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Treatment data from the Brazilian fibromyalgia registry (EpiFibro)

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Abstract

Background: EpiFibro (Brazilian Epidemiological Study of Fibromyalgia) was created to study patients with fibromyalgia (FM). Patients were included since 2011 according to the classification criteria for FM of the American College of Rheumatology of 1990 (ACR1990).

Objective: To analyze the therapeutic measures prescribed by Brazilian physicians.

Materials and methods: Cross-sectional study of a multicenter cohort. The therapeutic measures were described using descriptive statistics.

Results: We analyzed 456 patients who had complete data in the registry. The mean age was 54.0 ± 11.9 years; 448 were women (98.2%). Almost all patients (98.4%) used medications, 62.7% received health education, and less than half reported practicing physical exercise; these modalities were often used in combination. Most patients who practiced exercises practiced aerobic exercise only, and a significant portion of patients combined it with flexibility exercises. The most commonly used medication was amitriptyline, followed by cyclobenzaprine, and a minority used medication specifically approved for FM, such as duloxetine and pregabalin, either alone or in combination. Combinations of two or three medications were observed, with the combination of fluoxetine and amitriptyline being the most frequent (18.8%).

Conclusion: In this evaluation of the care of patients with FM in Brazil, it was found that the majority of patients are treated with a combination of pharmacological measures. Non-pharmacological methods are underused, with aerobic exercise being the most commonly practiced exercise type. The most commonly prescribed single drug was amitriptyline, and the most commonly prescribed combination was fluoxetine and amitriptyline. Drugs specifically approved for FM are seldom prescribed.

Keywords: Fibromyalgia, Treatment, Registries, Chronic pain

Introduction

Fibromyalgia (FM) is characterized by chronic generalized pain, with other central symptoms such as fatigue, sleep disorders and cognitive symptoms. It is often accompanied by other functional syndromes such as irritable bowel syndrome, depressive syndrome, anxiety syndrome and migraine. Its prevalence is between 2 and 10% of the adult population, and it is estimated to be 2.5% in Brazil [1].

The need for epidemiological studies to clinically characterize FM and its management in our population led the Brazilian Society of Rheumatology (Sociedade Brasileira de Reumatologia - SBR) to create the Epidemiological Fibromyalgia Registry (EpiFibro). These data will improve the diagnostic accuracy and therapeutic approach of FM in Brazil. Patients who met the classification criteria for FM of the American College of Rheumatology (ACR1990) [2] were included. Clinical data were published in 2013, and disease progression data were published in 2016 [3, 4].

FM treatment involves non-pharmacological measures such as health education, physical exercise, and cognitive behavioral therapy. The SBR has focused on analyzing the literature on FM treatment and

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published recommendations for its treatment based on international and national studies [5]. However, it is also important to identify how treatments are developed in the “real life” scenario.

Objective

The primary objective of this study was to describe the pharmacological and non-pharmacological treatment of patients with FM in Brazil. The secondary objective was to determine whether there is a correlation of demographic data and pharmacological and non-pharmacological interventions with the clinical parameters studied.

Materials and methods

This is a multicenter cross-sectional study of patients with FM whose data in EpiFibro databank were collected between 2013 and 2015.

EpiFibro contains epidemiological and clinical data, and therapeutic modalities prescribed to the patients who fulfill 1990 Classification Criteria for Fibromyalgia of the American College of Rheumatology. All the information on this convenience sample was included online by the authors who were responsible for the enrolled sites, according to a tutorial created by the SBR Commission on Fibromyalgia, Pain and other Rheumatisms of Soft Tissues. Fibromyalgia Impact Questionnaire and the Widespread Pain Index and the Symptoms Severity Index were recorded and patients with incomplete data were excluded.

We collected data on use of pharmacological and non-pharmacological treatments at the moment of the patient evaluation but with no specification of dosage or time of usage/practice. We classify walking, exercise bike and treadmill as aerobic exercise. Flexibility exercise and muscle strengthening records were based on self-report of stretching exercises and weight lifting exercises, respectively. Pilates was considered a combination of flexibility exercise and muscle strengthening. The variables studied included age, public or private care (individual or group-based), pharmacological and non-pharmacological modalities; the clinical variables pain, fatigue and non-restorative sleep intensity; the impact of FM according to the Fibromyalgia Impact Questionnaire; and indices composing the Preliminary Criteria for Fibromyalgia Diagnosis published in 2010 and modified in 2011 (generalized pain index – GPI and symptom severity scale – SSS), alone or summed to generate the fibromyalgia index (FI).

Descriptive statistics were calculated and the Pearson and Spearman correlation tests were performed.

