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Interdisciplinary Consensus Document for the treatment of fibromyalgia

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Backgrounds. The elevated prevalence and enormous clinical and social impact of fibromyalgia, together with the complexity of its treatment, require action consensuses that guide health care professionals. Although there are some similar documents in our language, most have been made from the perspective of a single discipline.

Objective. To develop a consensus on the treatment of fibromyalgia made by selected representatives and supported by the principal medical associations that intervene in its treatment (rheumatology, neurology, psychiatry, rehabilitation and family medicine) and representatives of the associations of patients. On the other hand, understanding the disease not as a homogenous disorders but also as the sum of different clinical subtypes, having specific symptomatic characteristics and different therapeutic needs is stressed. This approach represented a need perceived by the clinicians and a novelty regarding previous consensuses.

Methods. The different clinical classifications proposed in fibromyalgia and the scientific evidence of the treatments used in this disease were reviewed. For the selection of the classification used and performance of the therapeutic recommendations, some of the usual techniques to obtain the consensus (nominal group and brainstorming) were used.

Conclusion. The classification of Giesecke of fibromyalgia into 3 subgroups seems to have the greatest scientific evidence and the most useful for the clinician. The guide offers a series of general recommendations for all the patients with fibromyalgia. However, in addition, for each subgroup, there are a series of specific pharmacological and

psychological-type recommendations and those of modification of the environment, which will make it possible to have a personalized approach to the patient with fibromyalgia in accordance with their individual clinical characteristics (pain, catastrophizing levels, etc.).

Key words:
 Consensus, fibromyalgia, Giesecke classification

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Documento de Consenso interdisciplinar para el tratamiento de la fibromialgia

Antecedentes. La elevada prevalencia y enorme impacto clínico y social de la fibromialgia, junto a la complejidad de su tratamiento, exigen consensos de actuación que sirvan de guía a los profesionales de la salud. Aunque existían algunos documentos similares en nuestro idioma, la mayoría habían sido realizados desde la perspectiva de una única disciplina.

Objetivo. Desarrollar un consenso sobre el tratamiento de la fibromialgia realizado por representantes seleccionados y avalados por las principales sociedades médicas que intervienen en su tratamiento (reumatología, neurología, psiquiatría, rehabilitación y medicina de familia), así como representantes de las asociaciones de pacientes. Por otra parte, se enfatizó la comprensión de la enfermedad no como un trastorno homogéneo, sino como la suma de diferentes subtipos clínicos, con características sintomáticas específicas y necesidades terapéuticas distintas. Este abordaje representaba una necesidad percibida por los clínicos y una novedad respecto a consensos previos.

Método. Se revisaron las diferentes clasificaciones clínicas que se han propuesto en fibromialgia, así como

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la evidencia científica de los tratamientos utilizados en esta enfermedad. Para la selección de la clasificación empleada y para la realización de las recomendaciones terapéutica, se emplearon algunas de las técnicas habituales para realizar los consensos (grupo nominal y brainstorming).

Conclusion. La clasificación de Giesecke de la fibromialgia en 3 subgrupos parece ser la que cuenta con mayor evidencia científica y la más útil para el clínico. La guía ofrece una serie de recomendaciones generales para todos los pacientes con fibromialgia. Pero, además, para cada subgrupo existen una serie de recomendaciones específicas de tipo farmacológico, psicológico y de modificación del entorno, que permitirán un abordaje personalizado del paciente con fibromialgia en dependencia de sus características clínicas individuales (dolor, depresión, niveles de catastrofización, etc).

Palabras clave:
Consenso, fibromialgia, clasificación Giesecke

RATIONALE OF THE DOCUMENT AND OBJECTIVES

Fibromyalgia is a health care problem because of its elevated prevalence, its important effect on the quality of life of the patients, the numerous specialists involved in its diagnoses and treatment, limitations regarding the knowledge of its etiology, the nonexistence of a standard treatment and the many treatments proposed with or without efficacy.

There are many guidelines and consensus documents in Spain, almost all of which have been elaborated from the point of view of a specialty or oriented towards fibromyalgia understood as a uniform entity.¹⁻⁵ However, this approach to the disease as a uniform entity is controversial, as shown by the continuous publication of different proposals on classifications and reorganizations into subgroups of patients with fibromyalgia.⁶⁻⁸

A more realistic approach to the treatment of these patients, that would be useful for the clinicians, should focus on the point of view of the different specialties involved in its differential diagnoses and treatment and, in turn, consider the possible typologies of the patients, which make it possible to differentiate them. Furthermore, this approach should be based on contrasted information and on conclusive and scientific-based studies of quality. Unfortunately, information having these characteristics is not always available and it is often necessary to seek the opinion of experts to supplement this information deficiency.

In order to elaborate this document, the representatives of the medical specialties involved in the diagnoses, follow-up and treatment of fibromyalgia were gathered in order to achieve a consensus that unified criteria, based on

different concepts and priorities. An attempt has been made to surpass the mere compiling of bibliography of the documents and guidelines that already exist and to reach an agreed-upon strategic position based on the best scientific information available.

