus and Cochrane Library databases (until December 2010). The grading of the strength of the evidence followed the scheme of the Oxford Centre for Evidence-Based Medicine. The formulation and grading of recommendations was accomplished using a multi-step, formal consensus process. The guidelines were reviewed by the boards of the participating scientific medical societies.

Results and conclusion. The use of multicomponent therapy (the combination of aerobic exercise with at least one psychological therapy) for a minimum of 24 h is strongly recommended for patients with severe FMS. The English full-text version of this article is available at SpringerLink (under “Supplemental”).

Keywords
Fibromyalgia syndrome · Review, systematic · Meta-analysis · Guideline · Multimodal therapy

Zusammenfassung


Ergebnisse und Schlussfolgerung. Der Einsatz von multimodaler Therapie (Kombination von aerobem Training mit mindestens einem psychologischen Verfahren) mit mindestens 24 h Therapiedauer wird für Patienten mit schweren Verläufen des FMS stark empfohlen.

Schlüsselwörter
Fibromyalgiesyndrom · Systematische Übersicht · Metaanalyse · Leitlinie · Multimodale Therapie

References


fundamentals used in developing the guideline” by W. Häuser, K. Bernardy, H. Wang, and I. Kopp in this issue.
Psychotherapy for patients with fibromyalgia syndrome
Systematic review, meta-analysis and guideline

For the planned revision of the guideline the steering group posed the following questions:

1. Is psychotherapy in fibromyalgia syndrome (FMS) effective in short- and long-term?
2. What are the risks involved when implementing psychotherapy in FMS?
3. Which types of psychotherapy are not recommended in FMS?

Methods

The methods used in the literature search and analysis, and preparation of the recommendations can be found in the article “Methodological fundamentals used in developing the guideline”.

Results

Preliminary note

The following findings pertain to adults. For information on the psychotherapy of children and adolescents with chronic pain in several body regions, refer to the paper “Definition, diagnosis and therapy of chronic widespread pain and so-called fibromyalgia syndrome in children and adolescents”. Key recommendations are italicized.

Indication for psychotherapy

Note: The following recommendation of the first version of the guideline is still valid.

Clinical consensus
Psychotherapy in FMS is recommended in the following clinical constellations:

- maladaptive disease management (e.g. catastrophizing, inappropriate physical avoidance behavior or dysfunctional perseverance) and/or
- relevant modulation of the symptoms due to stress of daily life and/or interpersonal problems and/or
- comorbid mental disorders.

Strong consensus

Strong recommendations

Relaxation training combined with aerobic exercise (multicomponent therapy)

Evidence-based recommendation
Relaxation training combined with aerobic exercise (multicomponent therapy) should be used. EL 1a, strong recommendation, strong consensus

Comment. Four studies of multicomponent therapy [3] with 414 patients and an average study duration of 16 (6–26) weeks used a combination of relaxation training and aerobic exercise (Evidence Report, Tab. 38; [11, 30, 36, 37]). The quality of the evidence was moderate (Evidence Report, Tab. 39). The efficacy was low. Low effects on pain and quality of life were found at the end of treatment (Evidence Report, Tab. 40 and Fig. 12).
Cognitive behavioral therapy combined with aerobic exercise (multicomponent therapy)

Evidence-based recommendation
Cognitive behavioral therapy combined with aerobic exercise (multicomponent therapy) should be used. EL1a, strong recommendation, strong consensus

Comment. Six studies with 7 study arms of multicomponent therapy [3] with 542 patients and an average study duration of 10 (6–16) weeks used a combination of cognitive behavioral therapy and aerobic exercise (Evidence Report, Tab. 41; [8, 18, 26, 50]). Methodological quality was moderate (Evidence Report, Tab. 42). The efficacy was moderate: moderate effects on fatigue at the end of treatment and follow-up and moderate effects on quality of life at the end of treatment were found (Evidence Report, Tab. 43 and Fig. 13).

Open recommendations

Biofeedback

Evidence-based recommendation
Biofeedback can be used. EL2a, open recommendation, strong consensus

Comment. The literature search resulted in 147 hits. Seven RCTs (5 with EMG biofeedback, 2 with EEG biofeedback) with 321 patients and an average therapy duration of 22 (1–104) weeks were included in the analysis. Four studies conducted a follow-up after an average of 13 (1–26) weeks (Evidence Report, Tab. 44; [4, 7, 15, 29, 33, 41, 51]).

The quality of the evidence was moderate (low methodological quality, moderate external validity; Evidence Report, Tab. 45). The low methodological quality resulted in a downgrade of the level of evidence.

The efficacy was low: the standardized mean difference (SMD; biofeedback vs. controls) of pain at the end of therapy was significant (Evidence Report, Tab. 46 and Fig. 14). The dropout rate was 12% and did not significantly differ from controls (Evidence Report, Fig. 14).

Side effects were reported inconsistently. One study of EEG biofeedback reported twice as many side effects in the biofeedback group as in the control group [33], whereas another study reported no "significant" side effects in both groups [41]. No indication of serious side effects was found in the literature.

The availability of biofeedback is limited (can be an element of cognitive behavioral therapy).

Hypnosis and guided imagery

Evidence-based recommendation
Hypnosis/guided imagery can be used. EL3a, open recommendation, strong consensus

Comment. The literature search resulted in 55 hits. The data of one study were specified in two publications [19, 20]. Four studies were excluded because they were either experimental (one single session) [10, 19, 20] or because they were combined with cognitive behavioral therapy [9, 39]. Five randomised controlled trials (RCTs) with an average therapy duration of 16 (6–26) weeks and 146 patients and were analysed. A follow-up examination was reported in two studies with an average duration of 8 weeks (4 and 12 weeks; Evidence Report, Tab. 47; [1, 23, 25, 40, 45]).

The quality of the evidence was moderate (low methodological quality, moderate external validity; Evidence Report, Tab. 48). The low case number and the low methodological quality in the studies resulted in a downgrade of the level of evidence by 2 levels.

The efficacy was average. The SMDs of pain at the end of therapy and follow-up were high compared to controls (conventional therapy, cognitive behavioral therapy, relaxation training; Evidence Report, Tab. 49, Fig. 15). Side effects were not documented systematically. Risks were probably infrequent but potentially severe [32]. The dropout rate in the studies was 15% and did not differ from controls (Evidence Report, Fig. 15).

Hypnosis is covered in compulsory health insurance (psychosomatic primary care).

Cognitive behavioral therapy

Evidence-based recommendation
Cognitive behavioral therapy can be used as monotherapy. EL1a, open recommendation, consensus

Comment. The umbrella term cognitive behavioral therapy includes studies involving cognitive therapy, operant conditioning, behavior therapy and cognitive behavioral therapy. Studies involving mindfulness-based stress reduction (MB-SR) can be found in the paper “Complementary and alternative therapies for fibromyalgia syndrome”. Studies covering psychoeducation can be found in the paper “Multicomponent therapy of fibromyalgia syndrome”.

Literature research resulted in 439 hits. Three studies were excluded because they combined cognitive behavioural therapy with other psychotherapeutic methods [10, 34, 39]. One study was published twice [52, 53]. A total of 13 studies with 659 patients and an average study duration of 11 (5–15) weeks were evaluated. Eleven studies conducted a follow-up after an average of 52 (6–208) weeks (Evidence Report, Tab. 50; [2, 8, 13, 14, 18, 21, 28, 31, 42, 43, 46, 47, 48, 53, 54]).

The quality of the evidence was moderate (moderate methodological quality, moderate external validity; Evidence Report, Tab. 51).

Cognitive behavioral therapy was not effective in relation to the target variables. However, the SMDs (cognitive behavioral therapy vs. controls) at the end of therapy and at follow-up showed a positive trend regarding pain (Evidence Report, Tab. 52, Fig. 16).

The SMDs (cognitive behavioral therapy vs. controls) of depression at the end of therapy and at follow-up were low. The SMDs (cognitive behavioral therapy vs controls) of self-efficacy regarding pain at the end of therapy and at time of catamnesis were high [5].
The dropout rate was moderate (14%) and did not differ significantly from controls (Evidence Report, Fig. 16). Side effects were not reported systematically (possible symptom increase). Severe side effects were not illustrated in the literature [32].

Cognitive behavioral therapy is included in the guidelines for psychotherapy of the statutory health insurance and is therefore covered.

Due to the low risks and wide availability, the recommendation was upgraded by one level.

**Negative recommendations**

**Relaxation training**

**Evidence-based recommendation**

Relaxation training should not be used as monotherapy. EL 2a, negative recommendation, strong consensus

**Comment.** The literature search resulted in 207 hits. One study was excluded because the target variables of the study did not fulfill the inclusion criteria of the systematic review [35]. Eight studies with 460 patients and an average study duration of 10 (3–26) weeks were analysed. Three studies conducted a follow up after an average of 22 (16–26) weeks. In all studies relaxation training served as the control group and was compared with other forms of active therapy [16, 17, 24, 26, 30, 38, 44, 45] (Evidence Report, Tab. 53). The quality of the evidence was moderate (low methodological quality, moderate external validity; Evidence Report, Tab. 54). Due to the low methodological quality the recommendation was downgraded.

Relaxation training was not effective. As far as pain reduction, relaxation training was inferior to active controls at the end of therapy. No significant differences in sleep disturbance and restrictions on quality of life were found (Evidence Report, Tab. 55 and Fig. 17).

The dropout rate was moderate (16%) and did not differ significantly from controls (Evidence Report, Fig. 17). Side effects were not reported systematically. Severe side effects were not described in the literature.

**Psychotherapy for patients with fibromyalgia syndrome. Systematic review, meta-analysis and guideline**

**Abstract**

**Background.** The scheduled update to the German S3 guidelines on fibromyalgia syndrome (FMS) by the Association of the Scientific Medical Societies (“Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften”, AWMF; registration number 041/004) was planned starting in March 2011.

**Materials and methods.** The development of the guidelines was coordinated by the German Interdisciplinary Association for Pain Therapy (“Deutsche Interdisziplinären Vereinigung für Schmerztherapie”, DIVS), 9 scientific medical societies and 2 patient self-help organizations. Eight working groups with a total of 50 members were evenly balanced in terms of gender, medical field, potential conflicts of interest and hierarchical position in the medical and scientific fields. Literature searches were performed using the Medline, PsycInfo, Scopus and Cochrane Library databases (until December 2010). The grading of the strength of the evidence followed the scheme of the Oxford Centre for Evidence-Based Medicine. The recommendations were based on level of evidence, efficacy (meta-analysis of the outcomes pain, sleep, fatigue and health-related quality of life), acceptability (total dropout rate), risks (adverse events) and applicability of treatment modalities in the German health care system. The formulation and grading of recommendations was accomplished using a multi-step, formal consensus process. The guidelines were reviewed by the boards of the participating scientific medical societies.

**Results and conclusion.** Cognitive behavioral therapy combined with aerobic exercise (multicomponent therapy) is strongly recommended. Relaxation as single therapy should not be applied. The English full-text version of this article is available at SpringerLink (under “Supplemental”).

**Keywords**

Fibromyalgia syndrome · Systematic review · Meta-analysis · Guideline · Psychotherapy

**Psychotherapie von Patienten mit Fibromyalgiesyndrom. Systematische Übersicht, Metaanalyse und Leitlinie**

**Zusammenfassung**

**Hintergrund.** Die planmäßige Aktualisierung der S3-Leitlinie zum Fibromyalgiesyndrom AWME-Registerummer 041/004 wurde ab März 2011 vorgenommen.


**Ergebnisse und Schlussfolgerung.** Kognitive Verhaltenstherapie in Kombination mit Ausdauertraining (multimodale Therapie) wird stark empfohlen. Entspannungs- und Muskeltraining als Monotherapie soll nicht eingesetzt werden.