The protocol was approved by the Research Ethics Committee of the main research center (Federal University of Paraná) and registered with the National Research Ethics Commission (Comissão Nacional de Ética em Pesquisa – CONEP) under number 15982413.4.1001.0096. All patients were informed and consented to the

publication of their data, ensuring confidentiality. Database is property of the Brazilian Society of Rheumatology.

SBR have supported the development and the maintenance of database in the project named EpiFibro and the English editing service of the manuscript provided by American Journal of Experts.

Results

We analyzed 456 patients who had complete data in the registry. The mean age was 54.0 ± 11.9 years; 448 were women (98.2%). Most of them (80%) were seen at the public system.

Almost all patients used medications, and the treatment modalities were mostly used in combination. The number of patients and percentage of the total samples were 449 (98.4%) for medications, 286 (62.7%) for health education, 181 (39.7%) for physical exercises, and 97 (21.2%) for others modalities, that include acupuncture, relaxing therapy, balneotherapy, psychotherapy and homeopathy.

Most patients used medications, and less than one-third of them received health education (Table 1). Most patients used more than one drug, but either alone or in combination, most patients used amitriptyline and the minority used duloxetine and pregabalin (Fig. 1). The medication use was divided in approved by the Food and Drug Administration (FDA) for use in FM and off-label use drugs. In addition to medications whose use for FM is supported by the literature other drugs to treat pain and sleep disturbance have been mentioned. (Table 2).

Almost half of the patients exercised, most of them practiced only aerobic exercise, such as walking (Table 3). Among other non-pharmacological modalities patients cited mainly the practice of physical exercises in a heated swimming pool and relaxation techniques as like deep breathing and progressive muscle relaxation (Table 4).

There was a weak negative correlation between age and FIQ score, fatigue intensity and non-restorative sleep intensity. There was no difference in the clinical parameters between patients treated in the public or private healthcare system.

No difference was observed in the number of medications used and the performance of physical exercise; patients who performed aerobic exercise had better FIQ scores, lower non-restorative sleep intensity, and better GPI, SSS and FI values. There was no difference in clinical parameters regarding practice of strengthening exercises, heated pool therapy or psychotherapy.

Patients using amitriptyline or fluoxetine had lower FIQ scores. There were also no differences in clinical parameters between patients using medications alone or combined with physical exercise.

Discussion

This analysis of data from EpiFibro regarding the treatment of FM reflects the difficulties faced by patients and

Table 1 Combination of the therapeutic modalities used by patients with fibromyalgia

| Therapeutic modalities | Number of patients (%) |
|--|------------------------|
| Medications + health education | 134 (29.4) |
| Medications + health education + physical exercises | 79 (17.3) |
| Exclusively medications | 79 (17.3) |
| Medications + health education + physical exercises + others | 34 (7.5) |
| Medications + physical exercises | 55 (12.1) |
| Medications + health education + others | 29 (6.4) |
| Medications + physical exercises + others | 13 (2.9) |
| Medications + others | 11 (2.4) |
| Health education + others | 10 (2.2) |
| Exclusively physical exercises | 6 (1.3) |
| Exclusively health education | 5 (1.1) |
| Physical exercises + others | 1 (0.2) |
| Total | 456 (100) |

health professionals in Brazil, especially in the public system, which was the predominant care environment in this study. Particularly in the Brazilian Unified Health System, the scarce availability of non-pharmacological measures and of FM medications makes access difficult for most of the population.

There is no standardized FM treatment, but multimodal treatment involving FM education, physical activity, cognitive-behavioral therapy and medication use is the most accepted treatment strategy.

Although an ideal treatment should include three pillars – education, physical activity and medication [6] – only one quarter of the analyzed patients use this triad.

All FM guidelines and consensuses indicate that non-pharmacological treatment is fundamental and probably the most effective in the long term in maintaining the functionality and quality of life of these patients [7, 8]. In the present study, the proportion of patients receiving education about their condition was 62.7%, and that of patients practicing some type of physical exercise was only 39.7%. This finding

