Clinical Rheumatology (2021) 40:3853–3858
https://doi.org/10.1007/s10067-021-05818-0

PERSPECTIVES IN RHEUMATOLOGY

Refractory fibromyalgia

Luis F. Vidal[1,2] · Osvaldo Messina[3,4] · Tamara Rodríguez[5] · Maritza Vidal[1] · Carlos Pineda[6] · Rasec Morales[2] · Antonio Collado[5,7]

Received: 23 April 2021 / Revised: 9 June 2021 / Accepted: 12 June 2021 / Published online: 24 June 2021

Abstract

In the medical literature, there are only a few references on refractory fibromyalgia and there is no consensus definition available on this concept. Some definitions of refractory fibromyalgia have been proposed based on the lack of response to a number of medications, and perhaps the most appropriate term is treatment-refractory fibromyalgia. To achieve the definition of treatment-refractory fibromyalgia, it is necessary to consider several previous steps, such as making sure the diagnosis has been made properly and a differential diagnosis with entities that can mimic fibromyalgia symptoms (including complete physical examination and laboratory test) has been made. The possibility that another factor that alters the response to treatment should be investigated, and in particular review all prescribed medication and search for some non-medical reasons that could mask the response to treatment (e.g., legal compensation). The definition of refractory fibromyalgia is complex and probably should include a lack of response to a specified number of drugs or to combination therapy with at least two non-pharmacological measures. In this article, it is not our purpose to present a formal definition, but to raise the possible bases for this purpose. We believe that it is a subject that must be discussed extensively before reaching a consensus definition.

Key Points

- *There is no appropriate definition to classify fibromyalgia patients who do not respond to the usual pharmacological and non-pharmacological measures according to the national or international guidelines.*
- *A consensus definition is required to classify these patients, which could help standardize future management strategies. In this article, we propose the bases on which refractory fibromyalgia could be defined.*

✉ Maritza Vidal
maritza.vidal55@hotmail.com

1 Centro de Diagnóstico de Osteoporosis y Enfermedades Reumáticas (CEDOR), Lima, Perú

2 Servicio de Reumatología, Hospital Nacional María Auxiliadora, Lima, Perú

3 Investigaciones Reumatológicas y Osteológicas (IRO), Buenos Aires, Argentina

4 Servicio de Reumatología, Hospital Argerich, Buenos Aires, Argentina

5 Servicio de Reumatología, Hospital Clinic, Barcelona, España

6 División de Enfermedades Musculoesqueléticas y Reumáticas, Instituto Nacional de Rehabilitación Luis Guillermo Ibarra Ibarra, México City, México

7 Fibromyalgia Unit Coordinator, Hospital Clinic, Barcelona, España

Keywords Consensus definition · Musculoskeletal pain · Refractory fibromyalgia

Introduction

Fibromyalgia is a chronic disorder characterized by widespread musculoskeletal pain, which is associated with a range of other symptoms such as fatigue, sleep disturbance, and somatic and cognitive symptoms. In contrast to the broad symptom complex, the findings on physical examination are often limited to the well-localized tender points on palpation [1, 2].

In fibromyalgia, the symptom array, the association with other pain conditions and the lack of laboratory biomarkers or characteristic imaging studies, make fibromyalgia diagnosis challenging particularly for primary care physicians. Even among specialists, the diagnosis depends on the clinical judgment and the experience of each physician in the management of generalized musculoskeletal pain syndromes [2, 3].

There are many controversial issues in fibromyalgia, particularly on the pathogenesis, the association with other "chronic overlapping pain conditions," and peripheral changes consistent with small nerve fiber pathology. Advances in the field of functional neuroimaging, as well as several lines of physiological experimentation, have highlighted the role of central sensitization with changes in the functional brain connectivity and in neurotransmitters in the central nervous system, as the pathogenic mechanisms involved in fibromyalgia. Additionally, familiar aggregation and genetic background have also been described [2, 4].

There are no biologic markers or gold standard outcome measures to predict a therapeutic response to interventions in fibromyalgia, and the individual variations in response to a specific medication can only be ascertained by trial and error [5]. In medical literature, the term "refractory fibromyalgia" has rarely been cited. The purpose of this article is to review the meaning of refractory fibromyalgia and the necessary requirements to propose an appropriate definition, if this term should really exist.