**Schlüsselwörter**

Fibromyalgiesyndrom · Systematische Übersicht · Metaanalyse · Leitlinie · Psychotherapie

Relaxation training is included in the list of medical services covered by the statutory health insurance (psychosomatic primary care, element of cognitive behavioral therapy).
**Schwerpunkt**

<table>
<thead>
<tr>
<th>Tab. 1</th>
<th>Modifications of level of recommendation for psychotherapy in the first and second version of the guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy method</td>
<td>Level of recommendation 2008</td>
</tr>
<tr>
<td>Biofeedback</td>
<td>Negative recommendation</td>
</tr>
<tr>
<td>Cognitive behavioral therapy</td>
<td>Strong recommendation</td>
</tr>
<tr>
<td>Therapeutic writing</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

**Therapeutic writing**

**Evidence-based finding**

Therapeutic writing should not be used as monotherapy. EL 2a, negative recommendation, strong consensus

**Comment.** The literature search resulted in 13 hits. One study was published twice [6, 27]. Two studies with 166 patients were analysed [6, 22]. Due to the short study duration (one week), the first examination was not conducted at the end of therapy but rather after 4 and 12 weeks, and the last follow-up after 12 and 40 weeks respectively. To have comparable time intervals the data was chosen for the analysis 12 weeks after the end of the intervention (Evidence Report, Tab. 56).

The quality of the evidence was moderate (high methodological quality, moderate external validity) (Evidence Report, Tab. 57). The evidence level was downgraded due to insufficient data.

No efficacy was found compared to controls (conventional writing; Evidence Report, Tab. 58, Fig. 18).

Acceptability was moderate. The dropout rate was 16% and did not differ from controls (Evidence Report, Fig. 18). Side effects were not reported. Based on psychotherapeutic experience, psychological decompensation resulting from the measure is possible.

Principally, the measure may be used based upon psychosomatic primary care or psychotherapeutic guidelines.

**Other forms of psychotherapy (client-centered therapy (Rogers), couple and family therapy, humanistic therapy, systematic therapy)**

**Evidence-based finding**

Neither a positive nor negative recommendation of other forms of psychotherapy (client-centered therapy (Rogers), couple and family therapy, humanistic therapy, systematic therapy) is possible due to insufficient data. Strong consensus

**Comment.** The literature search resulted in 60 hits. Neither controlled or uncontrolled nor case studies were found in other forms of psychotherapy used as monotherapy (client-centered therapy (Rogers), couple and family therapy, humanistic therapy, systematic therapy). In a Dutch non-randomized study, 50 patients received a combination of cognitive behavioral therapy (9 sessions) and couple therapy (10 sessions) over a period of 9 months. No significant differences in pain and sleep were found at the end of therapy when compared to controls [12].

**Psychodynamic psychotherapy and psychoanalysis therapy**

**Evidence-based finding**

Due to insufficient data, neither a positive nor negative recommendation of psychodynamic psychotherapy and psychoanalysis therapy is possible. Strong consensus

**Comment.** The literature research resulted in 21 hits. Neither (un-)controlled studies of psychodynamic therapy nor studies of interpersonal therapy were found.

In Germany, 2 RCTs were found using psychodynamic therapy in patients with FMS/somatoform pain disorder, the results of which have not yet been published (Egle 2007, personal communication; Scheidt 2010, personal communication).

In 1 RCT, 54 patients received equal parts of cognitive behavioral therapy and interpersonal therapy over a period of 8 weeks, 2 h per week. They were compared with the waiting group of 47 patients. No significant differences were found in pain and quality of life at the end of therapy and at follow-up (12 weeks) [34].

**Discussion**

In comparison with the first version of the guidelines [49], lower recommendations for cognitive behavioral therapy were made because of the modifications made in establishing the recommendations (taking into account the quantity and quality of evidence, meta-analysis, taking into consideration the risks and availability instead of qualitative analysis of the main results of the studies). Due to the quantitative data synthesis, the recommendation for therapeutic writing changed from positive to negative, and for biofeedback, from negative to positive (Tab. 1).

Research desiderata:
- studies of dose–response relationships of psychotherapy,
- randomized clinical trials comparing standard psychotherapy with "customized" psychotherapy (e.g. different approaches for subgroups of various types of pain management or with comorbid major depression) and
- development of easily assessable short-term psychotherapy for minor manifestations and review of cost effectiveness.

**Corresponding address**

Prof. Dr. V. Köllner
Department of Psychosomatic Medicine, Mediclin Blesiastal Clinics
66440 Blieskastel
Germany
Volker.Koellner@mediclin.de
Conflict of interest. See Tab. 5 in “Methodological Fundamentals used in Developing the Guideline” by W. Hauser, K. Bernardy, H. Wang, and I. Kopp in this issue.

References


Pharmacological treatment of fibromyalgia syndrome

Systematic review and meta-analysis

For the revision of the guideline the working groups asked the following questions:
1. Is pharmacological treatment effective in the short- and long-term in fibromyalgia syndrome (FMS)?
2. Which risks are associated with pharmacological treatment of FMS?
3. Which drugs should be avoided in treatment of FMS?

Materials and methods

The methodology of literature search and analysis, and preparation of recommendations are presented separately in the article “Methodological fundamentals used in developing the guideline”.

Results

Preliminary notes

a) The following findings apply to adults. For the pharmacological treatment of FMS and chronic widespread pain and so-called fibromyalgia syndrome in children and adolescents”.

b) In Germany no drug is licensed for the treatment of FMS. We performed quantitative analyses for drug classes but not for individual drugs. Exceptions are duloxetine, milnacipran (MLN) and pregabalin (PGB), since these substances have been investigated in several large studies during registration trials.

Recommendations

Duloxetine

Evidence-based recommendation

FMS patients with comorbid depressive disorder and/or generalized anxiety disorder should be treated with duloxetine (60 mg/day) for a limited period of time.

EL 1a, recommendation, consensus

Remark: In Germany duloxetine is not licensed for the treatment of FMS. It is licensed for the treatment of depressive disorders and generalized anxiety disorders.

Comment. Duloxetine is a serotonin-noradrenalin reuptake inhibitor with a five-fold stronger effect on serotonin than on noradrenalin.

Literature search revealed 46 hits. One study was excluded from meta-analysis, because it contained an 8 week non-blinded pre-phase and did not have a placebo group during the double-blind phase [29]. For quantitative analysis of data on drug effectiveness five randomized, controlled trials (RCT) with 8 drug treatment arms (different dose regimens of duloxetine) were included investigating 1,397 patients. The mean study duration was 20 (12–26) weeks (Evidence Report, Tab. 59; [4, 5, 8, 30, 94]).

Quality of evidence was moderate (Evidence Report, Tab. 60). In contrast to the RCT with milnacipran (MLN) and pregabalin (PGB), patients with major depression (all studies) and with generalized anxiety disorders (one study) were included in duloxetine studies. The effectiveness of duloxetine was moderate (Evidence Report, Tab. 61 and Fig. 19). Standardized mean differences (SMD) of duloxetine versus placebo for pain, sleep, and health-related quality of life were low. Small pos-
itive effects of duloxetine on sleep were reported only in one study, although data were obtained in all studies. Sleep disturbance is a frequent side effect of duloxetine; therefore the reported positive results should be interpreted with caution.

The acceptance of duloxetine was low: the dropout rate was high (33%) and did not differ from placebo controls (Evidence Report, Fig. 19). Risks were high: several subjectively relevant side effects of duloxetine were observed in >10% compared to placebo. Very rare severe (potentially life-threatening) complications like suicidality and liver toxicity have been reported during duloxetine treatment [29].

The recommendation was downgraded due to the limited availability and the potential risks.

Tricyclic antidepressants

Evidence-based recommendation
Amitriptyline (AMT; 10–50 mg/day) should be used for a limited period of time. EL 2a, recommendation, strong consensus

Remark. In Germany AMT is not licensed for the treatment of FMS. It is licensed for the treatment of chronic pain in the context of a comprehensive therapy concept.

Comment. Literature search revealed 103 hits. Three studies were excluded due to inappropriate endpoints [20, 66, 83]; 3 studies were excluded due to the combination of AMT with other treatment methods [44, 64, 106], and 1 study because of missing randomization. Data of 1 study were only available as an abstract [40].

For quantitative analysis 18 studies with 19 drug treatment arms and a mean study duration of 8 (2–24) weeks were assessed investigating 1,014 patients. AMT was applied in 14 studies, nortriptyline and dothiepin were used in one study each (Evidence Report, Tab. 62, [11, 13, 24, 25, 26, 27, 28, 39, 46, 49, 52, 53, 67, 59, 61, 69, 99, 114]).

Quality of evidence was moderate; methodological quality and external validity were low (Evidence Report, Tab. 63). Evidence was downgraded by one point due to low methodological quality.

Effectiveness was moderate. SMD of tricyclic antidepressants versus placebo at the end of treatment were moderate for pain, sleep, and fatigue and also for health-related quality of life (Evidence Report, Tab. 64, Fig. 20).

Acceptance was moderate with a drop-out rate of 14% that did not differ from placebo (Evidence Report, Fig. 20).

Side effects were not assessed systematically. According to the Summary of Product Characteristics (SmPC) subjective relevant side effects are reported in >10% of patients under AMT compared to placebo. These include symptoms like drowsiness and dry mouth. Potentially life-threatening side effects like liver and bone marrow toxicity were very rarely reported (<0.1%).

AMT is licensed for the treatment of chronic pain in the context of a comprehensive therapy concept.

Open recommendations

Duloxetine

Evidence-based recommendation
Treatment with duloxetine (60 mg/day) can be considered for a limited time period in patients without comorbid depressive disorder or generalized anxiety disorder, if treatment with AMT is not possible (e.g. due to contraindications), was not effective or was not tolerated (“off-label use”). EL 1a, open recommendation, consensus

Comment. When using duloxetine in patients without comorbid depressive disorder or generalized anxiety disorder the following criteria for “off-label use” should be considered:

- proven effectiveness,
- positive risk–benefit profile,
- lack of alternatives,
- individual trial for curing the disease.

Therefore “off-label use” is permitted only in severe cases when treatment alternatives are lacking. The perspective for treatment success on the basis of current scientific knowledge is mandatory. Moreover, detailed patient information is obligatory. Patients must be informed about of “off-label use” and about possible liabilities. It is necessary to reach a decision in consensus with the patient.

Pregabalin

Evidence-based recommendation
Treatment with pregabalin (PGB; 150–450 mg/day) can be considered for a limited time period, if treatment with AMT is not possible (e.g. due to contraindications), was not effective or was not tolerated (“off-label use”). EL 1a, open recommendation, consensus

Comment. When using PGB in patients without comorbid depressive disorder or generalized anxiety disorder the following criteria for “off-label use” should be considered:

- proven effectiveness,
- positive risk–benefit profile,
- lack of alternatives,
- individual trial for curing the disease.

Therefore “off-label use” is permitted only in severe cases when alternative treatment options are missing. The perspective for treatment success on the basis of current scientific knowledge is mandatory. Moreover, detailed patient information is obligatory. Patients must be informed about of “off-label use” and about possible liabilities. It is necessary to reach a decision in consensus with the patient.

Literature search for anticonvulsants revealed 154 hits. Studies on PGB and gabapentin (GPT) were found. The study using GPT is referred to in the section on evidence-based recommendations for GPT.

One study investigating PGP could not be used for quantitative analysis [34]; 4 studies with 12 drug treatment study arms and a study duration of 12 (8–14) weeks investigating 4,132 patients were analyzed (Evidence Report, Tab. 65; [7, 33, 76, 86]).

Quality of evidence was moderate with moderate quality of methods and low external validity. Patients with generalized anxiety disorders were not explicitly included (Evidence Report, Tab. 66). The effectiveness of PGB was moderate: SMD of PGB versus placebo at the end of treatment were small for pain and sleep and not significant for fatigue and health-re-
The scheduled update to the German S3 guidelines on fibromyalgia syndrome (FMS) by the Association of the Scientific Medical Societies ("Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften", AWMF; registration number 041/004) was planned starting in March 2011.

Materials and methods. The development of the guidelines was coordinated by the German Interdisciplinary Association for Pain Therapy ("Deutsche Interdisziplinäre Vereinigung für Schmerztherapie", DIVS), 9 scientific medical societies and 2 patient self-help organizations. Eight working groups with a total of 50 members were evenly balanced in terms of gender, medical field, potential conflicts of interest and hierarchical position in the medical and scientific fields. Literature searches were performed using the Medline, PsycINFO, Scopus and Cochrane Library databases (until December 2010). The grading of the strength of the evidence followed the scheme of the Oxford Centre for Evidence-Based Medicine. The recommendations were based on level of evidence, efficacy (meta-analysis of the outcomes pain, sleep, fatigue and health-related quality of life), acceptability (total dropout rate), risks (adverse events) and applicability of treatment modalities in the German health care system. The formulation and grading of recommendations was accomplished using a multi-step, formal consensus process. The guidelines were reviewed by the boards of the participating scientific medical societies.