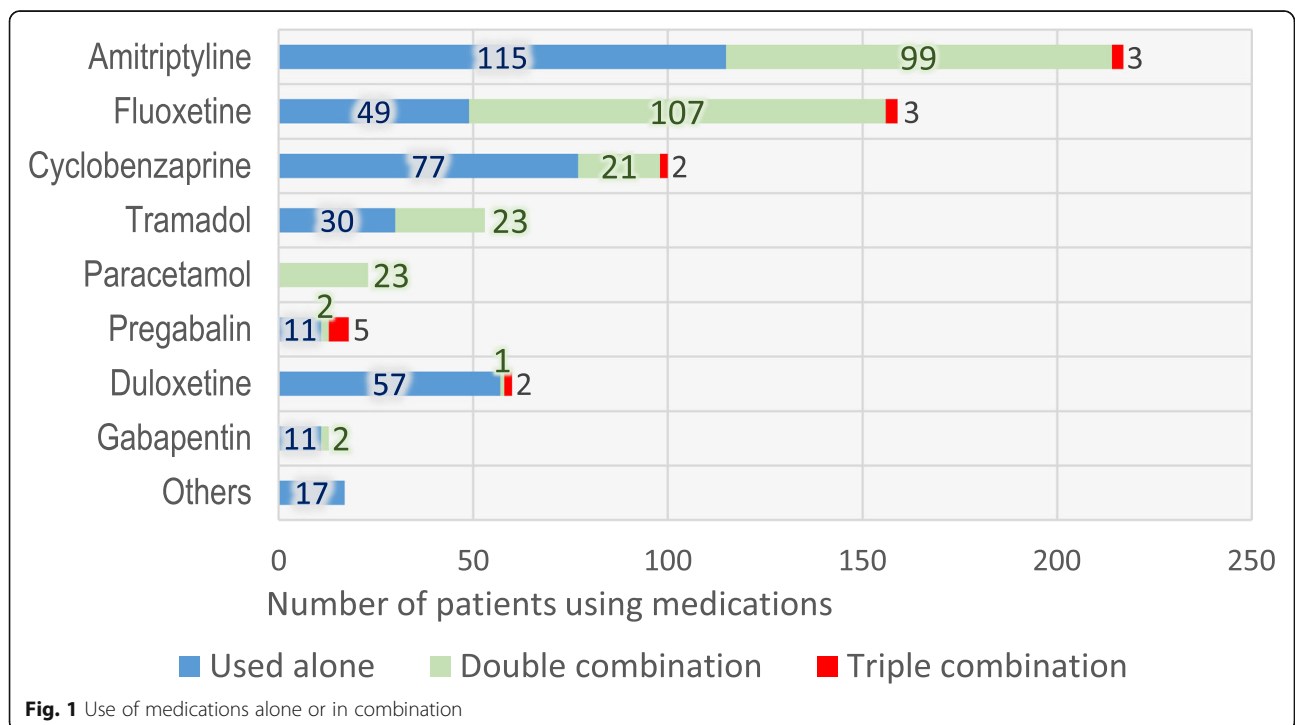


Fig. 1 Use of medications alone or in combination

Table 2 Painkillers and sleeping pills used by patients with fibromyalgia

| Therapeutic modalities | n | (%)* |
|------------------------|-----|--------|
| NSAIDs | 204 | (45.4) |
| Analgesics | 164 | (36.5) |
| Benzodiazepines | 73 | (16.3) |
| Other antidepressants | 31 | (6.9) |
| Topiramate | 16 | (3.6) |
| Carbamazepine | 12 | (2.7) |
| Opioids | 4 | (0.9) |
| Zolpidem | 4 | (0.9) |
| Pramipraxole | 2 | (0.4) |

NSAIDs nonsteroidal anti-inflammatory drugs; *: percentage over the total of 449 patients using any off-label medication

warns of possible devaluation of non-pharmacological therapies in the public system and the difficulty of implementing them, in contrast to the finding that almost all patients are using medications (98.4%).

This finding indicates the many difficulties faced in the prescription of exercise for patients with FM and the common lack of rehabilitation services structured for this purpose. Psychotherapy, in its various forms, is extremely underused (1.9%), revealing the low availability of this service in the public system. In patients who practice some form of exercise, the most common is aerobic activity, probably because it is more practical and less costly. In the latest recommendations from the European League Against Rheumatism (EULAR) for the treatment of FM, aerobic activity together with muscle strengthening were the modalities that received the highest degree of recommendation [8].

Tricyclic antidepressants (including cyclobenzaprine) were predominantly cited and used alone by 35% of patients. These older drug classes have lower cost and higher availability in the public system which may be the reason for its greater use.