In order to achieve this objective, first those that would best adapt to the clinical practice had to be chosen from among the possible existing classifications of fibromyalgia subgroups. To do so, the information published on the disease as a whole and the different studies on the subgroups of fibromyalgia were gathered and then the Giesecke classification was chosen by consensus as being the one that best adapted to the practical reality of the medical visit for both primary care as well as specialized care. Given that there are no therapeutic guidelines or consensus documents presently available that help to consider the patient with fibromyalgia according to their subgroup based on their specific characteristics, the final purpose of this work has been to obtain a multidisciplinary consensus on how to individualize the treatment of patients in these selected subgroups.

CONCEPT, DEFINITION AND EPIDEMIOLOGY

Fibromyalgia is a chronic alteration that is characterized by the existence of a history of disseminated pain and the presence of pain on pressure and palpation in defined anatomic locations in an individual.^{8,9} The nature and existence of this entity were identified in 1904 and have been revised since then. The World Health Organization (WHO) incorporated fibromyalgia in its tenth revision of the International Classification of Diseases in 1991, assigning fibromyalgia number M79.0 and classifying it as non-articular rheumatism.

In 1990, and under the direction of the *American College of Rheumatologist* (ACR), a large multicenter clinical trial was published. It established the diagnostic criteria of fibromyalgia that are commonly used at present. An 88.4% sensitivity and 81% specificity was attributed to that definition compared to the expert's opinion.⁹

The natural history of fibromyalgia has been followed and monitored prospectively for years in different studies in which the patients expressed the intensity of their pain, functional performance and affective symptoms in a protocolized and periodic way. In general, the findings indicate that once the disease has been established, the patients continue symptomatic and do not improve for long periods of time. Furthermore, functional performance slowly deteriorates.¹⁰⁻¹³ In other follow-up studies, it was found that all the patients continued to have fibromyalgia 15 years later. A total of 66% of the patients indicated that they had some type of improvement, but

another 59% stated that there was still significant asthenia, 55% considered that they continued with moderate-to-intense pain or inflammation, and 48% had sleep disorders.^{14,15}

Fibromyalgia is a frequent problem in the clinical practice. Its prevalence differs according to the population studied and ranges from 0.7 to 20%. In Spain, it occurs in between 2.1 and 5.7% of the general adult population and accounts for 10 to 20% of visits to rheumatology and 5 to 8% of those to primary care. Therefore, it is the most frequent cause of generalized and chronic osteomuscular pain.^{16,17}

DIAGNOSES AND CLINICAL CLASSIFICATION

The ACR criteria have had the important function of granting a specific nosologic identity to fibromyalgia and have made it possible to develop reliable and growing research, recognizing fibromyalgia as a legitimate and specific entity within the medical setting. However, these criteria were elaborated in order to develop research allowing for the use of an orthodox and standardized methodology, but they have important limitations in their clinical utility. Thus, for example, the ACR, based on the collection of an extensive clinical, diagnostic and therapeutic experience of more than 20,000 patients with fibromyalgia, by means of a collective consensus of their experts panels, has stated that for the clinical purposes, other variables such as psychological dysfunction, that are also an intrinsic part of this disease¹⁰ must be included in addition to the musculoskeletal pain in the diagnoses of the patients. Using this as a starting point, a series of processes, identifications of the definition and strategic clinical divisions or groupings that are described in the following, have been proposed.

Classification de Giesecke et al.⁶

This classification is based on variables obtained from 3 different domains: a) mood: it measures depression with the *Center for Epidemiologic Studies Depression Scale* and the anxiety traits evaluated by the *State-Trait Personality Inventory*; b) cognitive aspects: it evaluates catastrophism and control of pain through the subscales of the same name of the *Coping Strategies Questionnaire*, and c) biological variables: it includes hyperalgesia/sensitivity to pain, evaluated through the pain meter and painful pressure applied randomly on pre-threshold levels. Three groups are obtained with these variables (table 1).

This classification adapts well to the clinical reality, because it not only includes aspects as other classifications but also biological and cognitive ones. Furthermore, it was developed using adequate statistical models such as cluster analysis.

Table 1	Classification of the fibromyalgia subgroups of Giesecke
Group 1	Moderate values of depression and anxiety Moderate values of catastrophism and pain control Low hyperalgesia/sensitivity to pain
Group 2	Elevated values in depression and anxiety More elevated values of catastrophism and lower values of perceived control of the pain Higher values of hyperalgesia
Group 3	Normal levels of depression and anxiety Very low levels of catastrophism and the highest levels of perceived control of the pain Elevated hyperalgesia and sensitivity to the pain

Classification of Müller et al.⁷

It is based on associated clinical signs and symptoms. It divides the patients with fibromyalgia into 4 subtypes:

- fibromyalgia with extreme sensitivity to pain that is not associated to psychiatric disorders.
- fibromyalgia and depression related with comorbid pain.
- depression with concomitant fibromyalgic syndrome
- fibromyalgia due to somatization.

This is a descriptive classification proposed on the basis of the clinical experience of the author, but that was not obtained by statistical analysis. On the other hand, the final group is debatable because somatization is a concept that is currently questioned in psychiatry and may disappear in future classifications. Both of these are an important limitation for the choice of this classification.