Results and conclusion. Amitriptyline and—in case of comorbid depressive disorder or generalized anxiety disorder—duloxetine are recommended. Off-label use of duloxetine and pregabalin can be considered in case of no comorbid mental disorder. Strong opioids are not recommended.

The English full-text version of this article is available at SpringerLink (under "Supplemental").

Keywords
Fibromyalgia syndrome · Systematic review · Meta-analysis · Guideline · Combined modality therapy

Medikamentöse Therapie des Fibromyalgiesyndroms. Systematische Übersicht und Metaanalyse

Zusammenfassung
Hintergrund. Die planmäßige Aktualisierung der S3-Leitlinie zum Fibromyalgiesyndrom (FMS; AWMF-Registernummer 041/004) wurde ab März 2011 vorgenommen.


Schlüsselwörter
Fibromyalgiesyndrom · Systematische Übersicht · Metaanalyse · Leitlinie · Multimodale Therapie

Abstract · Zusammenfassung
Pharmacological treatment of fibromyalgia syndrome. Systematic review and meta-analysis

Abstract
Background. The scheduled update to the German S3 guidelines on fibromyalgia syndrome (FMS) by the Association of the Scientific Medical Societies ("Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften", AWMF; registration number 041/004) was planned starting in March 2011.

Materials and methods. The development of the guidelines was coordinated by the German Interdisciplinary Association for Pain Therapy ("Deutsche Interdisziplinäre Vereinigung für Schmerztherapie", DIVS), 9 scientific medical societies and 2 patient self-help organizations. Eight working groups with a total of 50 members were evenly balanced in terms of gender, medical field, potential conflicts of interest and hierarchical position in the medical and scientific fields. Literature searches were performed using the Medline, PsycINFO, Scopus and Cochrane Library databases (until December 2010). The grading of the strength of the evidence followed the scheme of the Oxford Centre for Evidence-Based Medicine. The recommendations were based on level of evidence, efficacy (meta-analysis of the outcomes pain, sleep, fatigue and health-related quality of life), acceptability (total dropout rate), risks (adverse events) and applicability of treatment modalities in the German health care system. The formulation and grading of recommendations was accomplished using a multi-step, formal consensus process. The guidelines were reviewed by the boards of the participating scientific medical societies.

Results and conclusion. Amitriptyline and—in case of comorbid depressive disorder or generalized anxiety disorder—duloxetine are recommended. Off-label use of duloxetine and pregabalin can be considered in case of no comorbid mental disorder. Strong opioids are not recommended.

The English full-text version of this article is available at SpringerLink (under "Supplemental").

Keywords
Fibromyalgia syndrome · Systematic review · Meta-analysis · Guideline · Combined modality therapy

Serotonin reuptake inhibitors

Evidence-based recommendation
Serotonin reuptake inhibitors (SSRI; fluoxetine: 20–40 mg/day, paroxetine: 20–40 mg/day) can be considered for a limited time period in patients with comorbid depressive disorder and anxiety disorder. EL 2a, open recommendation, consensus

Note: In Germany fluoxetine and paroxetine are licensed for the treatment of depressive and anxiety disorders, but not for FMS.

Comment. The literature search revealed 130 hits. Three studies were excluded because study endpoints did not fulfill inclusion criteria [23, 48, 81]. Thirteen studies with a mean study duration of 10 (4–26) weeks were qualitatively analyzed including 610 patients (Evidence Report, Tab. 68; [1, 3, 11, 24, 40, 53, 54, 56, 64, 80, 83, 100, 115]).

Methodological quality of evidence was low; external validity was moderate (Evidence Report, Tab. 69). Therefore the level of evidence was downgraded.

Effectiveness was moderate. SMD of SSRI versus placebo were significant for pain, sleep, and health-related quality of life; effect size was small (Evidence Report, Tab. 70, Fig. 22).

Acceptance was moderate. The dropout rate was 19% and did not differ from practices.
placebo (Evidence Report, Fig. 22). Side effects were not systematically assessed in the studies. Rare severe side effects are described in literature, e.g. bleedings [2].

Practicability is limited: in Germany the analyzed SSRI are not licensed for the treatment of FMS, but for the treatment of depression and partly of anxiety disorders. The evidence level was downgraded due to potential risks and the lack of a license for FMS in Germany.

Strong negative recommendations

Antiviral drugs

Evidence-based recommendation

Antiviral drugs should not be used. EL 2b, strong negative recommendation, strong consensus

Comment. The literature search revealed five hits. In one RCT 30 patients each received valaciclovir 1 g or placebo for 6 weeks. At the end of treatment no differences were found regarding pain and health-related quality of life. In both groups 4 out of 30 patients stopped treatment [70]. Severe side effects of virostatics are reported in the literature. Virostatics are neither licensed for FMS nor for frequent comorbidities. Due to the high risks, the ethical commitment to protect patients from harm, and the limited availability the negative recommendation was further downgraded.

Anxiolytics

Evidence-based recommendation

Anxiolytics should not be used. EL 2a, strong negative recommendation, strong consensus

Comment. The literature search revealed five hits. One study each with alprazolam and bromazepam [88, 92]. A quantitative data synthesis could not be performed. Due to the limited data the evidence level was downgraded.

Quality of evidence was moderate [see studies on nonsteroidal antirheumatics (NSAR)]. Anxiolytics were ineffective: in a study over 8 weeks no difference was found between treatment with placebo plus alprazolam (up to 3 mg/day; 17 patients) and treatment with double placebo (14 patients) with regard to pain reduction and improvement of health-related quality of life [92]. In a study over 8 weeks no difference was found between treatment with bromazepam (3 mg/day; 42 patients) and placebo (42 patients) with regard to the number of patients that experienced a reduction in pain intensity or in morning stiffness of at least 25% [88]. Bromazepam is not licensed for the treatment of FMS, but for the treatment of chronic anxiety and of chronic stress (limited practicability). Anxiolytics can be used for the treatment of anxiety disorders [12]. Due to the high risks, the ethical commitment to protect patients from harm, and the limited availability the negative recommendation was further downgraded.

Dopamine agonists

Evidence-based recommendation

Dopamine agonists should not be used. EL 2a, strong negative recommendation, strong consensus

Comment. The literature search revealed 56 hits. Three studies with a study duration of 12 weeks including 300 patients were analyzed (Evidence Report, Tab. 71; [37, 51, 62]). Due to the limited data the evidence level was downgraded.

The quality of evidence was moderate with moderate quality of methodology and external validity (Evidence Report, Tab. 72).

Dopamine agonists were not effective (no superiority to placebo in reducing pain or increasing health related quality of life; Evidence Report, Tab. 73, Fig. 23).

Acceptance was low: the dropout rate was 55.5% and was not higher than in the placebo group (Evidence Report, Fig. 23). Frequent side effects (>10% compared to placebo) were sleep disturbance, nausea, weight loss, and abdominal pain. Rare severe side effects of dopamine agonists are reported in the literature.

Dopamine agonists are licensed for the treatment of FMS. Pramipexole is licensed for the treatment of Parkinson’s disease and of the moderate and severe restless legs syndrome.

The level of negative recommendation was downgraded by one point because dopamine agonists are not licensed for FMS and due to the low patients’ acceptance.

Hormones (calcitonin, testosterone, estrogens, glucocorticosteroids, thyroid hormones, growth factors)

Evidence-based recommendation

Hormones (calcitonin, testosterone, estrogens, glucocorticosteroids, thyroid hormones, growth factors) should not be used. EL 3a, strong negative recommendation, strong consensus

Comment. The literature search revealed 128 hits. The level of evidence was downgraded due to the limited number of studies. Due to the potential risks and the lacking license for FMS or for frequent comorbidities a downgrading of evidence levels by one point was performed for all substances.

One RCT was found for calcitonin. In a cross-over RCT 11 patients received 100 IU calcitonin s.c. or saline for 4 weeks. No intergroup difference was found with regard to pain, fatigue, sleep, and pain reduction. One of the 11 patients stopped treatment with calcitonin because of side effects. Side effects appeared frequently (nausea, erythema) [18].

One RCT was found using testosterone-like substances. In a cross-over RCT 52 postmenopausal women were treated with dehydroepiandrosterone (DHEA; 50 mg/day) for 1 month; results were not different compared to placebo with regard to pain, sleep disturbance, and fatigue [53].

One RCT was found using estrogen-like substances. In an Iranian study 50 postmenopausal women were treated with the selective estrogen modulator raloxifene 60 mg for 16 weeks; 50 women received placebo. Raloxifene was superior to placebo with regard to pain, sleep, and fatigue. The dropout rate was 4% [95]. No relevant side effects were reported.

Estrogens or the combination of estrogen and gestagen can be used for the treatment of climacteric symptoms like hot flush considering possible risks [36].

One RCT was found investigating the effect of glucocorticosteroids. In a US-American cross-over RCT with 20 patients, oral prednisone (15 mg/day) treat-
ment for 14 days was not superior to placebo in reducing pain, sleep disturbance, and fatigue [31].

In another RCT of 8 and 9 months duration, 7 and 4 euthyroid patients, respectively, were alternately treated with supraphysiological doses of T3 (93.75–150 μg/day) or placebo. Significant pain reduction was reported at the end of the T3 treatment phase. No side effects were reported in this study; however, they seem possible (induction of hyperthyroidism; [71, 72]).

Two studies were found investigating growth hormones [15, 35]. Quantitative analysis was not possible. In one study 25 patients were treated with growth hormone (0.0125 mg/kg s.c.) or placebo for 9 months. Health-related quality of life was higher in the growth hormone group compared to the placebo group. In another study 12 patients were treated with growth hormone (0.0125 mg/kg s.c.) or placebo for 1 year in addition to a multimodal and pharmacological treatment (AMT, fluoxetine, tramadol). At the end of the study health-related quality of life was higher in the group with additional growth hormone treatment; also pain and fatigue were lower compared to the placebo group.

Dropout rates were low (0–13.6%). Side effects (edema, anemia, carpal tunnel syndrome, hyperglycemia, hypertriglyceridemia) were observed only in the growth hormone group.

Hypnotics

Evidence-based recommendation
Hypnotics should not be used. EL 3a, strong negative recommendation, strong consensus

Comment. The literature search revealed 143 hits. Three RCT were found. A quantitative analysis was not possible due to a lack of appropriate data. Due to the low methodological quality of evidence and the limited number of RCT available the level of evidence was downgraded by two points.

The effectiveness of hypnotics is not proven. In a cross-over RCT 19 patients were treated with 5–15 mg zolpidem or placebo for 2 weeks [76]. No intergroup differences were found for pain, sleep, and fatigue. In another RCT 14 patients were treated with zopiclone 7.5 mg/day and 19 patients with placebo [55]. After 8 weeks no significant differences were found with regard to pain and sleep. In one RCT 22 patients were treated with zopiclone 7.5 mg/day and 23 patients with placebo [38]. At the end of treatment zopiclone was superior to placebo in reducing sleep disturbances and fatigue, but not in pain reduction. Dropout rates were 4–10%.

Hypnotics can be misused. Hypnotics are not licensed for the treatment of FMS. However, they are licensed for the treatment of sleep disturbances during a limited time period. Due to the high risks and the limited practicability the negative recommendation was further downgraded by one point.

Interferons

Evidence-based recommendation
Interferons should not be used. EL 3a, strong negative recommendation, strong consensus

Comment. The literature search revealed 5 hits. In one RCT 28 patients each received placebo, 15 IU, 50 IU or 150 IE interferon-a s.c. At the end of treatment no intergroup difference was found for pain, sleep, and fatigue. Dropout rates were not reported separately for each group [93]. The side effects reported were mild and as for the authors not related to the medication. Severe side effects are reported in the literature after treatment with high doses of interferons. Due to the high risks and the low practicability the negative recommendation was further downgraded by one point.

Intravenous (i.v.) ketamine

Evidence-based recommendation
I.v. ketamine should not be used. EL 4a, strong negative recommendation, strong consensus

Comment. The literature search revealed 17 hits. Two experimental studies (infusion therapy once and twice) were excluded [10, 104]. No studies with oral ketamine application were found.

In a cross-over study 20 patients received ketamine 1 mg/kg body weight for 3 days versus placebo [78]. No intergroup differences were found for pain intensity and health-related quality of life. Study quality was low. Due to the limited data and the low methodological quality the recommendation was downgraded by two points.

Severe neuropsychiatric side effects are reported. Due to the potential risks and the low practicability the negative recommendation was further downgraded by one point.

