Fibromyalgia and chronic fatigue syndrome: recommendations on diagnosis and treatment

QUICK GUIDE

INTRODUCTION AND OBJECTIVES

In May 2008, as a result of the presentation of a new popular law, the Parliament of Catalonia approved the 203/VIII resolution that required the government to implement an intervention protocol for fibromyalgia (FM) and chronic fatigue syndrome (CFS) and the development of specialised hospital units (SHUs) with guaranteed accessibility. The minister's later order, published in the DOGC (Official Gazette of the Generalitat of Catalonia, a local government magazine), regulates the regional scope of care, staff and operation of these units, as specified in the resolution itself. One year after the resolution, in May 2009, the Department of Health elaborated a report to fulfil this 203/VIII resolution, and asks the Catalan Agency for Health Information, Assessment and Quality (CAHIAQ, previously Catalan Agency for Health Technology Assessment and Research, CAHTA) to update the review of current scientific evidence on diagnostic criteria and treatments for FM and CFS. It is also charged with defining strategies to update the evidence and identify key variables that make it possible to carry out the follow-up and assessment of the treatment indicated in these two entities, a rough draft of a potential Catalan clinical registry.

METHODOLOGY

Objective 1. Systematic review (SR) of the scientific evidence of clinical practice guidelines (CPGs), systematic reviews (qualitative or quantitative) of randomized controlled trials (RCTs) and observational studies, RCTs and other designs published between August 2007 and October 2009. The usual information sources have been consulted (Medline/Pubmed, Cochrane Library Plus in Spanish, DARE, HTA, NHS-EED, National Guidelines Clearinghouse, Trip database, UK National Library for Health, ECRI, HAYES, Clinical Evidence). After applying the selection criteria and assessing the quality of the evidence with critical appraisal sheets according to study design, the evidence was classified and synthesised. In order to formulate recommendations, the SIGN system has been used and consensus for the final version has been reached with the entire working group after assessing the comments of external reviewers. During the review performed by the working group and the external reviewers, studies published after the search closing date have been considered.

Objective 2. Review of Updating CPGs in the Spanish National Health System: Methodology Handbook (November 2009).

Objective 3. Review of relevant articles to meet objective 1 plus the taking into account of variables of some registries created by the experts from the working group. Based on this data, the CAHIAQ then proceeded to elaborate a proposal of variables that was presented at a plenary meeting to the rest of the working group until a basic list and an optional list of variables were created (without consensus).

RESULTS

Objective 1. Tables of evidence on diagnostic criteria and efficacy/effectiveness and safety of FM (**Table I**) and CFS (**Table II**) treatments. These tables show the level of evidence for each intervention (design and quality according to the SIGN or GRADE system) and the degree of recommendation (the higher the degree of recommendation, the more likely that the observed effect is true: degree A, highest confidence). In addition to the degree of recommendation, the tables show whether a given practice is recommended or not, or whether any cautions need to be taken.

At present there are no drugs approved by the Spanish Agency for Drugs and Healthcare Products or by the European Medications Agency with a specific indication for the treatment of FM or CFS. Under these circumstances, Royal Decree 1015/2009, dated June 19 regulating the availability of drugs under special circumstances, shall apply. In relation to the provisions set forth in the aforementioned Royal Decree 1015/2009, it should be mentioned that the CatSalut (05/2010) has an instruction on the use of authorised drugs under circumstances different to those established in the technical data sheet, the CatSalut and the Integrated System of Public Use Healthcare (acronym in Catalan SISCAT) being its area of application.

Generalitat de Catalunya
Departament de Salut

Agència d'Informació, Avaluació i Qualitat en Salut

The Catalan Agency of Health Information, Assessment and Quality (CAHIAQ) is a public non-profit company of the Catalan Department of Health reporting to the Catalan Health Service. Its mission is generating relevant knowledge to contribute to the improvement of the quality, safety and sustainability of the Catalan Health Care System and thus easing the decision-making process for citizens and health care managers and professionals. CAHIAQ mission is pursued through acting and organizing the integration of the ICT systems and technologies for the evaluation of health technologies, of research and quality in health.