Response to treatment in fibromyalgia

A clinically important difference represents a change that would be considered meaningful and worthwhile by the patient such that he/she would consider repeating the intervention if it were his/her choice to make again. "Minimum clinically important difference (MCID)" is a threshold value for such a change. Any amount of change greater than the MCID threshold is considered to be meaningful or important. Any patient whose answers allow them to reach the MCID threshold are considered ''responders'' [6].

MCID would be particularly helpful in the evaluation of patient-reported outcomes (PROs). In fibromyalgia, the common PROs are pain, fatigue, depression, sleep, physical function, quality of life, dyscognition, anxiety, stiffness, and tenderness [7]. To compare the change in PRO scores some measure of variability is used such as the standard mean difference (SMD). However, in determination of MCID, most common studies compare PRO scores to the patients' answers to another subjective assessment, typically a patient global impression of improvement (PGII) [8].

The MCID has been published specially in pharmacological trials. Using the PGII, the improvement at 3-month follow-up on patients selected to pharmacological clinical trials was classified in "improved" (very much improved, much improved, or improved) and "not better" (no change, worse, much worse, or very much worse). Optimistic responses were recorded in most of the patients who answered that they were better at 66% and 72% of patients treated with pregabalin [9] or minalcipram [10] respectively. These responses are related particularly to improvement of pain, fatigue, sleep, and physical function [10–12]. Thus, the concept of "responder for clinical trials" has been developed [13]. The fibromyalgia responder definitions that were identified as the most sensitive in identifying response to treatment in analyses of existing clinical trials are FM30 version 3 (FM30 short version) and 6 (FM30 long version). These definitions share common features in that they require $\geq 30\%$ reduction in pain and $\geq 10\%$ improvement in physical function. Then, we could define that those patients with fibromyalgia who are treated with some drugs and do not achieve these responses would be considered refractory to pharmacological treatment [13].

However, it should be stressed that one of the limitations of studies with PRO scores depends on the characteristic of initial baseline sample and patient status, making it difficult to transfer the results from clinical trials to clinical practice. Although it has been reported that the improvement of the different variables (PROs) is better with more complex interventions (when non-pharmacological interventions are added in multidisciplinary treatment context) compared with placebo in trials conducted in patients with fibromyalgia [14], we do not know which is MCID in these interventions in clinical practice.

Refractory fibromyalgia or treatment-refractory fibromyalgia?

Several years ago, Holman defined refractory fibromyalgia as "partially responsive to multiple medications after working with multiple physicians" in a retrospective chart

analysis presented as an abstract to evaluate the efficacy and safety of lorazepam [15]. Dwonkin in an open-label trial presented as an abstract of long-term treatment of neuropathic pain and fibromyalgia syndrome with pregabalin, defined "treatment-refractory patients" as an inadequate pain relief or intolerable adverse events during 2-week treatment with (A) a tricyclic antidepressant (≥ 75 mg/day), (B) gabapentin (≥ 1800 mg/day), and (C) ≥ 1 third-line neuropathic pain treatment [16].

Stayce evaluated the efficacy of pregabalin in treatment-refractory fibromyalgia. To be eligible in this clinical trial, patients had to be refractory to treatment, defined as "inadequate pain relief despite treatment for at least 2 weeks at or above the minimum dose and/or intolerable side-effects with each of the three medications: gabapentin ≥ 1800 mg/day, a tricyclic antidepressant (TCA ≥ 75 mg/day), and a third line neuropathic-pain treatment" [17].

In the Cambridge English dictionary, "refractory" means "difficult to control" or "unwilling to obey," but in the medical context, this term appears closer related to the disease than the response to the treatment. However, in the literature, it appears to have been employed in relation to the therapeutical lack of response more than in relation with the nature or severity of the symptoms.