Local anesthetics

Evidence-based recommendation
Intravenous local anesthetics should not be used. EL 3a, strong negative recommendation, strong consensus

Comment. The literature search revealed 62 hits. Three studies investigating 177 patients and with a study duration of 4 weeks each were included in qualitative analysis. The quality of evidence and methodology were low and also the number of patients investigated. Therefore the level of evidence was downgraded by two points.

Local anesthetics were ineffective. A quantitative data analysis was not possible due to insufficient data presentation in the publications. In both placebo-controlled studies no intergroup difference was found for pain reduction when using lidocaine or placebo [73, 86]. In one study no intergroup difference was found for the reduction of fatigue [73]. The add-on therapy with lidocaine or placebo in addition to AMT did not increase pain reduction [112].

Acceptance was moderate (dropout rate: 0–16%). The risks are high. Pain was >10% more frequently reported during lidocaine infusion than during placebo [73]. In an observational study using 550 mg lidocaine/6 h for 6 consecutive days lung edema and supraventricular tachycardia were reported [91].

Due to the potential risks, the ethical commitment to protect patients from harm, and the low practicability the nega-
tive recommendation was downgraded by two points.

**Sodium oxybate**

**Evidence-based recommendation**

Sodium oxybate should not be used. EL 3a, strong negative recommendation, strong consensus

**Comment.** Sodium oxybate increases the turnover of 5-hydroxytryptamine, interacts with the opioid system, and GABA antagonistic effects are assumed.

The literature search revealed 13 hits. Three studies with five study arms investigating 358 patients were included in the analysis; the mean study duration was 7 (4–8) weeks (Evidence Report, Tab. 74; [77, 95, 98]).

Methodological quality of evidence was low (Evidence Report, Tab. 75). The obtained data were incompletely reported (selective reporting). Therefore the level of evidence was downgraded by two points.

The effectiveness of sodium oxybate was moderate (Evidence Report, Tab. 76, Fig. 24). SMD of sodium oxybate versus placebo for pain, sleep, fatigue, and health-related quality of life were significant at the end of treatment. SMD was low for health-related quality of life and moderate for pain, fatigue, and sleep.

Acceptance was moderate (dropout rate: 24%) and was not different from placebo (Evidence Report, Fig. 24). Risks were high. Frequent side effects (>10% difference to placebo) were nausea, drowsiness, and headache or paresthesias. In 6% of the patients treated with 6 g/day urinary incontinence was observed. In Germany sodium oxybate is neither licensed for the treatment of FMS nor for the treatment of frequent psychiatric comorbidities. Sodium oxybate is licensed for the treatment of narcolepsy. Due to the high risks, the ethical commitment to protect patients from harm, and lack of license the recommendation was downgraded by two points.

**Neuroleptics**

**Evidence-based recommendation**

Neuroleptics should not be used. EL 3a, strong negative recommendation, strong consensus

**Comment.** The literature search revealed 17 hits. One RCT and three case series were found. Due to the limited data the grade of evidence was downgraded.

In the RCT 24 female patients were treated with ritanserin 10 mg/day and 27 female patients were treated with placebo for 16 weeks [81]. At the end of treatment no intergroup difference was found for pain, sleep, and fatigue. Three patients in the ritanserin group discontinued the study.

In Germany neuroleptics is neither licensed for the treatment of FMS nor for the treatment of frequent psychiatric comorbidities. Due to the potential risks, the ethical commitment to protect patients from harm and the low practicability the negative recommendation was downgraded by two points.

**Strong opioids**

**Evidence-based recommendation**

Strong opioids should not be used. EL 4b, strong negative recommendation, strong consensus

**Comment.** One RCT was excluded from analysis, because it was an experimental study with one-time morphine application [103]. No RCT were found for other strong opioids (buprenorphine, fentanyl, hydromorphone, oxycodone). In one case series 16 patients received fentanyl 25 µg/h transdermally over 72 h. Treatment was continued for 4–8 weeks. No pain reduction or increase in health-related quality of life was found. All patients reported on side effects (confusion, nausea, vomiting). Seven of the 16 patients discontinued treatment [22].

The availability is limited. In Germany fentanyl is not licensed for the treatment of FMS, but for the treatment of severe pain.

Due to the low patients’ acceptance, the high risks, and the limited license the recommendation was downgraded by two points.

**Serotonin receptor (5-HT3) antagonists**

**Evidence-based recommendation**

Serotonin receptor (5-HT3) antagonists should not be used. EL 3a, strong negative recommendation, strong consensus

**Comment.** The literature search revealed 43 hits. Three RCT were analyzed. In one study three different dosages of tropisetron (5, 10, 15 mg) were compared with placebo. For quantitative analysis only the 5 mg study arm was considered, because the two other study arms did not differ from placebo [104]. Three studies investigating 260 patients and with a mean study duration of 1 week (5–10 days) were analyzed (Evidence Report, Tab. 77; [41, 63, 105]).

Due to the limited data and the low quality of evidence (low methodological quality and low external validity) the level of evidence was downgraded by two points (Evidence Report, Tab. 78).

The difference of SMD comparing serotonin receptor (5-HT3) antagonists with placebo was not significant (Evidence Report, Tab. 79, Fig. 25).

The dropout rate was low (4.6%) and was not different from placebo (Evidence Report, Fig. 25).

One frequent subjective side effect (>10% versus placebo) was obstipation. Serotonin receptor (5-HT3) antagonists are not licensed for the treatment of FMS or of comorbidities.

Due to the side effects and the lack of license the negative recommendation was further downgraded by one point.

**Cannabinoids**

**Evidence-based recommendation**

Cannabinoids should not be used. EL 3a, negative recommendation, strong consensus

**Comment.** The literature search revealed 9 hits. Two RCT were analyzed [101, 113]. A quantitative data analysis was not possi-
ble, because none of the studies were placebo-controlled. Due to the limited data the evidence level was downgraded by one point.

The quality of evidence was moderate. A quantitative data analysis was not possible. The effectiveness was low. In a cross-over study 32 patients were treated with nabilone 0.5 mg or AMT 10 mg [113]. Nabilone was superior to AMT in improving sleep quality. No intergroup difference was found for pain reduction or improvement of health-related quality of life. In a RCT 20 patients received nabilone 0.5–1 mg/day and 20 patients received placebo for 4 weeks. At the end of the study nabilone was superior to placebo with regard to pain reduction and improvement of health-related quality of life. In one study 3 of 32 patients discontinued. The other study does not give details [101]. Frequently observed side effects were dizziness (nabilone: 47%; placebo: 6%; [110]), drowsiness (nabilone: 35%; AMT: 14%), and nausea (nabilone: 31%; AMT: 14%; [101]). Misuse of nabilone is rare [114].

In Germany nabilone is neither licensed for the treatment of FMS, nor for the treatment of frequent psychiatric comorbidities.

Due to potential risks and the lack of license the recommendation was downgraded by one point.

**Flupirtine**

**Evidence-based recommendation**

Flupirtine should not be used. EL 4, negative recommendation, consensus

**Comment.** Flupirtine is not a muscle relaxant [109].

Only two small case series are available investigating the effect of flupirtine in FMS; both report on pain reduction [106, 116]. Severe liver toxicity as a side effect is reported in the literature [87].

Due to a lack of licence and the potential side effects the recommendation was downgraded by one point.

**Milnacipran**

**Evidence-based recommendation**

Milnacipran (MLN) should not be used. EL 1a, negative recommendation, consensus

**Comment.** MLN is a serotonin–noradrenalin reuptake inhibitor with a three-fold higher effect on serotonin than on noradrenalin.

Literature search revealed 37 hits. Two studies were published twice [47, 111]. Five studies with 8 study arms and investigating 4,088 patients were analyzed; mean study duration was 19 (15–27) weeks (Evidence Report, Tab. 80; [9, 21, 32, 75, 111]).

The quality of evidence and of methodology was moderate; external validity was low (Evidence Report, Tab. 81).

SMD of MLN versus placebo at the end of therapy were significant for pain and health-related quality of life but not substantially (Evidence Report, Tab. 82, Fig. 26). Acceptance for MLN was low: dropout rate was high (33%) and was not different from placebo (Evidence Report, Fig. 26). The risks of MLN were high: the difference of the frequency of some subjectively relevant side effects was >10% compared to placebo. In Germany MLN is neither licensed for the treatment of FMS nor for the treatment of frequent psychiatric comorbidities.

**Monoamine oxidase inhibitors**

**Evidence-based recommendation**

Monoamine oxidase inhibitors should not be used. EL 2a, negative recommendation, strong consensus

**Comment.** The literature search revealed 45 hits. Eleven studies were analyzed. One study was excluded from quantitative analysis, because carisoprodol was combined with caffeine and acetaminophen [110]. Due to a lack of standard deviations one study with several study arms (e.g. 7 patients treated with cyclobenzaprine 10 mg) could not be used for quantitative analysis [46].

Nine studies with a mean study duration of 6 (1–26) weeks and investigating 527 patients could partially be used for analysis; six of these studies were performed placebo-controlled [14, 23, 26, 45, 46, 85, 97, 110]. In eight RCT the centrally active agent cyclobenzaprine was applied. Cyclobenzaprine additionally has properties of tricyclic antidepressants. In one RCT chlor mezanone was used; chlor mezanone additionally has properties of benzodiazepines (Evidence Report, Tab. 86).

The quality of evidence was moderate (Evidence Report, Tab. 87). Due to the low methodological quality the level of evidence was downgraded by one point. The quantitative data synthesis was limited due to a lack of standard deviations in the majority of studies. Drug effectiveness can only be assessed for the endpoint pain. Effectiveness was low: SMD of muscle relaxants versus placebo at the end of treatment was low for pain (Evidence Report, Tab. 88, Fig. 28).

Acceptance and tolerability were moderate: the dropout rate in the RCT was...
20% and did not differ from placebo (Evidence Report, Fig. 28). The relative risk for dropout was lower compared to placebo. The risks of cyclobenzaprine are high: very rare, but potentially life-threatening side effects (confusion, skin lesions, liver toxicity) are described in the literature. None of the substances that have been investigated in the studies is licensed in Germany. Due to the potential risks, the lack of license, and ethical commitment to protect patients from harm the recommendation was downgraded by two points.

**Nonsteroidal antiinflammatories**

**Evidence-based recommendation**

Nonsteroidal antiinflammatories (NSAR) should not be used. EL 3a, negative recommendation, strong consensus

**Comment.** The literature search revealed 79 hits. Four studies with a mean duration of 5 (1.2–8) weeks and investigating 181 patients were considered for quantitative analysis (three studies with ibuprofen, one study with tenoxicam; Evidence Report, Tab. 89; [42, 45, 92, 118]). No studies were found with cyclooxygenase (COX)-2 inhibitors.

The quality of evidence was moderate with moderate methodological quality and high external validity (Evidence Report, Tab. 90). Due to the low methodological quality and the low number of cases the level of evidence was downgraded by two points.

A quantitative data synthesis was only possible for the outcome pain. No effectiveness was reported. SMD of NSAR versus placebo was not significant at the end of treatment (Evidence Report, Tab. 91, Fig. 29). One study found no intergroup difference between placebo and tenoxicam concerning the number of subjects that reached pain reduction and reduction in morning fatigue scores of at least 25% [42]. Reduction of pain and of sleep disturbance was not different between cyclobenzaprine monotherapy and the combination of cyclobenzaprine with ibuprofen 600 mg [45].

Side effects were not systematically assessed in the studies. In the SmPC on NSAR, e.g. gastrointestinal bleeding is reported as frequent and severe side effect. The dropout rate was moderate in the studies (20%) and was not different compared to placebo (Evidence Report, Fig. 29). In Germany NSAR are not licensed for the treatment of FMS, but for the treatment of mild and moderate pain of the musculoskeletal system.

Due to potential risks and the ethical commitment to protect patients from harm the recommendation was further downgraded by one point.

**No positive or negative recommendation possible**

**Gabapentin**

**Evidence-based recommendation**

Due to the limited data available for gabapentin (GPT) neither a positive nor a negative recommendation is possible. Strong consensus

**Comment.** One RCT was found which investigated the effect of GPT 1,200–2,400 mg versus placebo in 75 patients each for 12 weeks [6].

The quality of evidence was moderate with high methodological quality and low external validity.

At the end of treatment GPT was superior to placebo in reduction of pain and sleep disturbance and improvement of health-related quality of life.