Classification of Thieme et al.¹⁸

Using the *West Haven-Yale Multidimensional Pain Inventory* (MPI) questionnaire, three subgroups were identified:

- dysfunctional. These are patients who perceive their sensitivity to pain as elevated. They state that the pain interferes greatly in their lives and report high psychological malaise and limited activity due to the pain
- patients who are stressed in their interpersonal aspect. They consider that the significant others in their lives (partner, parents, children, caretakers in general) do not support them greatly in their problems with the pain. Furthermore, they have associated psychiatric disorders, and
- patients who have adaptive coping. Individuals who feel that they receive good social support, and who describe relatively low levels of pain and high activity

Table 2		Experts Panel	
Society		Author	City
Spanish Society of Rheumatology		Cayetano Alegre de Miquel	Barcelona
Spanish Society of Rheumatology		Javier Vidal Fuentes	Madrid
Spanish Society of Primary Care Physicians		Emilio Blanco Tarrio	Salamanca
Spanish Society of Neurology		José María Gómez Arguelles	Madrid
Spanish Society of Psychiatry		Javier García Campayo	Zaragoza
Spanish Society of Rehabilitation and Physical Medicine		Mariano Tomás Florez	Alcorcón (Madrid)
Spanish Society of Family and Community Medicine		Álvaro Pérez Martín	Santander
Spanish Society of Rheumatology		Milena Globbo Montoya	Madrid
Foundation of the Affects by Fibromyalgia and Chronic Fatigue Syndrome		Emilia Altarriba Alberch	Barcelona
Coordinator Agustín Gómez de la Cámara			Madrid

Although these classifications have been used in other diseases that occur with pain¹⁹ in addition to fibromyalgia, its principal limitation is that it bases the identification of the groups exclusively on psychological aspects without including biological variables.

Classification of Hasset et al.¹⁹

This is based on the *affect balance style*, using the *Positive and Negative Affect Schedule* (PANAS) questionnaire. Taking the standard values of the population as a basis, these authors consider that a positive affect (PA) in the PANAS implies a score over 35 and an elevated negative affect (NA) consists in obtaining a score greater than 18.1. In this way, 4 groups were obtained:

- a) Healthy: elevated PA/low NA;
- b) Low: Low PA/low NA;
- c) Reactive: elevated PA/elevated NA
- d) Depressive: low PA/elevated NA

Again, the fact that the classification is limited to the use of a single psychological questionnaire is an important limitation for its use.

After analyzing the existing classification proposals, it was decided that for practical effects, the classification of Giescke would be considered for the elaboration of this consensus.

METHODOLOGY

Experts panel

The work group was made up of representatives of the different specialties that attend to patients with fibromyal-

gia. A proposal was made to all of the possible disciplines involved in the management of these patients, through their respective scientific societies, for them to name their experts to form a part of the consensus group. Some of these societies refused to participate. Table 2 shows the scientific societies and professional associations that were finally involved in the elaboration of the document as well as the professionals who participated in it.

Elaboration of the recommendations

In the first meeting held with the panel, a coordinator group was established and it was agreed to perform the consensus following the modified Delphi method according to RAND-UCLA.²⁰ Communication with the panelists in the successive rounds was performed by e-mail. The coordinator group, using the classification of Giescke⁶ as a basis, elaborated an initial list of items with therapeutic indications to perform the first Delphi round. The adequacy of this list was evaluated by all the panel members, who in turn, could add new indications if they considered them pertinent. In the second round, after re-elaborating the items based on the results of the first one, the evaluation of the adequacy of each proposal was also added. Each item could be scored with an ordinal scale from 1 to 9 points, 1 point being very inappropriate and 9 points very appropriate. In the third and last round, each item was re-evaluated again. After the third one, it was observed that the disagreement of the scorers did not make it possible to use the consensus procedures of RAND-UCLA so that a traditional weighting system was adopted in the Delphi method.²¹ Each item or contribution was weighted, that is, it received a score for each participant, and it was prioritized. A hierarchy of agreed on interest was created, which implies that some items could disappear. In this case, the items on the lower third were eliminated, with which an

Table 3	Levels of quality of the evidence (QE)
1++	High quality meta-analysis, systematic reviews of clinical trials or high quality clinical trials with very little risk of bias
1+	Well-conducted meta-analysis, systematic reviews of clinical trials or clinical trials that are well-conducted with very little risk of bias
1-	Meta-analysis, systematic reviews of clinical trials or clinical trials with very little risk of bias
2++	High quality systematic reviews of cohort studies or cases and controls. Cohort studies or case-control studies with very low risk of bias and with high probability of establishing a causal relationship.
2+	Well-conducted cohort studies or case and controls with low risk of bias and with moderate probability of establishing a causal relationship
2-	Studies of cohorts or of case and controls with high risk of bias and significant risk that the relationship is not causal
3	Non-analytic studies, such as case and case series reports
4	Experts' opinion

Table 4	Strength of the recommendation (SR)
A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the target population of the guide; or a volume of scientific evidence made up of studies classified as 1+ and with great consistency between them
B	A body of scientific evidence made up of studies classified as 2++, directly applicable to the target population of the guide and that show great consistency between them, or scientific evidence extrapolated from studies classified as 1++ or 1+
C	A body of scientific evidence made up of studies classified as 2+ directly applicable to the target population of the guide and that show great consistency between them, or scientific evidence extrapolated from studies classified as 2++
D	Scientific evidence with level 3 or 4; or scientific evidence extrapolated from studies classified as 2+
√	Practice recommended, based on the clinical experience and consensus of the editorial team

acceptance or final rejection was reached for each statement and the recommendations were written.