This is a summary of the report: Working group on fibromyalgia and chronic fatigue syndrome. Fibromyalgia and chronic fatigue syndrome: recommendations on diagnosis and treatment. Barcelona: Catalan Agency for Health Information, Assessment and Quality. Catalan Health Service. Department of Health. Generalitat de Catalunya; 2011.

The working group has formulated 30 recommendations aimed at FM, 7 of which are degree A, 3 are degree B, 8 are degree C, 3 are degree D, and 9 are good clinical practice [√]. In the case of CFS, the number of recommendations is 15, 2 of which are degree A, 1 degree B, 7 degree C and 5 are good clinical practice [√]. The technical consultation proposes some future lines of research of interest in this field.

Objective 2. Five methodological guidelines based on the recommendations of the CPG updating manual of the Spanish National Health Service (NHS) (**Table III**) are suggested to ensure that the scientific evidence of this technical consultation on diagnostic criteria and interventions in the field of FM and CFS remains updated.

Objective 3. During a plenary session, the working group agreed on the fact that it is very complicated to complete a registry of patients with FM and/or CFS due to their plurality of symptoms, the frequent existence of comorbidities and the diversity of pharmacological and non-pharmacological interventions that are applied throughout the entire care process. In addition, the working group believed that its implementation was not justified and were unsure as to which professionals and on which healthcare levels the selected variables would have to be recorded. Finally, the working group, in spite of not having reached consensus, proposed that a first phase of this registry be carried out, in which basic information (key variables) on the sociodemographic characteristics of the patients and some clinical care delivery aspects would be collected; the rest of variables were to be left as optional. **Table IV** shows twelve basic variables. Selection criteria included availability in the clinical history or in the patient's administrative data.

DISCUSSION

The current criteria for diagnosing FM and CFS are the American College of Rheumatology (ACR) 1990 and Fukuda 1994, respectively.

Currently, only symptomatic treatments are available aimed at relieving clinical manifestations such as pain, fatigue, sleep disturbance, etc. shown by FM and CFS patients. Research is still needed on the pathogenesis of these two entities. It should be also improved the methodological rigor of studies in this field. This review identified only few RCTs of good quality. There are few interventions that have robust evidence to be recommended in clinical practice. In the case of FM, pharmacologic interventions are: amitriptyline, cyclobenzaprine, duloxetine and pregabalin; and non-pharmacological therapies are: CBT and multidisciplinary therapy (CBT+ education+ symptomatic pharmacological treatment). As for the SFC, remain effective only CBT and progressive physical exercise which should be moderate so as not to worsen symptoms. Importantly, the effect of these interventions has been shown in experimental studies and factors related to actual clinical practice should be taken into account as potentially modifying outcomes.

At present there are no drugs approved by the Spanish Agency for Medicines and Health Products (acronym in Spanish AEMPS) or by the European Medicines Agency (acronym in Spanish EMA) with a specific indication for the treatment of FM or CFS. Under these circumstances, Spanish Royal Decree 1015/2009, dated June 19, regulating the availability of drugs under special circumstances, shall apply. It is also important to note that virtually no evidence of comparative clinical effectiveness and harms of the different drugs was identified. Some of them are new active ingredients of the same family (me-too drug) that have only been compared to with placebo. They show similar efficacy and safety profiles but without demonstrating a clear superiority in head-to-head comparisons and being usually more expensive. They find in these indications a niche that no have other similar drugs (as has happened with the new-generation antidepressants -duloxetine-).

The coordinators of the SHUs agreed that it was very difficult to complete a register of patients with FM and CFS, due to the multiplicity of symptoms, the frequent presence of comorbidities and the diversity of pharmacological interventions and non-pharmacological therapies that are administered across all process. On the other hand, they believed that its implementation would not be justified and in case of starting the registry should be assessed if future stages are to be identical to both entities, FM and CFS.