The frequent use of non-hormonal anti-inflammatory drugs (43.6%), not recommended for the treatment of

Table 3 Types of physical exercises practiced by patients with fibromyalgia

| Types of physical exercises | n | (%) |
|---|-----|--------|
| Exclusively aerobic | 108 | (57.4) |
| Aerobic + flexibility | 48 | (25.5) |
| Exclusively flexibility | 26 | (13.8) |
| Exclusively muscle strengthening | 2 | (1.1) |
| Aerobic + muscle strengthening | 2 | (1.1) |
| Flexibility + muscle strengthening | 2 | (1.1) |
| Total of patients practicing any exercise | 188 | (100) |

Table 4 Non-pharmacological therapeutic modalities used by patients with fibromyalgia

| Therapeutic modalities | n | (%) |
|---|----|--------|
| Heated pool exercises | 17 | (27.4) |
| Relaxation techniques | 10 | (16.1) |
| Acupuncture | 9 | (14.5) |
| Psychotherapy | 9 | (14.5) |
| Massage | 6 | (9.7) |
| Infiltration of tender points | 6 | (9.7) |
| Homeopathy | 3 | (4.8) |
| Hypnosis | 1 | (1.6) |
| Biofeedback | 1 | (1.6) |
| Total of patients using any non-pharmacological therapy | 62 | (100) |

FM, indicates the greater availability and popularity of these medications.

The use of medications with formal approval for FM treatment by the FDA, often considered “anchor drugs”, such as pregabalin and duloxetine, was seldom observed in this survey. Although these medications have not yet provided a major beneficial effect in patients with FM [9] and their retention rate is fairly low, they have the potential to act in more than one clinical domain, and reduce the polypharmacy [10]. The fact that these higher-cost medications are not included in the Brazilian Ministry of Health’s Clinical Protocols and Therapeutic Guidelines (*Protocolos Clínicos e Diretrizes Terapêuticas – PCDT*) is certainly a major reason for their low utilization. New generic and similar presentations may change this scenario.

Almost 20% of patients on medication are on a combination of amitriptyline and fluoxetine, which are widely available in primary care. The synergistic effect of this combination was demonstrated in a study from 1996, although there is concern about possible drug interactions [11]. The large number of patients using drug combinations also increases this concern due to the sum of adverse effects, especially serotonergic syndrome [7].

The use of tramadol was low (6.4%) despite the scientific evidence in treating FM. In more recent studies, tramadol is classified outside the opioid class because of its weak action on opioid receptors and its ability to inhibit the reuptake of serotonin and noradrenaline [12].

The use of benzodiazepines was significant, although no drug in this class is recommended for FM. These low-cost and commonly prescribed compounds in Brazil are mainly used for the treatment of comorbidities such as insomnia and anxiety. Both benzodiazepine and opioid use have also been observed in other studies [9].

Most patients used analgesics, a very commonly prescribed class of drugs consumed as over-the-counter medications worldwide. Regarding anti-inflammatories, we suppose that their indication was based on the

diagnosis of peripheral pain generators, as the literature does not indicate their prescription for FM [5].

There are no other exclusively Brazilian studies on the general management of patients with FM. A 2013 study [13] compared prescription habits in Mexico, Venezuela and Brazil with those in Europe. Pharmacological therapies were more commonly prescribed in Latin America than in Europe, except for analgesics, in contrast to the case for non-pharmacological therapy.

EpiFibro has been undergoing evolutions in the form of data collection aiming at improving quality and practicality with the use of the program to feed the database, as well as increasing the participation of rheumatologists in the country. Further studies should reveal more details on therapeutics including the drugs dose used.

This study shows that in Brazil the pharmacological treatment of patients with FM is based on off-label drugs. Based on these data, we assume that duloxetine and pregabalin, drugs approved for use in FM, should be included in the protocol for chronic pain management. Additionally, we suggest the development of a public policy that includes non-pharmacological measures such as exercise and psychological therapies in primary care. This study has limitations, such as the low proportion of data collected in the private system and the lack of detail on medication doses. Because most patients have been treated in the public system, the findings may not apply to the private system. Recent studies have shown that initial medication doses, mainly of pregabalin and gabapentin, are rarely adjusted in patients with FM, regardless of the treatment response [9].

Conclusions

This evaluation of FM patient care in Brazil revealed that most patients are treated with a combination of pharmacological measures; non-pharmacological methods are underused; and aerobic conditioning is the most commonly practiced type of exercise. The most prescribed single drug was amitriptyline, and the most prescribed drug combination was fluoxetine and amitriptyline. Drugs specifically approved for fibromyalgia are seldom prescribed.

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Authors' contributions

All the individuals contribute on data collection and manuscript writing. Statistical analyses were made by MRA, ESP, JEM. All authors read and approved the final manuscript.

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Availability of data and materials

Database is property of the Brazilian Society of Rheumatology.

Ethics approval and consent to participate

The protocol was approved by the Research Ethics Committee of the main research center (Federal University of Paraná) and registered with the National Research Ethics Commission (Comissão Nacional de Ética em Pesquisa – CONEP) under number 15982413.4.1001.0096.

Consent for publication

All patients were informed and consented to the publication of their data, ensuring confidentiality.

Competing interests

The authors declare that they have no competing interests.

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