The final recommendations were supported according to the grade of evidence to formulate the strength of the recommendation, following the criteria of the methodological manual of the *GuíaSalud del Consejo Interterritorial de Salud del Ministerio de Sanidad and Política Social*²² (Health Care Guide of the Interterritorial Council on Health of the Ministry of Health and Social Policy) (tables 3 and 4).

RECOMMENDATIONS FOR THE THERAPEUTIC APPROACH OF PATIENTS WITH FIBROMYALGIA

The objectives of the treatment in fibromyalgia are those of relieving pain, maintaining or reestablishing emotional balance, improving quality of sleep, physical capacity, asthenia and associated problems. Keeping this objective in mind, a series of recommendations were established that are common to all the patients with fibromyalgia, and others that are specific for the treatment of the patients based on their Giesecke subgroup.

General recommendations for all the patient groups

In order to adequately classify the patients and manage them in the best possible way, the usual physical variables and also certain psychological aspects that are key to the disease course should be evaluated. A directed anamnesis and appropriate diagnostic algorithm would help to place the patient within the corresponding subgroup proposed and to proceed to their therapeutic management (table 5).

As in other chronic diseases, information and education are key for the treatment of the patients, regardless of their subgroup.

The patients have expressed the need to be informed on the cause of the disease and the best strategies to reduce the symptoms and improve performance as one of their priorities.²³ Furthermore, chronic diseases, due to their nature, require the patient to assume some responsibility in their care.²⁴ A patient who is well-informed regarding his/her disease, prognoses and treatment, is better prepared to cope with it and minimize its consequences. Correct information may also facilitate treatment compliance. Although some professionals have suggested that the diagnosis of fibromyalgia may have negative effects, a systematic review and demonstrated that there is evidence of moderate-good quality that it reduces care pressure by these patients.²⁵

There are few randomized clinical studies (RCS) that analyze efficacy of the information/education in fibromyalgia as an isolated factor. Burchkhard et al.²⁶ observed a significant improvement in self-efficacy and quality of life, and Oliver et al.²⁷ observed a decrease of the catastrophism. In a clinical trial performed by Bosch et al.²⁸ in a healthcare site of Barcelona, one of the groups, that received 4 education sessions, significantly improved their perception of quality of life versus the control group.

In most of the clinical trials, information/education is associated with exercise programs or forms a part of multidisciplinary treatments. Combination of education and exer-

Table 5		
General recommendations for all the groups		
Recommendation	Grade of recommendation	Quality of the evidence
In patients with fibromyalgia, the levels of depression and catastrophism should be evaluate because these data have therapeutic implications	B	2+
It is advisable to perform well-designed educational interventions since they can improve some result parameters (self-efficacy, decrease of catastrophism, quality of life, etc.)	B	1-
The exercise programs are one of the basic treatments. Aerobic exercise (walking, bicycle) is the one that has demonstrated the best scientific evidence of efficacy. It can improve the global sensation of well-being, physical performance, and probably the pain and hyperalgesia	A	1+
Adequate information on the diagnosis, prognosis and therapeutic alternatives should be the first step in the approach in all patients with fibromyalgia	D	4
The use of experimental therapies or alternatives of any type is not recommended	√	4

cises has been shown to be especially effective in clinical trials.²⁹

Most of the clinical practice guidelines stress that correctly informing the patient with fibromyalgia must be the first step. A German guidelines published in 2008³⁰ (of multi-professional character and in which associations of patients also participated) stresses that although the level of evidence based on RCS is limited, informing the patients on the diagnoses and the therapeutic possibilities should have the *maximum* grade of recommendation because: *a) from the perspective of the patients*, the diagnosis of fibromyalgia often serves to end a long period of uncertainty and lack of information and hateful frustration through the healthcare system; the information on the diagnoses has long been considered an essential right of the patient. *b) from the perspective of the physician*, there is the ethical obligation to inform the patients on the diagnoses and therapeutic possibilities.

There is practically unanimous agreement that the physical exercise program should be one of the basic treatments in all of these patients.

Three options should fundamentally be evaluated:

- a) Aerobic exercises:* These use the large muscle groups, involving them in repeated movements, with increase in the heart rate but without surpassing the anaerobic threshold (up to 70-85% of the maximum heart rate for the age). Included among them are weight-bearing exercises (walking, dances, etc.) and non-weight bearing exercises (bicycle, swimming, etc.).
- b) Muscle strengthening exercises.* They aim to improve strength, resistance and muscle force, performing muscle contractions against certain resistances such as elastic bands, weights or the patient's own weight.

c) Stretching or flexibility exercises. Their objective is to improve muscle and soft tissue flexibility.