RECOMMENDATIONS

The technical consultation presents forty five recommendations for clinical practice in the management of patients affected by FM or CFS, worded taking into account the best scientific evidence available and the consensus of a panel of experts from the Catalan setting who are coordinators of SHUs in Catalonia. It also proposes a strategy that makes it easier to maintain these recommendations up to date, in accordance with the suggestions of experts on CPG updating of the Spanish NHS. The working group proposes a group of 12 basic variables for this potential registry, selected based on their availability in information systems, such as the patient's clinical history. The other variables are considered optional and should be studied before undertaking new development phases of this registry.

Table I. Summary of the evidence and recommendations[a] for fibromyalgia (FM)

DIAGNOSTIC CRITERIA	
Use the 1990 classification criteria of the American College of Rheumatology (ACR) for FM.	√ (recommended)
Yunus' criteria (1985) are available for the clinical diagnosis of juvenile FM. However, from a practical point of view, it is better to use the ACR's 1990 criteria. Studies performed on children and adolescents are needed to assess these new criteria.	√ (recommended)
TREATMENT	
Pharmacological treatment[b]	
Antidepressants	
Amitriptyline[b]	
There is sufficient evidence on the efficacy of amitriptyline to reduce pain and improve sleep in patients with FM. There is one meta-analysis of RCT[1] of moderate quality (1+), according to the SIGN system.	A (recommended)
Amitriptyline's side effects limit its use.	√ (caution)
Cyclobenzaprine[b]	
There is sufficient evidence on the efficacy of cyclobenzaprine to reduce pain and improve sleep in patients with FM. There is one meta-analysis of RCT[2] of moderate quality (1+), according to the SIGN system.	A (recommended)
Duloxetine[b]	
There is sufficient evidence on the efficacy of duloxetine to reduce pain and improve overall functioning in patients with FM. There is one meta-analysis of RCT[1] of moderate quality (1+), a RCT[3] of moderate quality (1+) and a meta-analysis of RCT[4] of high quality (1++) according, to the SIGN system.	A (recommended)
The possibility of side effects at the beginning of treatment with duloxetine should be monitored.	√ (caution)
Fluoxetine[b]	
The evidence on the efficacy of fluoxetine for the treatment of pain in patients with FM is contradictory. There is one meta-analysis of RCT[1] of moderate quality (1+) according to the SIGN system, that includes three RCTs[5-7].	A (not recommended)
Anticonvulsants	
Pregabalin[b]	
There is sufficient evidence on the efficacy of pregabalin for the reduction of pain in patients with FM. There are three RCTs[8-10] of moderate quality (1+) according to the SIGN system.	A (recommended)
When pregabalin is administered dizziness and vertigo are common until the therapeutic dose is achieved.	√ (caution)
Gabapentin[b]	
The evidence on the efficacy of gabapentin for the treatment of symptoms in FM is insufficient. There is one RCT[11] included in one meta-analysis of RCT[12] of moderate quality (1+) according to the SIGN system.	C (not recommended)
Analgesics	
Tramadol[b] with or without paracetamol[b]	
There is sufficient evidence on the efficacy of tramadol alone or in combination with paracetamol for reducing pain in patients with FM. There is one RCT[13] of moderate quality (1+) according to the SIGN system.	B (recommended)
At therapeutic doses, tramadol may produce side effects in the central nervous system and constipation.	√ (caution)
Non-steroid anti-inflammatory drugs (NSAIDs) (NSAIDs)[b]	
There is no evidence on the beneficial effect of NSAIDs on the symptoms of patients with FM[14].	D (not recommended)
Glucocorticoids[b]	
There is no evidence on the beneficial effect of glucocorticoids on the symptoms of patients with FM[14].	D (not recommended)
Others	
Lidocaine injection[b]	
The scientific evidence of lidocaine injection for the treatment of symptoms in FM is insufficient. There is one RCT[15] of low quality (1-) according to the SIGN system.	C (not recommended)