Patients’ acceptance was moderate: the dropout rate was 24% for GPT and 17.3% for placebo. Side effects with a difference of >10% to placebo were dizziness and drowsiness. Very rare (<0.01%) severe side effects (hematological impairment, liver toxicity, acute renal failure, dermatological problems) are given for GPT in expert reports.

The practicability is low: in Germany GPT is licensed for the treatment of epilepsy and of neuropathic pain, but not for the treatment of FMS or comorbid psychiatric disorders.

**Noradrenaline reuptake inhibitors**

**Evidence-based recommendation**

Due to the limited data available for noradrenaline reuptake inhibitors (NRI) neither a positive nor a negative recommendation is possible. Strong consensus

**Comment.** The results of one study with esreboxetine [79] were not yet published. One published study with the NRI esreboxetine was found [10]. In this study 134 patients were treated with esreboxetine (dose increase from 1 to 8 mg/day) and 133 patients received placebo for 8 weeks. The dropout rate was 20.1% in the esreboxetine group and 20.3% in the placebo group. Esreboxetine was superior to placebo in terms of reducing pain, fatigue, and improving health-related quality of life. Study quality was high, the external validity was low. Reported side effects were insomnia, drowsiness, dry mouth, nausea, hyperhidrosis, voiding disturbance (only in men) and urinary retention (only in men).

Esreboxetine is not available worldwide. Pfizer has stopped registration trials for esreboxetine in FMS.

**Weak opioids**

**Evidence-based recommendation**

Due to the limited data available (tramadol) or lack of data (other weak opioids) neither a positive nor a negative recommendation is possible for weak opioids. Strong consensus

**Comment.** The literature search revealed 74 hits. Only RCT with tramadol, but not with tilidine or codeine were found. One RCT was excluded from the analysis, because it was an experimental study with twice i.v. application of tramadol [19]. One further study was excluded due to double publication [16, 17].

One study with tramadol and tramadol/acetaminophen, respectively, was included into the analysis investigating 384 patients and with a mean treatment duration of 9.5 (6–13) weeks [16]. Due to the limited number of studies the level of evidence was downgraded.

In both studies tramadol and tramadol/acetaminophen, respectively, were superior to placebo with regard to pain reduction and improvement of health-related quality of life. Acceptance was low (dropout rate: 40%). However, the dropout rate was higher the placebo groups
compared to the tramadol groups. The most frequently reported side effect with a difference of >10% to placebo was nausea. Rare severe side effects (misuse) are reported in the literature [108].

The availability is limited. In Germany tramadol is not licensed for the treatment of FMS, but for the treatment of moderate to severe pain.

Acetylsalicylic acid, acetaminophen, and metamizole

Evidence-based recommendation
Due to the lack of data neither a positive nor a negative recommendation is possible for acetylsalicylic acid, acetaminophen, and metamizole. Strong consensus

Comment. No studies were found for acetylsalicylic acid, acetaminophen, and metamizole.

Discussion
Compared to the first version of the guideline the basis of recommendations was changed: Quantity and quality of evidence were considered, meta-analysis was performed, risks and availability were considered instead of pure qualitative analysis of the main study results. This led to a downgrade of recommendations for some drugs (e.g. AMT) [102]. Taking into account the licensed indications, a positive recommendation resulted only for FMS with comorbid psychological disorders for duloxetine, fluoxetine, and paroxetine. Due to insufficient data the open recommendation for the weak opioid tramadol was abolished (Tab. 1).

The following research objectives were identified:

a) studies investigating the sustained effect after treatment cessation,
b) randomized, controlled studies comparing "old" (cheap) drugs like AMT with "new" (expensive) drugs like PGB,
c) direct comparison of active treatments (e.g. two forms of psychotherapy or psychotherapy versus pharmacological treatment) and
d) inclusion of patients with comorbid psychological disorders and eventually their subgroup analysis.

Corresponding address

Prof. Dr. C. Sommer
Neurologische Klinik,
Universitätsklinikum Würzburg
Josef-Schneider-Str. 11, 97080 Würzburg
Germany
sommer@uni-wuerzburg.de

Conflicts of interest. See Tab. 5 in the "Methodological fundamentals used in developing the guideline" by W. Häuser, K. Bernardy, H. Wang, and I. Kopp in this issue.
References


54. Gonzalez-Viejo MA, Avellanet M, Hernandez-Loaeza 17:68–73 (Turkish)


In revising the guidelines, the task groups considered the following questions:
1. Are the complementary and alternative therapies for fibromyalgia syndrome (FMS) effective over short and long periods of time?
2. What are the risks of using complementary and alternative procedures to treat FMS?
3. Which complementary and alternative procedures should be refused in treating FMS?

**Methodology**

The procedures utilized for researching and analyzing the literature are presented in the article “Methodological fundamentals used in developing the guideline”.

**Results**

The following findings apply to adults. Complementary and alternative procedures for chronic pain affecting multiple body regions in children and youths are discussed in the article entitled “Def-
Acupuncture

Evidence-based recommendation
Treatment with acupuncture for a limited period of time may be considered. EL 2a, degree of recommendation open, strong consensus

Comment. A search of the literature identified 340 reports. Three RCTs were excluded because the target variables did not fulfill the inclusion criteria [27] or because acupuncture was combined with other active therapeutic procedures [36, 54]. One review [10] included four Chinese trials: two compared acupuncture with amitriptyline and two compared acupuncture in combination (one with cupping and one with an antidepressant) with an antidepressant alone. These studies, which were not contained in the designated databanks and were only published in Chinese, were excluded from the analysis.

Thus, 9 RCTs with 414 patients treated for an average of 7 (2–15) weeks were analyzed. Three trials included follow-up assessments after a median of 17 (12–28) weeks (Evidence Report, Tab. 95; [2, 18, 29, 30, 34, 41, 43, 49, 53]).

The evidence was of moderate quality (poor methodological quality, moderate external validity) (Evidence Report, Tab. 96). The quality of evidence was downgraded due to the limited methodological quality.

Efficacy was limited. The standard mean deviation (SMD) (verum acupuncture vs. sham acupuncture) at the completion of therapy with regard to pain indicated a small effect size (Evidence Report, Tab. 97 and Fig. 31).

The dropout rate was 8.2%, which did not differ from that of the control group (Evidence Report, Tab. 31). Adverse effects were systematically reported in only one study. The frequency of severe adverse effects from acupuncture is controversial. However, severe complications such as bleeding or pneumothorax have been reported in the literature [16].

Acupuncture for comorbid back pain is covered by health insurance in Germany.

Because of its potential risks and limited availability, the strength of recommendation was downgraded one level.

Negative recommendation

Mindfulness-based stress reduction as monotherapy

Evidence-based recommendation
Mindfulness-based stress reduction should not be used as monotherapy. EL 2a negative recommendation, consensus

Comment. A search of the literature identified 8 relevant reports. Four RCTs with 371 patients treated with mindfulness-based stress reduction (MBSR) for an average of 8 weeks were analyzed [4, 26, 50, 51]. In three of the trials patients of both arms of the studies were assessed at follow-up an average of 8 weeks after treatment. In one of the trials [26] follow-up evaluations of the MBSR, but not the control group, were carried out after 3 years in 26 of 39 patients (Evidence Report, Tab. 98).

The evidence was of moderate quality (poor methodological quality, moderate external validity; Evidence Report, Tab. 99). The secondary end points of one trial were not reported and not made available upon inquiry [51]. Since it is possible that negative results had not been published, the level of evidence was downgraded.

MBSR was not effective and was not superior to control treatments with respect to reducing pain or improving quality of life (Evidence Report, Tab. 100 and Fig. 32).

Acceptance was moderate (dropout rate 22%) and did not differ significantly from that of the controls (Evidence Report, Fig. 32). Adverse effects were not reported nor have any been mentioned in the literature.

Availability is limited. MBSR is not covered by health insurance in Germany. MBSR is offered as part of multimodal therapeutic inpatient programs in a few hospitals.

Homeopathy

Evidence-based recommendation
Homeopathy should not be considered. EL 1a negative recommendation, consensus

Minority opinion (Complementary and Alternative Medicine Work Group: Langhorst J, Bernardy K, Lucius H, Settan M, Winkelmann A, Musial F): homeopathic therapy may be considered. EL 1a, recommendation open

Comment. A search of the literature identified 20 reports. The data of one trial were published twice [7, 8]. Five RCTs with 204 patients and an average trial length of 15 weeks were qualitatively analyzed (Evidence Report, Tab. 101; [7, 8, 23, 24, 46]).

The evidence was of moderate quality (moderate methodological quality, moderate external validity), and moderate external validity (Evidence Report, Tab. 102).

There was no consistent evidence that homeopathy was effective. Two trials could be quantitatively evaluated [8, 46]. The SMDs (homeopathy versus control at completion of therapy) showed that homeopathy tended to positively affect quality of life (Evidence Report, Tab. 103 and Fig. 33). In the two trials that could not be meta-analyzed, qualitative analysis revealed no consistent evidence that homeopathy was effective. In one trial there was no statistical difference in the reduction of pain and sleep disturbance. One subgroup analysis did show significantly reduced pain and sleep disturbance for those patients who presented at least more than three characteristic symptoms of the prescribed homeopathic medication [23]. One trial showed that a homeopathic treatment reduced pain and sleep disturbance better than a placebo [24]. A subsequent analysis of that trial with appropriate statistical methods did not confirm a significant difference between homeopathic and placebo treatments in the first crossover treatment phase [15].

Acceptance was moderate. The dropout rate, 13%, did not differ significantly from that of the placebo group (Evidence Report, Fig. 33). The risks are probably low: adverse effects were not determined. Relevant side effects are not known from the literature.
that the homeopathic treatment was sig-
ificant better than the placebo in the ini-
tial crossover treatment phase. The au-
thor assumed that there is a carry-over
effect, i.e., that the effects of the treat-
ment period being observed are partly
determined by the effects of the prece-
ding treatment period [15]. However, this
was not established by statistical analysis
(p = 0.07). Since the carry-over effect was
not formally demonstrated, the homeo-
pathic treatment would remain statisti-
cally superior.

**Nutritional supplements**

Evidence-based recommendation

Nutritional supplements (algae and ma-
lac acid/magnesium preparations; anths-
cyanins; carnitine; S-adenosyl methio-
nine, SAM; soy oil; vitamin–dietary min-
Anthocyanins are plant pigments. In the European Union, they are permitted in unlimited amounts as food additives under the number E163.

S-adenosyl methionine (SAM) is an essential amino acid. In the USA, SAM is sold as a nutritional supplement under the Dietary Supplement Health and Education Act of 1999. Under this law, nutritional supplements circumvent regulation by the Food and Drug Administration (FDA). SAM can be obtained over the internet.

Carnitine is a vitamin-like substance. It can be produced by the body but is usually provided by meat in the diet. In Germany it is permitted for treating the carnitine deficiency of renal insufficiency and special forms of muscular dystrophy. Carnitine can be obtained over the internet.

5-Hydroxytryptophan is an amino acid naturally occurring in bananas and the seeds of African black beans. The substance is not an authorized medication in Germany but can be obtained over the internet as a "natural mood-elevator".

A search of the literature identified 130 reports. Two trials with SAM were excluded from the analysis because the clinical endpoint [53] or the presentation thereof [54] was not suitable for analysis.

Eleven trials with 12 arms and 517 patients and an average length of treatment of 6 (1–12) weeks were analyzed. None of the trials included a follow-up [1, 12, 21, 22, 25, 35, 44, 47, 48, 57, 58]. Only one preparation (SAM) was the subject of more than one trial (3 trials, 121 patients) (Evidence Report, Tab. 104). The evidence was initially downgraded because so few trials were available. And since the quality of evidence was limited (limited methodological quality, limited external validity; Evidence Report, Tab. 105), it was further downgraded. The efficacy was limited. The SMDs (nutritional supplements versus controls) on pain, sleep, and fatigue at the completion of therapy were showed small effect sizes (Evidence Report, Tab. 106 and Fig. 34).

Acceptance was moderate (dropout rate 12%) and did not differ significantly from that of the placebo groups; Evidence Report, Fig. 34).

The risks were high: gastrointestinal adverse effects were 10% more frequent with SAM and 5-HT than in the control group.

The recommendation was downgraded a further level because of the high risks and low availability.