Several systematic reviews have been published that have analyzed the efficacy of the exercise programs, either alone,³¹⁻³³ combined with other intervention forms^{34,35} or within the context of a review of non-pharmacological interventions.^{36,37} All have concluded that there is moderate-strong evidence that exercise improves some result parameters. The review having the highest methodological quality is probably that published by the Cochrane Collaboration, whose last up-date was published in 2007.³¹ It includes 34 RCS and concludes, with a good level of evidence (see www.cochranemsk.org), that aerobic exercise, either isolated and practiced on the intensity levels recommended, has positive effects on the global sensation of well-being, physical performance and probably, the pain and hyperalgesia. To obtain the benefits indicated, the exercise should last at least 12 weeks. Several RCSs suggest that strengthening exercises can also produce significant improvements, but more studies are needed. There is little data on the utility of flexibility exercises.

Usually, patients with fibromyalgia tolerate exercises poorly. Jones et al.³² analyzed 46 clinical trials and concluded that the initial intensity should be less than that recommended for the general population since, if not, the number of drop-outs is very high. After, it should be increased step by step until reaching a moderate intensity level. Middle to long term compliance is another one of the important problems and several strategies have been noted to facilitate it.^{38,39}

Sufficient objective data are not available to recommend experimental or alternative therapies in fibromyalgia in any of the subgroups of patients.

In spite of the many existing alternative therapies, there is no evidence that any of them are effective in the treatment of FM. We stress, for example, one of the physical therapies, such as transcranial magnetic stimulation (TMS). TMS is a non-invasive technique with minimum side effects (mainly headache) that has demonstrated, although limited, efficacy in depression. In the treatment of fibromyalgia, a control pilot study with a very small sample, that confirmed some efficacy in some domains of the disease, was carried out.⁴⁰ Although it is being widely used in the clinical practice, at present, it should be considered as an experimental technique with very limited evidence.

Recommendations for treatment of group 1 of Giesecke

According to Giesecke et al.,⁶ this subgroup could represent the "typical" patient with fibromyalgia, especially those attended in the primary care setting. The differential trait is that they only have a moderate increase of painful sensitivity to pressure, much less than that observed in groups 2 and 3, although the subjective intensity of pain (measured with a visual analogue scale) is similar in the 3 groups. This subgroup is the most numerous and includes approximately 50% of the patients who meet the clinical criteria of fibromyalgia. It is characterized by low hyperalgesia, intermediate scores on the specific depression and anxiety questionnaires and a moderate level of catastrophism and capacity to cope with the pain.

Although paracetamol (acetaminophen) and non-steroid anti-inflammatory drugs (NSAID) are among the drugs prescribed the most in fibromyalgia,⁴¹ these drugs have not been demonstrated to be superior to the placebo in the RCS.⁴² With the current data, its use cannot be recommended in patients with fibromyalgia, except if the patient has another associated disease in which these drugs have been demonstrated to be effective, such as arthritis or soft tissue pain.⁴³

Several meta-analyses⁴⁴⁻⁴⁸ that analyze efficacy of antidepressants in fibromyalgia, some of them very recent, support the use of the tricyclic antidepressant amitriptyline. Häuser et al.,⁴⁶ in a meta-analysis of high methodological quality, have concluded that there is much evidence on the efficacy of antidepressants in the reduction of pain, fatigue, depression and sleep alterations. Tricyclic antidepressants have a greater effect on pain reduction. The doses used in the studies (between 12.5 and 50 mg of amitriptyline per day) were much less than those used to treat depression. This suggests an analgesic effect independent from that of the antidepressant effect. Another meta-analysis published in 2008⁴⁷ concluded that amitriptyline, at a dose of 25-50 mg/day, reduces pain and depression and also improves sleep and quality of life. One specific meta-analysis on the efficacy of amitriptyline in fibromyalgia⁴⁸ also concluded that,

with a dose of 25 mg/24 h, it was superior to the placebo in the results on pain, fatigue, sleep and global impression of the physician and patient.

Pregabalin was the first medication approved by the Food and Drug Administration (FDA) for the treatment of fibromyalgia. A Cochrane review⁴⁹ states that it is effective in this disease. A recent meta-analysis⁵⁰ located 5 RCSs that compared pregabalin with placebo. The authors concluded that there is strong evidence of efficacy in the reduction of pain and in the improvement of sleep and quality of life. A reduction in anxiety and fatigue was also observed although the magnitude of effect was small. No differences were observed in depression. One 6-month long RCS1 (The FREEDOM trial) analyzed if the durability of the effect was maintained over time in 1051⁵¹ patients who initially responded to pregabalin. At the end of the study, 68% of those treated with pregabalin compared to the 39% of those treated with placebo maintained the therapeutic response in relationship to improvement of pain, sleep alterations to the peak and performance level.