Perhaps the most appropriate term should be "treatment-refractory fibromyalgia," in reference to therapeutic failure associated with drug treatment or other interventions, but the absence of gold standard outcome measures also makes it difficult to achieve this definition. Additionally, it would be necessary to define several points as how many and which drugs and the time necessary to ensure a positive or negative response to them. In quantitative terms, the predetermined number of drugs should be homogenized to consider the definition of therapeutic failure. But also in qualitative terms, the therapeutic failure could be defined based on the lack of response to drugs with different mechanisms of action or from different therapeutic classes, as in some clinical trials mentioned above.

The other aspect to consider is how long to treat to expect a response, and the dose of each drug selected based on guideline recommendations or individual patient response. We can even consider a therapeutic failure after the lack of response to some combination of drugs with a different profile. The variability in the drug response among fibromyalgia patients makes it difficult to reach a conclusion or a homogeneous definition of "treatment-refractory fibromyalgia." Additionally, we must also consider that we are only referring to the pharmacological treatment, but not to non-pharmacological measures, whose effectiveness has been highlighted in different guidelines, and it can be a matter of debate to include or not the non-pharmacological measures in the refractory definition.

Fibromyalgia refractory to treatment or mistake in diagnosis?

In a patient who has therapeutic failure to different pharmacological and non-pharmacological interventions, it is important to consider different clinical scenarios before any conclusion. Initially, it would be necessary to review if there has been a mistake in the initial diagnosis and ensure that the diagnostic process has been adequate. Different metabolic, neurological, infectious, rheumatic, neoplastic diseases, or even mental disorders can mimic the fibromyalgia symptoms and induce a wrong initial diagnosis, so first we must ensure that the diagnosis of fibromyalgia has been correctly established.

Guidelines recommend a clinical evaluation and a minimum battery of laboratory tests during the initial patient evaluation (see Table 1), but the clinician can extend the laboratory or imaging studies according to his clinical judgment. If this step was not carried out initially, it is advisable to complement the evaluation or request the tests again, depending on the time elapsed since the initial evaluation or depending on the clinical suspicion or medical criteria.

Some diseases can mimic the symptoms of fibromyalgia; however, we must also consider that they can coexist with fibromyalgia, and in this clinical scenario, at least theoretically some of the symptoms of fibromyalgia could persist despite treatment, because they would form part of the clinical picture of the unidentified and untreated disease that coexists with fibromyalgia.

Rheumatic inflammatory disorders with concomitant fibromyalgia exhibit worse function, increase severity scores, and adversely affect global health status [20, 21]. In patients with an early stage of a systemic inflammatory rheumatic disease as rheumatoid arthritis, generalized body pain, fatigue, and stiffness may be present before the development of inflammatory polyarthritis [22]. The association

Table 1 Laboratory test for fibromyalgia from different guidelines

	Canada	Germany	Israel
Complete blood count	X	X	X
Erythrocyte sedimentation rate (ESR)	X		X
C-reactive protein (CRP)	X	X	X
Creatine phosphokinase (CPK)	X	X	X
Thyroid stimulating hormone (TSH)	X	X	X
Serum calcium		X	X
25-OH vitamin D			X
Creatinine/urea			X
Serum phosphorous			X
Liver function tests			X

Data from the references [18, 19]

with an unrecognized rheumatic disease, for example spondyloarthritis with pain and multiple enthesopathies, not only represents a diagnostic and treatment problem [23], but also it is expected to affect the response to fibromyalgia treatment if it is not recognized and treated appropriately.

Extensive osteoarthritis, with axial and peripheral involvement, can be accompanied by hyperalgesia and central sensitization phenomena that make the diagnostic and therapeutic process difficult, as has been observed in different models of osteoarthritis [24, 25].

We can have the same scenario in non-inflammatory conditions, for example, hypothyroidism. The relationship between thyroid disease and fibromyalgia has been extensively evaluated and there is evidence of an association, particularly with thyroid autoimmunity, and it is even postulated that it may be a marker of severity in fibromyalgia [26]. The symptom complex of thyroid disease can overlap with fibromyalgia, such as musculoskeletal widespread pain, arthralgias, chronic fatigue, insomnia, and tension headaches [27, 28]. If thyroid disease is not identified, some of the fibromyalgia-like symptoms may persist and simulate a lack of response to treatment.