Table I (continued)

Major opioids, ketamine and ozone therapy[b]	
The evidence on the efficacy of major opioids (morphine, oxycodone, buprenorphine and fentanyl), ketamine and ozone therapy for the treatment of symptoms in FM is insufficient.	**D (not recommended)**
Non-pharmacological treatment	
Cognitive-behavioural therapy (CBT)	
There is sufficient evidence on the beneficial effect of CBT on pain and physical discomfort management in patients with FM. There is one SR of CPG[16] of moderate quality (1+) and one RCT[17] of moderate quality (1+) according to the SIGN system.	**A (recommended)**
Physical exercise	
There is sufficient evidence on the efficacy of aerobic physical exercise to improve symptoms in patients with FM. There is one Cochrane SR of RCT[18] of high quality (1++), two SR of observational designs[19,20] of high quality (2++) and three RCTs[21-23] of low quality (1-) according to the SIGN system.	**B (recommended)**
Initial supervision of physical exercise is recommended. Caution is also advised as excess over-exertion may also worsen the course of FM.	√ **(caution)**
Physical exercise in warm water pool	
There is sufficient evidence on the efficacy of regularly performed moderately intense physical exercises in a warm water pool for the improvement of symptoms in patients with FM. There is one SR of CPG[16] of moderate quality (1+), two RCTs[24,25] of low quality (1-), two RCTs[26,27] of moderate quality (1+) according to the SIGN system and one meta-analysis of RCT[28]. However, there are no studies that demonstrate that the benefit of warm water is superior to non-warm water. This intervention is not part of the portfolio of services offered to patients by the CatSalut.	**B (recommended)**
Initial supervision of physical exercise in a warm water pool is recommended.	√ **(caution)**
Education	
The inclusion of an educational programme on the disease (FM) is recommended.	√ **(recommended)**
Multidisciplinary therapy	
There is sufficient evidence on the efficacy of multidisciplinary therapy for pain management, quality of life and physical capacity in patients with FM. There is one meta-analysis of RCT[29] of high quality(1++), one SR of CPG[16] of moderate quality (1+), one RCT[30] of moderate quality (1+) according to the SIGN system, and another RCT[31]..	**A (recommended)**
Acupuncture	
The evidence on the efficacy of acupuncture for the treatment of symptoms in FM is inconclusive. There is one meta-analysis of RCT[32] of high quality (1++), and one RCT[33] of moderate quality (1+) according to the SIGN system.	**C (not recommended)**
Alternative therapies	
Chiropractic	
The evidence on the efficacy of chiropractic for the treatment of symptoms in FM is insufficient. There is one SR of RCT[34] of moderate quality (1+) according to the SIGN system.	**C (not recommended)**
Massage	
The evidence on the efficacy of massage for the treatment of symptoms in FM is insufficient. There is one RCT[35] of moderate quality (1+) according to the SIGN system.	**C (not recommended)**
Reiki	
The evidence on the efficacy of reiki for the treatment of symptoms in FM is insufficient. There is one RCT[36] of high quality (1++) according to the SIGN system.	**C (not recommended)**
Qi gong	
The evidence on the efficacy of qi gong for the treatment of symptoms in FM is insufficient. There are two RCT[37,38] of low quality (1-) according to the SIGN system.	**C (not recommended)**
Bioelectric treatments	
The evidence on the efficacy of bioelectric treatments for the treatment of symptoms in FM is insufficient. There is one RCT[39] on transcranial magnetic stimulation of moderate quality (1+), one RCT[40] on transcranial direct current stimulation of moderate quality (1+), and one RCT[41] on stimulation using Low-frequency pulsed electromagnetic field therapy of moderate quality (1+) according to the SIGN system.	**C (not recommended)**

a http://portal.guiasalud.es/emanuales/elaboracion/apartado07/formulacion.html

b At present there are no drugs approved by the Spanish Agency for Drugs and Healthcare Products (acronym in Spanish AEMPS) or by the European Medications Agency (acronym in English EMEA) with a specific indication for the treatment of FM or CFS. Under these circumstances, Royal Decree 1015/2009, dated June 19 regulating the availability of drugs under special circumstances, shall apply. In relation to the provisions set forth in the aforementioned Royal Decree 1015/2009, it should be mentioned that the CatSalut (05/2010) has an instruction on the use of authorised drugs under circumstances different to those established in the technical data sheet, the CatSalut and the Integrated System of Public Use Healthcare (acronym in Catalan SISCAT) being its area of application.