First generation antidepressants (tricyclic antidepressants and monoamine oxidase inhibitors) [MAOI] are as effective as the selective serotonin reuptake inhibitors (SSRI) in the treatment of major depression, but that they are tolerated worse, have more adverse effects, greater drop out rates and greater danger in case of poisoning.⁵² Amitriptyline in antidepressive doses may be more effective than the SSRI in cases of severe depression that require hospitalization, but not in the depression that can be treated as an outpatient, and its tolerability is significantly worse.⁴⁶ The principal clinical practice guidelines include the SSRIs among the drugs of first choice in the treatment of depression.⁵³ A recent meta-analysis⁵⁴ located 13 RCS that analyzed the efficacy of the SSRI in fibromyalgia. All of them showed positive results except for two studies with citalopram and one with paroxetine. Three more RCSs also showed positive results with the dual serotonin and norepinephrine reuptake inhibitors (SNRIs) (milnacipran and duloxetine). The magnitude of the effect, when compared with the placebo, in the reduction of the pain, was small in both groups (-0.39 for the SSRIs and -0.36 for the SNRIs), much less than that of amitriptyline (-1.64). Based on the previous data, basically, 3 possibilities would exist:

- a) Use a SSRI (avoiding citalopram) and evaluate combining it with other analgesic action drugs in fibromyalgia (low dose amitriptyline, pregabalin, cyclobenzaprine, etc.).
- b) Use the dual norepinephrine duloxetine reuptake inhibitor (or milnacipran when this is marketed in Spain) and evaluate possible associations (avoiding tricyclic antidepressants since they have a very similar action mechanism).
- c) Use amitriptyline in antidepressant doses, assuming a greater risk of side effects.

Table 6		General recommendations for group 1	
Recommendation	Grade of recommendation	Quality of the evidence	
The use of paracetamol (acetaminophen) and NSAIDs are not recommended for fibromyalgia, except when there are associated diseases that justify their use	A	1+	
Depression associated to fibromyalgia may be treated with SSRI or with dual SNRI	A	1+	
Low dose amitriptyline (25-50 mg) may improve the pain, fatigue, sleep and quality of life	A	1+	
Pregabalin is superior to the placebo in the pain reduction, improvement of sleep and quality of life	A	1+	
Other treatment options are cyclobenzaprine, tramadol, gabapentin, pramipexole and sodium oxybate	B	1-	
NSAID: Non-steroid anti-inflammatory drugs; SNRI: dual serotonin and norepinephrine reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors			

There are no RCSs that compare these therapeutic strategies, but the 3 options seem valid. In other chronic pain pictures that associate depression, another alternative is to use tricyclic antidepressants with a better profile of side effects than amitriptyline. This option does not seem recommendable in fibromyalgia, since the only RCS with nortriptyline has not shown its superiority over the placebo.^{55,56}

In addition to antidepressants and pregabalin, there is a group of drugs that have demonstrated efficacy in at least one RCS and that should be considered as alternatives: cyclobenzaprine, tramadol, gabapentin, pramipexole and sodium oxybate.⁵⁷⁻⁵⁹ (table 6)

Recommendations for the treatment of group 2 of Giesecke

This subgroup is characterized by an elevated grade of pain together with the presence of high scores on questionnaires of depression and catastrophism. Depression is a key feature in the treatment of pain because it decreases the efficacy of the analgesics. Catastrophism also correlates with greater intensity and sensitivity to pain and to greater disability. On the other hand, it has been demonstrated that the role of catastrophism (an existing cognitive factor in all the chronic pain syndromes) as a factor of chronification and disability is more important in fibromyalgia than in other diseases.⁶⁰ (table 7)

The most recent and extensive meta-analysis on the efficacy of the antidepressants in the treatment of fibromyalgia⁶⁰ concluded that tricyclic antidepressants have an elevated efficacy (magnitude of effect [ME]: -1.64; confi-

dence interval [CI] of 95%, -2.7 to -0.71); the MAOI had a mean efficacy (ME: -0.54; 95% CI, -1.02 to -0.07), while both the SSRI and the SNRI only had limited efficacy (ME: -0.39; 95% CI, -0.77 to -0.01 for the SSRI, and ME: -0.36; 95% CI, -0.46 to -0.25). It seems to be especially useful not only in depression but also in pain, fatigue, sleep and quality of life.

Tricyclic antidepressants

Although according to some meta-analyses,⁶¹ they are the most effective antidepressants, their tolerability is limited and they have important interactions with other drugs, an aspect to keep greatly in mind in polymedicated patients such as these. On the other hand, the meta-analyses on the efficacy of specific tricyclic antidepressants show limited results. Therefore, when analyzing amitriptyline,⁶² which is the antidepressant that has been studied the most, it is confirmed that doses of 50 mg/day (4 controlled trials) do not have a therapeutic effect compared with placebo. There is some evidence that 25 mg/day of amitriptyline are effective in the short term (< 8 weeks). However, it does not seem that larger doses are effective or that any dose is effective in a period over 8 weeks.

Monoamine oxidase inhibitors

Although the efficacy of these drugs is moderate, they are not available in Spain and, furthermore, the large variety of pharmacological and food interactions they cause totally advises against their use in polymedicated patients such as these.