Reiki

Evidence-based recommendation
Reiki should not be applied. EL 2b, negative recommendation, strong consensus

Comment. A search of the literature identified 19 reports. One trial had no control group [19]. In one trial the 25 patients were treated for 8 weeks by either a reiki master or an actor, receiving either reiki (direct contact) or a "distance treatment". None of the treatments had a significant effect on pain, fatigue, sleep, or quality of life [3]. In spite of the limited data available, a statement on this treatment is included here because of the negative results of the trial.

Dance therapy

Evidence-based recommendation
Dance therapy should not be applied as monotherapy. EL 2b, negative recommendation, strong consensus

Comment. A search of the literature identified 34 reports. In a non-controlled Argentinean trial with 19 patients, 3 mg melatonin/day for 4 weeks improved sleep and decreased the tender-point score [14]. In a RTC, 24 patients received 5 mg melatonin/day, 24 patients 20 mg fluoxetine/day, 27 patients 20 mg fluoxetine/day plus 3 mg melatonin/day, and 23 patients 20 mg fluoxetine/day plus 5 mg melatonin/day. A placebo control was not carried out. Pain was significantly reduced.
in all arms of the trial, but sleep was significantly improved only in the melatonin groups [33]. Melatonin is approved for the short-term treatment of primary insomnia in patients older than 55 years.

Music therapy

Evidence-based assessment

Due to the limited data available, neither a positive nor a negative recommendation is possible. Strong consensus

Comment. In a US RCT with 26 patients and passive musical therapy, musically fluctuating vibrations (60–300 Hz) were not superior to sinusoidal vibrations in reducing the intensity of pain [13]. In a German controlled trial, a program of active music therapy in a group of 12 patients with various pain syndromes including FMS patients was superior to control therapy in reducing pain and pain-related disability at the completion of therapy [45].

Discussion

As pointed out in the first edition of the guidelines [40], complementary and alternative medicine (CAM) is widely used by patients with FMS (87–91%). However, these various therapies remain to be satisfactorily evaluated and their effectiveness established, since few good controlled trials on CAM therapies for fibromyalgia are available. Further research in this area is desirable and necessary.

In the first edition of the guidelines [40], the recommendations were designated “open” for breathing therapy, elimination/vegetarian diets, and foot massage therapy. In this update, they again cannot be either positively or negatively recommended because of the absence of satisfactory trials. The open recommendation for homeopathy has been changed to a negative recommendation due to the results of a quantitative data synthesis. However, the relatively sparse data can be interpreted in different ways (see Minority opinion). The recommendation for acupuncture was changed from negative to open as a result of new trials and quantitative data synthesis (Tab. 1).

As a rule, complementary procedures are applied in an interdisciplinary and integrative medical setting. Frequently they constitute a useful supplement within the framework of a multimodal therapeutic concept. One advantage of some complementary therapeutic procedures (e.g., qigong or tai chi) is that patients can apply the procedures themselves and are not dependent on a therapist.

Especially needed are randomized clinical trials on the effectiveness of music and dance therapies, homeopathy, and dietary intervention.

Many basic therapeutic approaches of complementary medicine, e.g., acupuncture, are thought to activate intrinsic physiological mechanisms. Frequently the exact mediators of potential therapeutic effects are still not understood. Thus, not only clinical trials to evaluate the complementary therapies are needed, but also trials in the realm of basic research. In addition, more information about how frequently FMS patients in Germany utilize complementary procedures and what motivates them to do so is needed.

Conclusion with regard to practice

FMS patients frequently utilize complementary and alternative medicine therapies. Complementary procedures as a rule are applied in an interdisciplinary and integrative medicine setting. They can be a useful supplement within the framework of a multimodal therapeutic concept. The use of meditative exercise therapies (tai chi, qigong, yoga) is strongly recommended. Acupuncture can be applied for a limited period of time. Dietary supplements and Reiki should not be utilized, nor should mindfulness-based stress reduction or dance therapy be utilized as the sole treatments.

Tab. 1 Changes from the first edition of the guidelines in the degree of recommendation for complementary and alternative therapies

<table>
<thead>
<tr>
<th>Therapeutic procedure</th>
<th>Recommendation 2008</th>
<th>Recommendation 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mindfulness-based stress reduction as sole treatment</td>
<td>No statement possible</td>
<td>Strongly negative</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>Strongly negative</td>
<td>Open</td>
</tr>
<tr>
<td>Breathing therapy</td>
<td>Open</td>
<td>Not considered</td>
</tr>
<tr>
<td>Elimination diet</td>
<td>Open</td>
<td>No statement possible</td>
</tr>
<tr>
<td>Foot reflexology massage therapy</td>
<td>Open</td>
<td>No statement</td>
</tr>
<tr>
<td>Homeopathy</td>
<td>Open</td>
<td>Negative</td>
</tr>
<tr>
<td>Meditative Movement Therapies</td>
<td>Open</td>
<td>Strongly positive</td>
</tr>
<tr>
<td>Reiki</td>
<td>No statement</td>
<td>Negative</td>
</tr>
<tr>
<td>Vegetarian diet/therapeutic fasting</td>
<td>Open</td>
<td>No statement possible</td>
</tr>
</tbody>
</table>

References


Definition, diagnosis and therapy of chronic widespread pain and so-called fibromyalgia syndrome in children and adolescents

Systematic literature review and guideline

Epidemiologic studies reveal a high prevalence (between 25% and 46%) of chronic pain in children and adolescents, an increased prevalence with age and a higher prevalence in girls [14, 32, 58, 68]. The most common locations of pain— in order of descending frequency—are head, abdomen and musculoskeletal system; some of the children and adolescents report pain in several regions [14, 32, 58, 67]. About 3% of children and adolescents develop severe, disabling chronic pain with negative effects on school attendance, recreational activities, contact with peers and family and emotional distress, such as anxiety and depression [32, 55]. A subset of these children and adolescents suffer from additional symptoms, for example disordered sleep [45, 57] or fatigue [19]. In children and adolescents who suffer from generalized pain of the musculoskeletal system, additional symptoms and muscle tenderness, the diagnosis juvenile fibromyalgia syndrome (JFMS) is used. The definitions of JFMS, however, have substantial operationalizational problems. The authors of the update of these guidelines therefore chose to use the term “so-called JFMS”.

For the planned update of the guidelines, the following research questions were addressed by use of a comprehensive literature review:

1. What are the core symptoms of the so-called JFMS?
2. What differences/overlap exist between so-called JFMS and somatoform pain disorder?
3. According to which criteria should the so-called JFMS be diagnosed?
4. Which diagnostic examinations are required to rule out alternative diagnoses?
5. When is a psychological evaluation reasonable?
6. Are there different courses or degrees of severity of the so-called JFMS?
7. Which information about symptoms, therapeutic goals and treatment opportunities should be made available at the time of diagnosis?
8. Is patient education useful?
9. Which subspecialty should coordinate the care of the so-called JFMS?
10. Is a graded treatment approach useful?
11. Which physical, physical therapeutic, psychotherapeutic, pharmacologic and complementary approaches are useful in the so-called JFMS?
12. Which physical, physical therapeutic, psychotherapeutic, pharmacologic and complementary approaches should be advised against in the so-called JFMS?
13. When is an inpatient multimodal treatment indicated?

Materials and methods

The methods of literature search and preparation of recommendations are presented in the article “Methodological fundamentals used in developing the guidelines”.

Results

The literature search yielded 265 hits. Due to the low number of high quality studies, there was no gradation of the level of evi-
dence according to the quantity or quality of the evidence.

**Definition and classification**

**Clinical consensus**

For children and adolescents there are currently no standardized and validated criteria for defining chronic pain in multiple body regions leading to clinically significant impairment in everyday life and that does not occur within a defined somatic disease. Strong consensus

**Comment.** In childhood and adolescence, pain, regardless of its location, is defined as chronic if it lasts for at least 3 months or is recurrent over this time period [33, 47, 54]. Persistent or recurrent pain may fluctuate greatly in intensity, quality, frequency, predictability and may occur either in single or multiple body regions. The focus on the temporal dimension of chronic pain has recently been criticized. Studies indicate that children, who suffer from shorter-lasting pain, are often significantly impaired in their daily lives and require treatment [28, 33]. The aspect of pain-related impairment has only recently been explicitly considered in the context of epidemiological and clinical studies [29, 30, 54]. Rief et al. [64] included the issue of impairment as a central criterion within a new diagnostic category of "chronic pain disorder with so significant impairment due to chronic pain, a study and thumb size) or even 5 kg/1.5 cm² were considered as pathologic [7]. Depending on age, gender and location of pressure application, many healthy children report pain at these pressures.

b) In the published studies, the so-called tender points were generally not standardized, often only examined by thumb pressure and not examined in a double-blind fashion. However, for the thumb pressure not only the compressive force, but also the support surface is critical.

c) When two pediatric rheumatologists examined tender points in the same child, their agreement was around 44%, not better than chance [9].

d) Some studies show that children with juvenile idiopathic arthritis (JIA) have identical tender point pain thresholds as children with so-called JFMS [62].

e) If tender points are positive, so-called control points are often positive as well [72]. Häfner et al. [21] found that tender points were variable and fluctuated.

2. The so-called minor symptoms of the Yunus criteria have not been defined. Headaches should be classified according to the International Headache Society (IHS) criteria, e.g., chronic tension headache, episodic tension headache, migraine, medication-induced headache. The same is true for the diagnosis irritable bowel syndrome, for which the Rome criteria should be required [20].

3. For psychological symptoms such as anxiety and depression and functional impairment due to chronic pain, a standardized survey with established instruments should be implemented (see below).

a) generalized musculoskeletal aching at ≥3 sites,

b) duration for at least 3 months,

c) normal laboratory test results,

d) at least 5 of 11 tender points,

e) at least 3 of the following 10 features:

1. chronic anxiety or tension,

2. fatigue,

3. poor sleep,

4. chronic headaches,

5. irritable bowel syndrome,

6. subjective soft tissue swelling,

7. numbness,

8. pain modulation of physical activity,

9. pain modulation by weather factors,

10. pain modulation by anxiety and/or stress.

Other publications on JFMS used the definition of the American College of Rheumatology (ACR) in 1990 for adults. The specificity and sensitivity of the Yunus criteria and the ACR criteria have rarely been investigated in children and adolescents. In a study by Reid [61], only 75% of pediatric patients fulfilled both the Yunus as well as the 1990 ACR criteria. The pain is typically highly variable; therefore, the Yunus criteria are met only irregularly. Both the Yunus and the 1990 ACR criteria have substantial problems in their operationalization:

1. The so-called tender points are problematic for the following reasons:

a) From studies on quantitative sensory testing (QST) in children and adolescents it is known that the pressure pain threshold when using a pressure gauge device (FDN 100, Wagner Instruments, USA) depends on the age and sex of the child and the location tested [3]. Fifty percent of healthy children report pain at a pressure ranging from 163–1,039 kPa (100 kPa=1 kg/cm²), whereas the upper and lower 95% confidence interval (95% CI) vary according to age, sex and location of pressure application between 82–1,890 kPa. The testing of tender points using thumb pressure or technical devices with a pressure independent of the age, sex and location of pressure application may not lead to valid results, since the pressure–pain threshold in healthy children is influenced by these factors. Tenderness thresholds from about 3 kg/cm² (300 kPa/cm²) or 3 kg/1.5 cm² (depending on the study and thumb size) or even 5 kg/1.5 cm² were considered as pathologic [7]. Depending on age, gender and location of pressure application, many healthy children report pain at these pressures.

b) In the published studies, the so-called tender points were generally not standardized, often only examined by thumb pressure and not examined in a double-blind fashion. However, for the thumb pressure not only the compressive force, but also the support surface is critical.

c) When two pediatric rheumatologists examined tender points in the same child, their agreement was around 44%, not better than chance [9].

d) Some studies show that children with juvenile idiopathic arthritis (JIA) have identical tender point pain thresholds as children with so-called JFMS [62].

e) If tender points are positive, so-called control points are often positive as well [72]. Häfner et al. [21] found that tender points were variable and fluctuated.

2. The so-called minor symptoms of the Yunus criteria have not been defined. Headaches should be classified according to the International Headache Society (IHS) criteria, e.g., chronic tension headache, episodic tension headache, migraine, medication-induced headache. The same is true for the diagnosis irritable bowel syndrome, for which the Rome criteria should be required [20].

3. For psychological symptoms such as anxiety and depression and functional impairment due to chronic pain, a standardized survey with established instruments should be implemented (see below).
Due to these limitations of operationalization, the term JFMS has been rejected by leading rheumatologists and researchers since it is not scientifically established or clinically helpful [73]. The guideline committee agrees to this opinion.