In some cases, due to the high prevalence of a pathological condition such as vitamin D deficiency, it is expected that fibromyalgia can coexist at least in some patients. Osteomalacia and myopathy are consequences of severe vitamin D deficiency and are associated with symptoms such as muscle weakness and generalized bone pain that could mimic the symptoms of fibromyalgia [29, 30]. Additionally, the association of another disease can lead to wrong therapeutic decisions, such as when fibromyalgia occurs as a comorbid condition with polymyalgia rheumatica and can lead to an unnecessary change in the dose of corticosteroids due to the persistence of musculoskeletal pain. We must also consider that some pathological situations can compromise the response to treatment if they are not identified and treated appropriately. Posttraumatic stress disorder or depression can have a negative impact on clinical course and prognosis of fibromyalgia [31].

Some comorbid conditions such as active myofascial trigger points can act as peripheral nociceptive pain generators and affect the widespread pain in fibromyalgia, probably through increased central sensitization by the peripheral input. Local anesthetic infiltration around the trigger points relieves local symptoms but also improves the widespread pain of fibromyalgia [32].

The possibility that an additional factor that alters the response to treatment being present should be carefully investigated, particularly reviewing all prescribed medication. Some drugs such as statins, aromatase inhibitors, bisphosphonates, and chemotherapy agents such as taxanes may be associated with musculoskeletal and neuropathic pain which can mimic fibromyalgia [22, 33], and could potentially alter the response to fibromyalgia treatment. Interestingly, some artificial additives, such as aspartame and monosodium glutamate, have been also reported as a cause of musculoskeletal symptoms similar to fibromyalgia, and this aspect should also be investigated, especially in patients with poor response to treatment [34]. Finally, some non-medical reasons that could mask the response to treatment should be considered, especially if there are situations of disability or legal compensation.

Searching for a definition of refractory fibromyalgia

As we have reviewed, it is difficult to reach a final definition of "refractory fibromyalgia" or "treatment-refractory fibromyalgia," but as we mentioned earlier, perhaps the most appropriate term is the last one. However, any definition could only be considered after ruling out other diseases or pathological conditions that may mimic or coexist with fibromyalgia and may alter the response to treatment, including peripheral pain generators, psychological disturbances, or drugs associated with musculoskeletal pain.

As far as we have reviewed, there is no consensus definition for refractory fibromyalgia, but different chronic diseases have defined the state of "refractory" based on the lack of response to a certain number and type of drugs, for example, hypertension or diabetes.

We could preliminarily propose that treatment-refractory fibromyalgia can be defined when there has been no change in the symptoms perceived by the patient or in the different evaluation scales used in fibromyalgia or more specifically when there is no minimal clinically relevant change. This definition would be valid only after ruling out any comorbidity that may alter the response to treatment, and after general measures and the usual pharmacological and non-pharmacological interventions.

However, we recognize that this definition has many unresolved issues, starting with the need to unify the initial differential diagnosis including laboratory tests, standardizing the instruments that should be used to assess disease activity, and clearly defining the cutoff points to differentiate or stratify the response to treatment, as well as the number of non-pharmacological or pharmacological interventions. It is important to consider that the differential diagnosis and laboratory tests may vary according to the prevalent pathology in each country, and a minimum differential diagnosis could be required according to the guidelines of each country.

Another important issue is what symptoms should be considered in addition to pain to assess the response to treatment measures. Perhaps due to the heterogeneity of the clinical manifestations, the assessment should be individualized using the instruments that are considered necessary for

Table 2 Considerations for the definition of refractory-treatment fibromyalgia

- Make sure the fibromyalgia diagnosis is correct
- Perform a differential diagnosis with entities that can mimic fibromyalgia symptoms (including complete physical examination and laboratory test as needed)
- Investigate if there are any unidentified pathological conditions contributing to the symptoms (including mental disorders)
- Identify peripheral pain generators that contribute to maintaining central sensitization (i.e., myofascial pain syndromes)
- Review the current medication (especially medications associated with musculoskeletal pain)
- Investigate whether there are non-medical reasons that may be falsely altering the response to treatment
- Verify if the compliance is correct with the behavioral indications to reduce stressors and have adequate functionally
- Inadequate response in pain control (or other symptoms) and limitation for daily activities or work to pharmacological treatment with at least two drugs of different chemical classes
- Inadequate response in pain (or other symptoms) control and cause limitation for daily activities or work with at least two drugs of different chemical classes and two non-pharmacological interventions

each particular case, but with well-defined cutoff points that stratify the severity of the disease.