Table 7		
General recommendations for group 2		
Recommendation	Grade of recommendation	Quality of the evidence
If there are moderate or severe levels of depression, using an antidepressant is recommended	A	1++
The antidepressants of choice are the so-called dual ones: duloxetine (60-120 mg/day) or milnacipram (100 mg/day). Tricyclic antidepressants have equal efficacy, but have multiple side effects and drug interactions, so that they are tolerated worse in polymedicated patients, as is common in fibromyalgia	A	1++
If there are elevated levels of catastrophism, it is recommendable to use cognitive-behavior psychotherapy. It does not seem that catastrophism decreases with drug treatment and it is a construct that significantly worsens the prognosis	D	3
If there are moderate or severe levels of anxiety, using an antidepressant (SSRI, duloxetine or venlafaxine) or pregabalin is recommend	B	1-
When there are elevated levels of hyperalgesia, the use of gabapentin or pregabalin is indicated	A	1+

Selective serotonin reuptake inhibitors

These are the antidepressants used the most. However, their utility in fibromyalgia is limited. Studies on specific drugs show the following:

- a) *Fluoxetine*. It was the first SSRI to be used in fibromyalgia, initially associated with amitriptyline. The conclusion has been reached that it is more effective when combined in the treatment of fibromyalgia than when used alone.⁶³ Subsequent studies are contradictory since while some have confirmed its efficacy in different domains of fibromyalgia, other have not found it to be more effective than placebo.⁶⁴
- b) *Paroxetine*.⁶⁵ It improves the general performance of the patients with fibromyalgia although they do not have depression or anxiety, but its effect on pain seems more limited.
- c) *Citalopram*. There are also positive studies for this drug in fibromyalgia,⁶⁶⁻⁶⁷ although the data are contradictory, since there are studies that do not find efficacy.

On these bases, we cannot recommend the systematic use of SSRI in fibromyalgia.

Antidepressants - serotonin and norepinephrine reuptake inhibitors

- a) *Duloxetine*. It is the non-tricyclic antidepressant that has the best scientific evidence.^{68,69} In usual doses (60-120 mg/day), it improves pain and general functioning of the patient with or without depression.
- b) *Milnacipram*. It is a dual antidepressant, serotonin and norepinephrine reuptake inhibitor which, in usual doses

(100-200 mg/day), improves pain and general functioning of the patient with fibromyalgia.⁷⁰

Anxiety is another frequent symptom in this subtype of fibromyalgia, as described in the definition of Giesecke.⁶ There is no scientific evidence that supports the use of benzodiazepines continuously in these patients. It is recommended to control this symptom with antidepressant (the SSRIs paroxetine and citalopram as well as the dual antidepressants duloxetine and venlafaxine have the indication of generalized anxiety disorder in the doses used as antidepressants) or with pregabalin⁷¹ which, in addition to helping in the control of the pain, also have the indication of generalized anxiety disorder (at a dose of 150-450 mg/day).

Some patients in this subgroup may have elevated levels of hyperalgesia. Treatment with gabapentin or pregabalin would be indicated in them.⁷²

Psychotherapy seems to be essential in this subgroup of patients who have measurable cognitive distortions such as catastrophism. Some of the psychotherapies that have been used are:

- a) *Cognitive-behavioral*. Although the studies show that isolated cognitive-behavioral therapy used in patients with fibromyalgia in general do not show clear benefits over group programs of education or exercise, in specific subgroups as this, in which there is great psychological malaise, it is especially effective.⁷³
- b) *Meditation*. It has been shown the meditation-based psychotherapy (one weekly session for 8 weeks) is effective in improving the depression symptoms in these patients and it is considered that it is especially useful in constructs such as catastrophism.⁷⁴

Table 8		
General recommendations for group 3		
Recommendation	Grade of recommendation	Quality of the evidence
In patients with fibromyalgia with high grade of coping of the disease and low catastrophist profile of their problem, pharmacological and/or psychological treatment of cognitive-behavior type cannot be recommended in a general way, since they begin with an adequate starting level for "living" with their disease	B	1-
Pharmacological treatment should be proposed to treat the pain and the added symptoms to the disease, according to the clinical evidence available and experience of the physical, as in the other subgroups	B	1-
Maintenance psychological therapies during the disease of the positive variables would be recommendable	A	1+
Supervised aerobic exercise should be recommended as in the rest of the subgroups, even with greater possibility of compliance continuity, due to the supposed greater motivation of the patients derived from their better initial emotional state and better level of hyperalgesia	B	1-

Recommendations for the treatment of group 3 of Giesecke

This subgroup is characterized by having normal values of depression and anxiety, very low values of catastrophism and more elevated control perceived on the pain, but elevated hyperalgesia and sensitivity to pain (table 8).

Given its characteristics, this group is the one that would theoretically benefit the least from a pharmacological treatment aimed at improving the emotional state, or at least that attempts to help cope with the emotional symptoms related with the disease. It would also not be the most indicated group in which to perform cognitive therapies aimed at reinforcing this emotional state and/or coping of the disease, since the patient has an adequate level.

There are few controlled middle to long term studies (a maximum of 6 months duration)^{75,76} for the palliative treatment of the symptoms associated to fibromyalgia that have demonstrated efficacy compared to the placebo. That is why the use of these treatments (pregabalin or duloxetine) is recommended in this subgroup of patients based on the previous clinical experience of the clinicians with these drugs.

The efficacy found in the studies mentioned seem to be independent of whether the patients have emotional alterations previously or not. However, efficacy has not been specifically studied for this classification in subgroups. New studies are needed to determine the behavior of the drugs in this subgroup of patients that do not have emotional disorders or altered psychological states, and since there would not be a superadded anti-depressive beneficial effect (in the case of duloxetine) or anxiolytic effect (in the case of pregabalin).