Table II. Summary of the evidence and recommendations[a] for chronic fatigue syndrome (CFS)

DIAGNOSTIC CRITERIA	
In order to diagnose CFS in adults, the use of international or Fukuda's criteria, 1994, is recommended. These criteria are based on the non-presence of other entities to diagnose CFS.	√ (recommended)
Jason's criteria, 2007, are available for the clinical diagnosis of CFS in children and adolescents. However, from a practical point of view, the use of Fukuda's criteria, 1994, is recommended. Studies performed on children and adolescents are needed to assess these new criteria.	√ (recommended)
TREATMENT	
Pharmacological treatment[b]	
Antidepressants	
Fluoxetine[b]	
Fluoxetine does not improve physical or mental fatigue in CFS patients. There are two RCT[42,43] of moderate quality according to the GRADE system.	B (not recommended)
Moclobemide, sertraline and galantamine[b]	
Moclobemide is not more effective than placebo at improving symptoms in CFS. There is one RCT[44] of high quality according to the GRADE system.	C (not recommended)
Sertraline is not more effective than placebo at improving symptoms in CFS. There is one RCT[45] of moderate quality according to the GRADE system.	
Galantamine is not more effective than placebo at improving symptoms in CFS. There is one RCT[46] of moderate quality according to the GRADE system.	
Corticosteroids[b]	
Corticosteroids are not more effective than placebo at improving symptoms in CFS. There are two RCT on fludrocortisones[47,48] of moderate quality according to the GRADE system and two RCT on hydrocortisone[49,50] of very low quality according to the GRADE system. There is one RCT[51] that combines fludrocortisone and hydrocortisone of very low quality according to the GRADE system.	C (not recommended)
Dietary supplements	
Dietary supplements and evening primrose oil	
The evidence on the efficacy of dietary supplements for the treatment of CFS is insufficient. There are three RCT[52-54] of low quality according to the GRADE system.	C (not recommended)
The evidence on the efficacy of evening primrose oil for the treatment of CFS is insufficient. There is one RCT[55] of moderate quality according to the GRADE system.	
Intramuscular magnesium[b] (Mg) and oral nicotinamide adenine dinucleotide[b] (NADH)	
The evidence on the efficacy of intramuscular Mg for the treatment of CFS is insufficient. There is one RCT[56] of moderate quality according to the GRADE system.	C (not recommended)
The evidence on the efficacy of oral NADH for the treatment of CFS is insufficient. There is one RCT[57] of very low quality according to the GRADE system.	
Immunotherapy	
Intravenous IgG[b], staphylococcus toxoid[b] and Interferon-alpha[b]	
Intravenous IgG is not more effective than placebo at improving the symptoms of CFS. There are four RCT[58-61] of low quality according to the GRADE system.	C (not recommended)
Staphylococcus toxoid is not more effective than placebo at improving the symptoms of CFS. There is one RCT[62] of low quality according to the GRADE system.	
Interferon-alpha is not more effective than placebo at improving symptoms in CFS. There are two RCT[63,64] of very low quality according to the GRADE system.	
Non-pharmacological treatment	
Cognitive-behavioural therapy (CBT)	
There is sufficient evidence on the beneficial effect of CBT on the reduction of symptoms, improvement of function and quality of life in patients with CFS. There is one Cochrane SR of RCT[65] of high quality (1++) according to the SIGN system. However, decreased efficacy in the long term is evidenced.	A (recommended)
Gradual physical exercise	
There is sufficient evidence on the efficacy of gradual physical exercise for improving tiredness and physical function measures in patients with CFS. There are two SR of RCT[66,67]. In the first SR, three RCTs[42,68,69] of low quality according to the GRADE system, are identified. In the other SR, a fourth RCT[70], also having low quality according to the GRADE system, is identified.	A (recommended)
Caution should be taken as excess over-exertion may worsen the course of CFS.	√ (caution)