In the context of the definition of treatment-refractory fibromyalgia, the other important aspect is whether pharmacological and non-pharmacological treatment should be included. Some authors have suggested that there should be inadequate pain control with at least three drugs of different chemical classes before classifying a patient as refractory to treatment (i.e., tricyclic antidepressant, gabapentinoids, serotonin, and norepinephrine reuptake inhibitors). The drugs to be considered must be approved for use in fibromyalgia in international consensus or local or national guidelines. It remains to be defined how long it should be treated with each of the drugs to consider that there is no response to it, but probably a 4- to 8-week period might be appropriate. It would also be necessary to define whether the use of combined therapy and at least two non-pharmacological treatment modalities should be considered before classifying a patient as refractory to treatment. In this sense, similar proposals have been made in other pathologies; for example, treatment-resistant depression (TRD) is generally defined as failure to respond to at least two antidepressant treatments, as well as augmentation therapies and behavioral adjuncts, which have been administered at an effective dose for a sufficient duration [35–37].

Conclusions and future directions

As we have reviewed, there is no consensus definition for refractory fibromyalgia; in this article, it is not our purpose to present a formal definition, but to raise the possible bases for this purpose (see Table 2). We believe that it is a subject that must be discussed extensively before reaching a consensus definition. Our position is that an appropriate definition of treatment-refractory fibromyalgia would be helpful in daily practice, and it would allow the future to design strategies for the identification and management for patients who do not respond with the usual measures according to the international or national guidelines. Perhaps a consensus group needs to be established to work out the details in fibromyalgia.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Disclosure form is attached in the submission.

Competing interests The authors declare no competing interests.

References

1. Häuser W, Fitzcharles MA (2018) Facts and myths pertaining to fibromyalgia. Dialogues Clin Neurosci 20(1):53
2. Arnold LM, Gebke KB, Choy EHS (2016) Fibromyalgia: management strategies for primary care providers. Int J Clin Pract 70(2):99–112
3. Heymann RE, Paiva ES, Martinez JE et al (2017) New guidelines for the diagnosis of fibromyalgia. Rev Bras Reumatol 57:s467-476
4. Ablin JN, Buskila D (2015) Update on the genetics of the fibromyalgia syndrome. Best Pract Res Clin Rheumatol 29(1):20–28
5. Bennett R (2016) Shining a light on fibromyalgia treatment. Nat Rev Rheumatol 12(10):568–569
6. Copay AG, Subach R, Glassman SD et al (2007) Understanding the minimum clinically important difference: a review of concepts and methods. Spine J 7(5):541–546
7. Choy EH, Arnold LM, Clauw DJ et al (2009) Content and criterion validity of the preliminary core dataset for clinical trials in fibromyalgia syndrome. J Rheumatol 36:2330–2334
8. Revicki D, Hays RD, Cella D et al (2008) Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol 61(2):102–109
9. Bennet RM, Bushmakin AG, Cappelleri JC et al (2009) Minimal clinically important difference in the fibromyalgia impact questionnaire. J Rheumatol 36:1304–1311
10. Geisser ME, Clauw DJ, Strand V et al (2010) Contributions of change in clinical status parameters to Patient Global Impression of Change (PGIC) scores among persons with fibromyalgia treated with milnacipran. Pain 149:373–378
11. Arnold LM, Zlateva G, Sadosky A et al (2011) Correlations between fibromyalgia symptom and function domains and