In this group, therapies aimed at maintaining and strengthening the beneficial parameters found (emotional status, catastrophism and coping) should be established.

It has been evaluated in several studies how catastrophism, coping and emotional states affect the clinical course and prognoses of fibromyalgia,^{77,78} and how these patients improve after modifying these variables.^{79,80} However, there are no specific studies on such improvement when the patients began with inadequate emotional status, high level of coping of the disease, and low catastrophism level. It seems obvious that in these cases a specific therapy to improve these parameters would be less indicated and that, on the other hand, a psychological therapy of reinforcement of these variables would be indicated. Nonetheless, a study should be performed with an adequate methodology to verify this line of argument.

There is a high level of evidence that supervised aerobic exercise has beneficial effects on physical capacity in certain symptoms associated to fibromyalgia.⁸¹ It must be known if these benefits are maintained in the long term. Although there are also no specific studies on such benefits in this subgroup of patients, it does not seem, a priori, that there is any impediment for its recommendation, but rather to the contrary, beginning with a good adaptation to the disease, it would be theoretically easier to initiate and maintain such treatment. In addition, these patients have elevated hyperalgesia and it has been seen that this type of therapy decreases the pain and the points painful to palpation.⁸¹

CONCLUSIONS

Those consensus that have been done with the coordination of different specialties that diagnose or treat

the syndrome are limited among the many consensus published on fibromyalgia. Furthermore, contrary to the majority proposal of the guidelines in force, that contemplate fibromyalgia in a unified way, all the professionals consulted in the experts group, each one from their own practice, classify fibromyalgia in different subgroups for its better approach. For this reason, the first step for the elaboration of the consensus consisted in choosing a classification of fibromyalgia that would make it possible to assign the patients to different subgroups according to a series of distinctive characteristics. After, in the analyses of the different classifications published, the experts group responsible for this document agreed that the classification that best adapted to the clinical practice, and that also had been elaborated in the most rigorous way was that proposed by Giesecke.⁶ This classification divides the patients into 3 different groups, based on their evaluation according to three key aspects: hyperalgesia, depression/anxiety and catastrophism. This evaluation makes it possible to follow an algorithm of diagnosis and evaluation of the fibromyalgia that could be used to study associated conditions and to be able to subclassify it. In any event, although at the present time, this is the best way available for classification, it is likely that in the future, other classifications will be elaborated that are more adapted to the clinical practice and that do not give so much value to the concept of psychological alteration.

The first Delphi round showed an important disagreement of criteria regarding the management of fibromyalgia. However, it was observed that there was consensus regarding the need to consider different subgroups of patients and to use a basic common treatment for all the subgroups, based on information, education and physical exercise. Round two already made it possible to establish differences between the treatments that are commonly used in each subgroup.

Thus, it was agreed that in the approach of the different subgroups, the common base of treatment consists in education and information to the patients (understanding as education the co-responsibility of the patient in the compliance of the different strategies) and physical exercise (aerobic, muscle strengthening and flexibility type/stretching, although the patients with fibromyalgia tolerate them poorly and the compliance is poor).

Regarding the pharmacological treatment, there is also a clear consensus in the non-recommendation of the use of analgesics. The NSAIDs and paracetamol (acetaminophen) are not effective (their action mode is not consistent with the pathophysiology of fibromyalgia). This is especially important since, in spite of the evidence, the experts, and even the patient, indicate this lack of efficacy, these drugs are generally erroneously the first therapeutic step. The major opiates also have not been demonstrated as effective. Tramadol, in clinical trial with low level of evidence, and

low dose amitriptyline, seem to have some analgesic effect, although the latter is commonly used to improve the quality of sleep and fatigue. However, pregabalin is the drug used the most, as it has demonstrated its efficacy in several clinical trials. It was the first drug approved by the FDA for this indication.

The use of antidepressants, whether SSRI, dual, SNRI, or amitriptyline in antidepressant doses is also common. Antidepressant treatment in fibromyalgia is also evolving and the FDA has recently approved two new drugs, duloxetine and milnacipram. These SNRIs seem to have more efficacy on pain than the currently used SSRIs.

Independently of these general recommendations in the management of subgroup 1, which is the group most frequently found in the clinical practice, special attention should be given to anxiety and depression, while in subgroup 2, where catastrophism is a chronicity factor, psychotherapy is essential in addition to the treatment of the anxiety and depression. Finally, in subgroup 3, in which depression/anxiety is low and coping high, we find the best response to the regimes indicated and the use of antidepressants or psychotherapy is not as necessary, but rather stress should be placed on individualized physical exercise.

This consensus document has attempted to establish some common regimes among the different specialties that attend the fibromyalgic patient so that, if followed, they would avoid or reduce the confusion suffered by the patient due to the changing therapeutic possibilities offered them in the different places they visit. It adds the advantage of being able to observe in the future if the regimes established clarify the grade of knowledge on the efficacy of the treatments proposed, either as a whole, or specifically on the specific subgroups. We know that each patient is unique and that they require individualized treatment. However, by following a common action framework such as that proposed, this would convert the search for the best treatment into a rational and efficient process.

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