Based on the work by Rief et al. the authors of the present guidelines suggest, that, in the future, the diagnosis “chronic pain disorder in several body regions with somatic and psychological factors” should be used for children with chronic widespread pain (CWP), who also suffer from other symptoms such as headache or abdominal pain, non-restorative sleep, muscle tenderness, fatigue, irritable bowel syndrome, anxiety, depression and a strong pain-related impairment in everyday life.

In adults, Rief et al. [64] suggested to optimize the classification of chronic pain in ICD-10 (section F) according to the biopsychosocial model. Thus far, chronic pain has been classified as “somatiform pain disorder” (F 45.4). For this diagnosis, psychologic factors were considered to trigger the pain. Since this relationship could not always be confirmed in studies, a new proposal for the diagnosis “chronic pain disorder with somatic and psychological factors” (F45.41) was created [64]. The clinical picture is dominated by pain lasting for at least 6 months in one or more anatomical regions. This pain is assumed to have been triggered either by psychological processes or a physical disorder. Psychological factors are considered to play an important role in the degree of severity, exacerbation or maintenance of pain, but to a minor degree a causative role. The pain causes clinically significant distress and impairment in social, occupational or other important areas of functioning. The pain is not voluntarily produced or pretended (as in factitious disorder or simulation). For children and adolescents, the pain disorder should last for at least 3 months (for reasoning, see above).

In this guideline we will use the term of the “so-called JFMS”, because the cited studies describe JFMS patients even though the diagnosis JFMS cannot be operationalized (see above). The authors of these guidelines agree that the diagnosis JFMS is neither scientifically established, scientifically not etabliert eingestuft. Die Therapie sollte multimodal erfolgen. In the case of severe pain-related disability, therapy should be primarily performed on an inpatient basis. The English full-text version of this article is available at SpringerLink (under “Supplemental”).

Keywords

Chronic pain · Fibromyalgia syndrome · Review, systematic · Guideline · Children and adolescents
nor helpful. Therefore, they propose to use the term “chronic pain disorder in several body regions with somatic and psychological factors” instead.

Clinical diagnosis

Clinical consensus

In children and adolescents with chronic pain in multiple body regions (CWP) a multidimensional diagnosis of pain and other physical and psychological symptoms is recommended. Validated tools and methods should be used. Strong consensus

Comment. As no pathognomonic individual diagnostic findings for so-called JFMS are available, the diagnosis is based on the presence or absence of a characteristic constellation of symptoms and signs after exclusion of all other diseases that may also have such a constellation of symptoms and signs. Therefore, the differential diagnosis and exclusion of other diagnoses is of particular importance. The differential diagnosis itself depends on the clinical picture. Various organic diseases have to be considered: (systemic) inflammatory conditions such as juvenile idiopathic arthritis, malignant conditions such as leukemias [8, 77] and endocrine–metabolic diseases [42, 49]. Psychological problems/disorders should be considered since they are even more common, e.g., depression (subtypes according to DSM-IV, see below), anxiety disorders (subtypes according to DSM-IV, see below), posttraumatic stress disorders (PTSD) and dissociative disorders with or without self-injurious behavior. There is also the possibility of mental illness of parents, as seen in Munchhausen by proxy syndrome.

In a study by Degotardi et al. [11] 2 of 77 children, all of whom met the Yunus criteria and all of whom were diagnosed by pediatric rheumatologists as JFMS, were eventually diagnosed with severe psychiatric disorders (“schizoaffective disorder” and “depression with suicidal ideation”) during further psychological evaluations. In the course of the study an additional 3% of the enrolled children had a “need for psychiatric referral.” Kashikar-Zuck et al. studied 102 adolescents with the diagnosis of so-called JFMS regarding psychiatric disorders using standardized tests and an extensive psychological exploration: 19% suffered from depression according to DSM-IV criteria [major depression (n=7), dysthymic disorder (n=8), depressive disorder not otherwise specified (NOS) (n=5)], 55% an anxiety disorder [panic disorder (n=6), agoraphobia (n=4), specific phobia (n=0), social phobia (n=11), obsessive-compulsive disorder (n=3), posttraumatic stress disorder (n=5), generalized anxiety disorder (n=17), or separation anxiety disorder (n=3)] and 24% suffered from attention deficit hyperactivity disorder (ADHD) [37, 38]. Therefore, the clinical assessment should include a profound medical and psychological examination, preferably by use of validated tools such as the German Paediatric Pain Questionnaire (“Deutscher Schmerzfragebogen für Kinder und Jugendliche”, DSF-KJ) [71]. Specifically, the following examinations should be conducted:

- basic laboratory diagnostic, e.g., erythrocyte sedimentation rate, complete blood count with differential count, C-reactive protein, creatine kinase.
- Further diagnostic studies (e.g., antinuclear antibodies, rheumatoid factor, imaging, electroencephalography, genetic studies, biopsy) are indicated if there is a clinical suspicion for an alternative cause of the pain, and
- psychological standard diagnostics such as the “Depressionsinventar für Kinder- und Jugendliche (DIKJ)” (depression inventory for children and adolescents), “Angstfragebogen für Schüler (AFS)” (fear questionnaire for students).

If applicable, polysomnography

Epidemiology

Evidence-based observation

The prevalence of CWP is strongly age-dependent and ranges between 1 and 15% in children and adolescents. Diffuse musculoskeletal pain in combination with other physical or psychological symptoms such as tension-type headaches, fatigue, sleep disturbance and emotional distress is present in <1% of children and adolescents between the ages of 8-15 years in international studies. There is a female predominance. Strong consensus

Comment. When reviewing epidemiological studies, distinction must be made with regard to the sample studied—specifically, between studies that examined only the presence of CWP [15, 50] and studies that studied children who also suffered from other symptoms indicative of the diagnosis of so-called JFMS.

Epidemiological studies in school children focused on children between 10 and 12 years and reported prevalences of CWP of 1% [50], 7.5% [52] and 9.9% [51]. In a follow-up study by Mikkelsen et al. [50], adolescents between the ages of 14 and 16 years had a prevalence of CWP of 15%.

In a German representative population sample, 302 adolescents were in the age group between 14 and 24 years; none of them fulfilled the FMS criteria according to the survey criteria [22]. Since the diagnosis of adult FMS by means of tender points was abandoned in the latest ACR criteria [81], epidemiological studies of the prevalence of so-called JFMS need to be re-evaluated. Of the 7 children who were classified as having so-called JFMS (prevalence approximately 1% among school children 9–15 years) in the study by Clark et al. in 1998 [9], there was only one child who fulfilled all examined additional criteria (sleep disturbances, morning stiffness, fatigue, sadness). Three children fulfilled only one criterion each; neither the severity of symptoms nor the impairment of the children by the symptoms was reported. Other studies that found a significantly higher prevalence of so-called JFMS of 6.2% for 9- to 15-year-old school children based their diagnosis mainly on muscle tenderness [7], which, due to the methodological difficulties described above, can be criticized.

Disease course

Evidence-based observation

In most patients with CWP, or so-called JFMS, the disease course is variable with alternating episodes of increased, decreased or absent symptoms. Evidence level 2b, strong consensus
Comment. In a study on the course of CWP in childhood and adolescence, only 10% of children who had CWP at baseline complained of persistent symptoms after 1 and 4 years [50].

The evaluation of studies on the course of the so-called JFMS is complicated by the fact that the diagnosis itself is not valid, due to the methodological problems described in detail above. Moreover, in most studies, the study population was not assessed with standardized instruments. Essentially, children and adolescents with a pain disorder diagnosed in a non-standard fashion were examined in a non-standard fashion, and described by the authors as having so-called JFMS.

In clinical studies, the persistence of long-term symptoms is described in a subset of patients. Malleson et al. [46] conducted a retrospective survey based on medical records. Twenty-eight of 35 patients diagnosed with JFMS had more than one appointment in the rheumatology clinic. After a variable observation period between 1 and 48 months, 17 of 28 patients with so-called JFMS had persistent symptoms after an average of 27 months [46]. In a retrospective study, Siegel et al. [74] assessed 44 patients over 6 years with so-called JFMS. Subsequent phone interviews, on average 2.6 years (range 0.1–7.6 years) after diagnosis, demonstrated an increase in the number of reported symptoms. On a visual analog scale (VAS) from 1–10 (1=complete disability; 10=no disability), the patients assessed their current impairment as being less pronounced than in the previous year (previous year 5.1±3.1 vs. currently 6.9±1.6). The patients received a standard outpatient treatment (tricyclic antidepressants, non-opioid analgesics, exercise program) [74]. The study results are promising; however, there is a core critical point: the authors changed their study methods between the time of outpatient treatment (unstructured survey) and the telephone interview (structured survey). In addition, no standardized instrument to assess pain-related disability was used, e.g., the Functional Disability Inventory [36, 79]. Gedalia et al. [18] conducted a retrospective study over a period of 4 years. Fifty of 59 patients with so-called JFMS were seen more than once in the outpatient clinic. At an average follow-up of 18 months (range 3–65 months), 60% of the children improved, 36% experienced no change, and 4% experienced a worsening of pain symptoms. The therapy consisted of a combination of pharmacological and nonpharmacological interventions; at the time of follow-up 74% of children were taking medications [18]. Of 48 U.S. American children and adolescents diagnosed with JFMS, after an average of 3.7 years, 62.5% suffered from CWP, and 60.4% fulfilled criteria for so-called JFMS [40].

Population-based studies in children and adolescents reveal a more favorable disease course: In a population of Israeli school age children, Buskila et al. [6] diagnosed so-called JFMS in 21 of 337 patients (6.2%) according to the ACR criteria; after 30 months of follow-up, the ACR criteria were met by only 4 of 21 children. In the Finnish study by Mikkelsen et al. [52], only 4 of 16 school age children with so-called FMS fulfilled the ACR criteria of so-called JFMS after a follow-up of 1 year.

Exacerbating factors for CWP include the following: daily hassles, pain-related catastrophizing, lack of self-efficacy and lack of positive family support [43].

Etiology

Somatic complaints (headache and abdominal pain), behavioral problems and increased physical activity

Evidence-based observation

Somatic complaints (headache and abdominal pain), behavioral problems and increased physical activity frequently occur prior to CWP. There are no studies on the relationship of these factors to so-called JFMS. Evidence level 2b, strong consensus

Psychosocial problems

Evidence-based observation

Studies regarding psychosocial problems in patients with so-called JFMS demonstrate controversial findings. Evidence level 3b, strong consensus

Comment. A biopsychosocial perspective is necessary to understand the origin and maintenance of chronic pain [78]. Chronic pain in children is the result of a dynamic process of biological factors (e.g., an underlying somatic disease), physical components (e.g., a lowered threshold of pain), psychological factors (e.g., pain-related fears, dealing with pain and pain coping) and sociocultural conditions (e.g., pain-related parenting, social attitudes, gender roles, social interactions in dealing with pain). All of these factors interact with each other.

Risk factors for the development of a so-called JFMS or chronic pain disorder of the musculoskeletal system have not been investigated to date.

In an English population-based prospective follow-up study over a study period of 12 months, 1,440 school children were examined for risk factors for the development of CWP. These risk factors included physical symptoms such as headache on more than 7 of 30 days (relative risk (RR) 2.50, 95% CI 1.16–5.39), abdominal pain at 1–7, but not less than one or more than 7 days per month (RR 1.8, 95% CI 1.1–2.9), as well as increased physical activity of more than 6 h per week (RR 2.03, 95% CI 1.05–3.94). Prosocial behavior was identified as a protective factor for CWP (RR 0.50; 95% CI 0.28–0.90) [34].

In a case control study, no significant differences in psychological distress were observed between patients with a so-called JFMS and JIA [60]. In contrast, Conte et al. [10] reported a higher incidence of anxiety and depression in patients with so-called JFMS compared to healthy subjects and patients with JIA. In a case control study of a private psychiatric hospital, 32 adolescents who met the criteria of so-called JFMS reported more physical and emotional problems than the control group of 30 adolescents with other mental disorders [44].