patient global impression of change: a pooled analysis of three randomized, placebo-controlled trials of pregabalin. Pain Med 12:260–267
12. Hudson JI, Arnold LM, Bradley LA et al (2009) What makes fibromyalgia patients feel better? Correlations between patient global impression of improvement and changes in clinical symptoms and function: a pooled analysis of four, randomized, placebo-controlled trials of duloxetine. J Rheumatol 36:2517–2522
13. Arnold LM, Williams DA, Hudson JI et al (2012) Development of responder definitions for fibromyalgia clinical trials. Arthritis Rheum 64(3):885–894
14. Nuesch E, Häuser W, Bernardy K et al (2013) Comparative efficacy of pharmacological and nonpharmacological interventions in fibromyalgia syndrome: network meta-analysis. Ann Rheum Dis 72:955–962
15. Holman A (1998) Effect of lorazepam on pain score for refractory fibromyalgia. Arthritis Rheum 41(9)
16. Dworkin R, Sharma U, Stacey B et al (2005) Long-term treatment of neuropathic pain and fibromyalgia syndrome with pregabalin in treatment-refractory patients. J Pain 6(3):S30
17. Stacey BR, Emir B, Petersel D et al (2010) Pregabalin in treatment-refractory fibromyalgia. Open Rheumatol J 4:35
18. Fitzcharles MA, Ste-Marie PA, Goldenberg DL et al (2013) Canadian guidelines for the diagnosis and management of Fibromyalgia syndrome: executive summary. Pain Res Manag 18(3):119–126
19. Fitzcharles MA, Shir Y, Ablin JN el at (2013) Classification and clinical diagnosis of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines. Evid Based Complement Alternat Med 2013:485272
20. Salaffi F, Gerardi MC, Atzeni F et al (2017) The influence of fibromyalgia on achieving remission in patients with long-standing rheumatoid arthritis. Rheumatol Int 37(12):2035–2042
21. Fitzcharles MA, Perrot S, Häuser W (2018) Comorbid fibromyalgia: a qualitative review of prevalence and importance. Eur J Pain 22(9):1565–1576
22. Häuser W, Perrot S, Sommer C et al (2017) Diagnostic confounders of chronic widespread pain: not always fibromyalgia. Pain Rep 2(3)
23 López-Medina C, Moltó A (2020) Comorbid pain in axial spondyloarthritis, including fibromyalgia. Ther Adv Musculoskelet Dis 12:1759720X20966123
24. Arendt-Nielsen L, Nie H, Laursen MB et al (2010) Sensitization in patients with painful knee osteoarthritis. Pain 149(3):573–581
25. Fingleton C, Smart K, Moloney N et al (2015) Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. Osteoarthr Cartil 23:1043–1056
26. Bazzichi L, Rossi A, Giuliano T et al (2007) Association between thyroid autoimmunity and fibromyalgic disease severity. Clin Rheumatol 26(12):2115–2120
27. Haliloglu S, Ekinci B, Uzkeser H et al (2017) Fibromyalgia in patients with thyroid autoimmunity: prevalence and relationship with disease activity. Clin Rheumatol 36(7):1617–1621
28. Tagoe CE, Sheth T, Golub E et al (2019) Rheumatic associations of autoimmune thyroid disease: a systematic review. Clin Rheumatol 38(7):1801–1809
29. Vidal M, Lane NE (2020) The importance of vitamin D. Rheumatol Orthop Med 5. https://doi.org/10.15761/ROM.1000171
30. Vidal LF, Morales R, Cueva C et al (2019) Serum levels of vitamin D in women treated at rheumatology services in Lima. Int J Clin Rheumatol 14(3):105–112
31. Häuser W, Perrot S, Clauw DJ et al (2018) Unravelling fibromyalgia—steps toward individualized management. J Pain 19(2):125–134
32. Affaitati G, Costantini R, Fabrizio A et al (2011) Effects of treatment of peripheral pain generators in fibromyalgia patients. Eur J Pain 15(1):61–69
33. Häuser W, Ablin J, Perrot S et al (2017) Management of fibromyalgia: practical guides from recent evidence-based guidelines. Pol Arch Intern Med 127(1):47–56
34. Smith JD, Terpening CM, Schmidt SO et al (2001) Relief of fibromyalgia symptoms following discontinuation of dietary excitotoxins. Ann Pharmacother 35(6):702–706
35. Dodd S, Horgan D, Malhi GS et al (2005) To combine or not to combine? A literature review of antidepressant combination therapy. J Affect Disord 89(1–3):1–11
36. Fava M (2003) Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 53(8):649–659
37. Souery D, Papakostas GI, Trivedi MH (2006) Treatment-resistant depression. J Clin Psychiatry 67(16)