Table II (continued)

Physical exercise in combination with other strategies	
Combination of symptomatic pharmacological treatment, education, gradual physical exercise and cognitive-behavioural therapy in the care of patients with CFS. There is one SR of RCT[66] that identifies one RCT of moderate quality according to the GRADE system.	√ **(recommended)**
Prolonged rest	
No SR or RCT on the efficacy of prolonged rest in people with CFS have been found, and this approach may be ineffective and potentially harmful.	√ **(caution)**
Alternative and/or complementary therapies	
Homeopathy	
The evidence on the efficacy of homeopathy is insufficient. There is one RCT[71] of moderate quality according to the GRADE system.	**C (not recommended)**
Acupuncture and phytotherapy	
The evidence on the efficacy of acupuncture is insufficient. There is one SR[72] that includes different designs (none of them randomized and all of them low quality) of low quality (2++) according to the SIGN system.	**C (not recommended)**
The evidence on the efficacy of phytotherapy is insufficient. There is one Cochrane SR of RCT[73] of high quality (1++) according to the SIGN system.	

a http://portal.guiasalud.es/emanuales/elaboracion/apartado07/formulacion.html

b At present there are no drugs approved by the Spanish Agency for Drugs and Healthcare Products (acronym in Spanish AEMPS) or by the European Medications Agency (acronym in English EMEA) with a specific indication for the treatment of FM or CFS. Under these circumstances, Royal Decree 1015/2009, dated June 19 regulating the availability of drugs under special circumstances, shall apply. In relation to the provisions set forth in the aforementioned Royal Decree 1015/2009, it should be mentioned that the CatSalut (05/2010) has an instruction on the use of authorised drugs under circumstances different to those established in the technical data sheet, the CatSalut and the Integrated System of Public Use Healthcare (acronym in Catalan SISCAT) being its area of application.

Table III. Methodological guidelines for updating evidence

Updating clinical practice recommendations for FM and CFS
The updating of the evidence of diagnostic criteria and treatments for FM and CFS should be considered three years after the last search in order to update clinical practice recommendations.
The use of alerts is proposed as a strategy to identify the new scientific information, which can affect the validity of recommendations.
Significant differences between the information with which recommendations were developed and new evidence found should be assessed and identified, as should the way in which this difference affects recommendations and their degree.
The work team, in order to carry out these monitoring and assessment tasks for new evidence, should be composed of clinical experts (one in FM and one in CFS) and AIAQS technicians. If possible, one of the experts should be one of the clinicians who participated in the working group of this technical consultation.
The methodology described in the updating manual of the Spanish NHS is proposed as the methodology to update recommendations.

Table IV. Proposal of basic variables for the follow-up and assessment of treatment in FM and CFS

- Date of birth
- Sex
- Marital status
- Educational level
- Occupation
- Family history
- Reason for referral to specialised hospital units
- Comorbidity:
  - psychological (anxiety, depression, personality disorders and adaptive disorders)
  - physical (arthrosis, carpal tunnel, headaches, migraine, obesity, chronic inflammatory rheumatic diseases, multiple chemical sensitivity, environmental sensitivity, dysautonomia, thyroid dysfunction, somatotropic axis disorder, gonadotropic axis disorder, associated syndromes (irritable colon, hyperactive bladder and Sicca syndrome))
- Main diagnosis using classification criteria from the American College of Rheumatology, 1990, for FM and Fukuda's criteria, 1994, for CFS.
- Time until diagnosis (years)
- Duration in years of the disease
- Degree of functional impairment

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