A case-control study of 55 patients with so-called JFMS and 55 healthy controls showed that adolescent patients with so-called JFMS described themselves as more withdrawn and less popular and, thus, were more likely than their peers to be socially isolated [39]. This was not the case for patients with JIA.
Family history

Evidence-based observation
So-called JFMS and adult FMS occur together in families. Evidence level 2b, strong consensus

Comment. The increased jointed occurrence of adult FMS and so-called JFMS in first-degree relatives has consistently been reported in several studies [1, 6, 53, 65, 76]. In an Israeli study of 37 families with FMS (at least 2 relatives), 74% of siblings and 53% of parents were diagnosed with FMS according to the ACR criteria [5]. The studies on familial clustering, however, do not provide evidence that the increased incidence of adult FMS and so-called JFMS is genetically determined. The results of an American study of over 40 families with FMS (at least 2 first-degree relatives) were consistent with a genetic linkage to the HLA region [82]. A Finnish longitudinal cohort study of 11-year-old twins (583 monozygotic pairs, 588 same-sex dizygotic and 618 different-sex dizygotic pairs) demonstrated a CWP prevalence of 9.9% and mostly discordance; a genetic basis could not be shown [51]. Non-genetic, psychological factors for the increased incidence of chronic pain in children of adult chronic pain patients are much more likely to play a role than genetic models (role modeling etc.) [2, 56].

Parental factors

Evidence-based observation
Parents of patients with so-called JFMS frequently show increased anxiety, a history of chronic pain, depressive symptoms and chronic diseases. Evidence level 3b, strong consensus

Comment. Parents of children and adolescents with so-called JFMS:
- more frequently report chronic pain [35, 70],
- tend to show increased anxiety [10],
- more frequently demonstrate depressive symptoms [10, 35], and
- suffer from more somatic symptoms [10].

Pathophysiology

Evidence-based observation
Due to the lack of studies, no comment can be made on the pathophysiology of so-called JFMS. Strong consensus

Coordination of care

Evidence-based recommendation
Children and adolescents with CWP should be presented to a clinical specialist familiar with chronic pain in childhood on an outpatient basis. In the case of long school absences, severe limitations in activities of daily living, physical inactivity or increasing social isolation, inpatient treatment in a facility that offers a special treatment program for children and adolescents with chronic pain, should be recommended. Evidence level 4, strong consensus

Comment. In a study by Hechler et al. [28] on the stratification of therapy in a sample of children and adolescents with chronic pain (headaches, abdominal pain or musculoskeletal pain), the criteria for stratification of therapy were studied. The intensity of initial therapy (outpatient therapy, outpatient group therapy, inpatient therapy) turned out to be correct for the majority of children. An intensification of therapy was rarely needed. In this study, children were assigned to multimodal inpatient treatment based on the following criteria: chronic pain for at least 3 months, no successful therapy in the previous setting, high pain-related impairment [Pain Disability Index (PDI) ≥36] and the presence of 3 of the following 4 criteria:
- pain duration >6 months,
- average pain intensity in the last 7 days ≥5 [visual analog scale (NRS) 0–10],
- pain peaks ≥8 (NRS 0–10) at least twice a week, and
- at least 5 school days of absence during the last 20 school days.

Children and adolescents with so-called JFMS who do not (yet) express this level of severe impairment, should initially be treated as outpatients. Local or part-time inpatient multimodal treatment is rarely offered for children and adolescents with chronic pain of the musculoskeletal system in Germany. Therefore, for the less severely affected children, an individual multimodal program should be planned based on the existing facilities in Germany (e.g., outpatient psychotherapy, physical therapy, regular visits to the pediatrician). There are only a few centers offering multimodal inpatient therapy; thus, treatment often takes place remote from the hometown. Even though only studies with a level of evidence grade 4 are available, the authors agreed in a unanimous consensus to recommend this modality with a strength level B given the following criteria are met: low risk, high acceptance rate among patients (adherence to therapy between 95% [13] and 98% [16]) and ethical necessity, since normal childhood development is endangered.

General principles of treatment

Therapeutic goals

Evidence-based recommendation
Goals of treatment should be pain relief, restoration of functioning, reduction of school absenteeism, dissolving social isolation, strengthening self-awareness, mobilizing domestic resources and the development of strategies for coping with pain. The inclusion of the family, the training of strategies in everyday life and the treatment of mental co-morbidities are also important. Evidence level 2c, strong consensus

Comment. The general principles of therapy have been formulated comprehensively in prospective outcome trials [12, 13, 16, 23, 24, 25, 26].

Patient education

Clinical consensus
Patient and parent education and self-help groups for children, adolescents and parents may be offered. Strong consensus
Psychotherapy

Clinical consensus
Scientifically established methods of psychotherapy should be used for children and adolescents with so-called JFMS part of a multimodal pain therapy. Strong consensus

Comment. A U.S. randomized study in cross-over compared active coping with pain to self-monitoring in 30 adolescents; at the end of the study both groups demonstrated a reduction of functional limitations and depression [41]. A significant reduction of pain could not be demonstrated. This study had major methodological problems; neither the sample size was calculated nor was a primary outcome measure predetermined.

The authors believe that, according to experts and studies about multimodal pain therapy, scientifically established psychotherapies (cognitive behavioral therapy, trauma therapy, systemic family therapy, analytical therapy) in children with so-called JFMS should only be carried out as part of a multimodal pain therapy or for treatment of psychiatric co-morbidity. The content of the therapy should be adjusted to the individual child or adolescent and his/her situation. Local outpatient psychotherapy should be considered on a case-by-case basis.

Physical therapy and physical measures

Clinical consensus
Physical therapy should be used as part of multimodal pain therapy. Strong consensus

Comment. In a randomized-controlled trial (RCT), 14 patients with so-called JFMS were treated with aerobic exercise of moderate intensity and 16 were treated with Qi-Gong. At the end of therapy, the group performing aerobic training reported a greater reduction in pain, fatigue and impairment in quality of life than the group performing Qi-Gong. In the Qi-Gong group, there was significant change in pain, fatigue and impairment in quality of life [75]. A recent study by Kashikar-Zuck [37] showed that adolescents who suffered from so-called JFMS and who were physically active ("high activity" as measured by actigraphy), had less pain, were judged by their parents as being less depressed and were functionally less impaired as compared to adolescents who were moving less ("low activity"). However, the cross-sectional design did not allow establishing a cause-effect relationship.

Studies on the efficacy of other methods of physical therapy and physical measures are not available. Nevertheless, these therapies are recommended by the authors with a level of recommendation grade B since they are preferred by the patients, are accompanied by a high level of adherence and have low risk of potential adverse effects, and since they are easy to implement in Germany, both on an outpatient and on an inpatient basis.

Pharmacologic therapy

Evidence-based recommendation
Pharmacologic therapy should not be performed in children with CWP or so-called JFMS. Co-morbidities (e.g., depression in adolescence) should be treated according to the available guidelines. Evidence level 4, consensus

Comment. Controlled drug studies are not available. In a U.S. case series of 15 patients, it was reported that aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) were not effective; 73% of children responded to cyclobenzaprine 5–25 mg/day [66]. Two observational studies reported on the use of NSAIDs and/or psychotropics in combination with exercise therapy [74] or a complex multimodal treatment [63]. Saccomani et al. [69] described a clinical improvement with trazodone or amitriptyline in 2 Italian patients. Children and adolescents were generally excluded from drug trials in adult FMS patients.

Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRI) are not approved for the treatment of children and adolescents in Germany (off-label therapy). Clinical experience suggests that there can be a role for drug therapy in the treatment of comorbidities of the individual multimodal therapy concept. However, focusing on medications must be avoided. The potential risks of drug therapy, the lack of approval of most drugs used as well as the failure to show a benefit for the individual patient justify, according to the authors’ opinion, a recommendation against drug therapy.

Multimodal therapy

Clinical consensus
In patients with so-called JFMS, multimodal pain management should be performed. In cases of severe impairment or unsuccessful other approaches, this should be pursued in an inpatient unit, in case of less severe impairment, initially in an outpatient unit. Strong consensus

Comment. Multimodal pain therapy, in the context of these guidelines, is understood to be a combination of at least one method of activating physical therapy with at least one method of psychotherapy, as described by the working group multimodal therapy [4]. In the case of outpatient multimodal pain therapy, the pediatric rheumatologist or pediatric pain specialist assumes the coordination of care. Stipulations of inpatient multimodal pain therapy for children in Germany are described in the OPS ("Operationen- und Prozedurenschlüssel") under paragraph 8–918.x.

There are no RCTs on the efficacy of multimodal therapies in so-called JFMS.

In pediatric studies on the effectiveness of multimodal treatment programs (outcome studies, level of evidence 2c), there was always a more or less large proportion of children and adolescents with CWP and additional psychosomatic/psychological complaints/abnormalities. The proportion of these children was 40% (n=23) in the study by Eccleston et al. [17], and in the study by Hechler and DoBe [25], the proportion of children with predominant musculoskeletal pain was 14% (n=28). In the latter work, the chronically ill children and adolescents in 40% of cases reported pain in more than one region (n=61). Three months after completion of inpatient multimodal pain therapy, 75% of children reported significant positive changes in pain intensity, 63% a significant improvement in pain-related ...
disability and 45% significant changes in the days absent from school (30% of the children had no significantly increased school absenteeism at baseline). Clinically significant changes in the emotional impairment were exhibited in 13–26% of patients, whereby 50–60% had no emotional distress at baseline. More than half of the children (55%) demonstrated overall improvement 3 months following treatment [25].

In their recent analysis of 200 children and adolescents with chronic pain, Dobe et al. [13] showed that the success of the multimodal inpatient program was independent of the site of pain.

It is recommended children and parents receive instructions for home therapy during multimodal inpatient treatment. The continuation of parts of the multimodal program in everyday life is crucial for the prognosis. Relaxation techniques and physical therapy, exercise therapy and other athletic activities, physical activities and the coping with stressors and psychological problems (e.g., by use of social support) are important tasks to take home [12, 23, 25, 27].

Contraindications for multimodal inpatient treatment are serious psychiatric illnesses such as the presence of psychosis or anorexia nervosa [13]. Suicidal ideation in adolescents with chronic pain or depression—a frequently described comorbidity in children with chronic pain in multiple body regions—has been reported. Therefore, the diagnosis and treatment of children and adolescents with so-called JFMS should always be conducted by a multidisciplinary team, involving child and adolescent psychologists or psychiatrists.

Discussion

The first version of the guideline for so-called JFMS was substantially revised [48]. It has been shown that the diagnosis of JFMS is not yet scientifically established, so that the concept of so-called JFMS was implemented in this paper. The question of how children and adolescents with chronic pain in several body regions accompanied by other symptoms should be diagnosed and classified is an urgent question for future research. This raises the question of whether the clinical picture of JFMS exists or whether the children and adolescents with these symptoms suffer from other specified diseases. A second new feature of the guidelines is the requirement for a standardized diagnostic procedure, which also includes validated psychological assessments. Since it is known that the so-called JFMS does not represent a well-established disease, it is even more important to recognize defined organic and mental diseases, such as posttraumatic stress disorder in order to identify and deliver appropriate therapy. As in the first version of the guideline, multimodal treatment approaches are warranted for affected children. In addition to the general principle of “outpatient before inpatient care”, we present criteria that, when present, suggest assignment to multimodal inpatient treatment. These criteria do not relate primarily to pain intensity or duration of the disease, but in particular to pain-related adverse effects such as school absenteeism, a marked reduction of the activities of daily living or social withdrawal. As in the first version of the guidelines, drug therapy is not recommended for the treatment of the so-called JFMS. Co-morbid mental disorders should be treated according to the respective guidelines.

In summary, the revised and updated second version of this guideline clearly recommends a comprehensive reassessment of the so-called JFMS taking into account current work on quantitative sensory testing (QST), psychological assessment of chronic pain as well as the success of multimodal pain management programs in children and adolescents. Controlled studies for the diagnosis of children who present with a symptom complex that reminds of adult FMS, and RCTS of children suffering from chronic musculoskeletal pain and other physical and mental symptoms, are urgently needed to clarify the diagnosis of JFMS and to provide evidence for multimodal pain treatment for these children.

Corresponding address

Prof. Dr. B. Zernikow
Deutsches Kinderschmerzcentrum, Vestische Kinder- und Jugendklinik, Universität Witten/Herdecke Dr. Friedrich-Steiner-Str. 5, 45711 Datteln Germany
b.zernikow@deutsches-kinderschmerzcentrum.de

Conflict of interest. See Tab. 5 in “Methodological fundamentals used in developing the guidelines” by W. Häuser, K. Bernardy, H. Wang, and I. Kopp in this issue.

References


