ESCOLA SUPERIOR DE SAÚDE
POLITÉCNICO DO PORTO

P.PORTO

M

MESTRADO EM FARMÁCIA
FARMACOTERAPIA E FARMACOEPIDEMIOLOGIA

Pharmacotherapy, treatment satisfaction and functional impact among fibromyalgia patients: characterization of a Portuguese sample

Joana Vaz Pereira

12/**2019**

ESCOLA SUPERIOR DE SAÚDE

Pharmacotherapy, treatment satisfaction and functional impact among fibromyalgia patients: characterization of a Portuguese sample

Autor

Joana Vaz Pereira

Orientador

Professora Doutora Marlene Santos, Professora Adjunta,

Escola Superior de Saúde do Instituto Politécnico do Porto

Dissertação apresentada(o) para cumprimento dos requisitos necessários à obtenção do grau de Mestre em **Farmácia** –Área de Especialização em **Farmacoterapia e Farmacoepidemiologia** pela Escola Superior de Saúde do Instituto Politécnico do Porto

"People need to be more compassionate. Chronic pain is no joke. And it's every day waking up not knowing how you're going to feel."

Lady Gaga

"Vive-se com a necessidade constante de justificar que, não é preguiça, é doença e ao mesmo tempo, ter a habilidade de não justificar tudo com ela, porque, ainda que seja a verdade, pode ser mal interpretado, como desculpa para a preguiça."

Sónia Tavares, The Gift

Resumo

Introdução: A fibromialgia é uma doença caracterizada por dor generalizada, fadiga, distúrbios de sono e problemas psicológicos e de cognição. A doença afeta maioritariamente o sexo feminino, na meia idade, sendo a sua prevalência de 1,7% em Portugal. Atualmente não existe cura e o tratamento da doença é realizado com base nos sintomas, sendo constituído por tratamento farmacológico e não farmacológico. A fibromialgia é de especial relevância no quotidiano do doente, e pode afetar a sua qualidade de vida negativamente. **Objetivos:** Caracterizar a farmacoterapia do doente português com fibromialgia, analisando a sua satisfação no que toca à medicação; e avaliar o impacto desta na condição de saúde e capacidade funcional do doente. **Metodologia:** Foi realizado um estudo observacional, onde foi aplicado um questionário online, à população portuguesa, através de associações portuguesas. Foi constituído por quatro partes: caracterização sociodemográfica; *Fibromyalgia Impact Questionnaire*; caracterização farmacoterapêutica e o *Treatment Satisfaction Questionnaire for Medication*. Os dados obtidos foram analisados estatisticamente e as variáveis foram relacionadas através de teste de ANOVA e correlação de Pearson. **Resultados:** A amostra apresentou um score de 64,89 $\pm$ 15,92 no *Fibromyalgia Impact Questionnaire*, que se evidenciou relacionado com a idade e a zona de residência (p = 0,039 e p = 0,047 respetivamente). Os grupos de fármacos mais comumente utilizados pelos doentes foram: anti-inflamatórios não esteróides (17,7%) e ansiolíticos (16,9%). Relativamente à satisfação com a medicação, os doentes evidenciaram um score de 67,87 na "Conveniência", 67,59 nos "Efeitos Adversos", 45,01 na "Eficácia" e 46,25 na "Satisfação Global". Esta mostrou-se influenciada pelo tempo de diagnóstico, número de medicamentos administrados e pela natureza da medicação. **Discussão e Conclusão:** Os resultados do score do *Fibromyalgia Impact Questionnaire* evidenciam que a doença tem um impacto negativo na vida doente, uma vez que o score apresenta um valor superior a 50. Os doentes com fibromialgia tendem a tomar mais que uma medicação, e os grupos farmacoterapêuticos dos anti-inflamatórios não esteróides e ansiolíticos são os mais usados, no entanto são também os menos aconselhados na literatura devido à falta de eficácia e/ou efeitos secundários. Também várias classes de antidepressivos e anticonvulsivantes são grupos usados para o tratamento da fibromialgia, que apesar de eficazes, não representam os grupos de maior consumo. Relativamente à satisfação com a medicação, os valores devem ser avaliados cuidadosamente devido à diversidade do tratamento. A fibromialgia tem um impacto negativo na qualidade de vida, e neste sentido são necessários mais estudos que explorem terapias eficazes na fibromialgia, com efeitos adversos mínimos, de forma a garantir a adesão ao tratamento, melhorando a qualidade de vida do doente.

Palavras-chave: *Fibromialgia; Dor Crónica; Treatment Satisfaction Questionnaire for Medication; Fibromyalgia Impact Questionnaire*

Abstract

Introduction: Fibromyalgia is characterized by widespread pain, fatigue, sleep disturbance, and psychological and cognitive problems. The disease affects mainly females in middle age and has a prevalence of 1,7% in Portugal. The treatment is based on experienced symptoms and consists in pharmacological and non-pharmacological treatment. Fibromyalgia has an important impact on patient's life and can negatively affect their quality of life. **Objectives:** Characterize the patient's pharmacotherapy and analyse their satisfaction with medication and understand if this affects patient's health condition and functional capacity. **Methodology**: An observational study was made with the application of an online questionnaire to the Portuguese population, through portuguese associations. It was composed by four parts: sociodemographic characterization; Fibromyalgia Impact Questionnaire; pharmacotherapeutic characterization and the Treatment Satisfaction Questionnaire for Medication The data obtained were statistically analysed and the variables were related trough ANOVA and Pearson correlation. **Results**: The population presented a score of 64,89 $\pm$ 15,92 in the Fibromyalgia Impact Questionnaire, and this was associated with age and the area of residence (p = 0,039 and p = 0,047). The most common medication among patients were the non-steroidal anti-inflammatory group (17,7%) and anxiolytics drugs (16,9%). Regarding the Treatment Satisfaction Questionnaire, the score was 67,87 for "Convenience", 67,59 for "Adverse Effects", 45,01 for "Effectiveness" and 46,25 for "Global Satisfaction" and was influenced by time of diagnosis, number of medications taken and by the drug classes. **Discussion and Conclusion:** From the average Fibromyalgia Impact Questionnaire score, it can be observed that the disease has a negative impact on life, since the score is greater than 50. Patients with fibromyalgia tend to take more than one medication: non-steroidal anti-inflammatory and anxiolytic groups are the most commonly used, however they are also the least advised due to lack of efficacy and/or side effects. In addition, antidepressants and anticonvulsants, despite being recommend in fibromyalgia patients, they are not very common drugs in this sample. The Treatment Satisfaction values should be carefully evaluated due to the diversity of treatment. Further research is needed to unravel effective therapies that can ameliorating the various symptoms of fibromyalgia with minimal adverse effects, in order to ensure treatment adherence and further improve patient's quality of life.

Key-Words: *Fibromyalgia; Chronic Pain; Treatment Satisfaction Questionnaire for Medication; Fibromyalgia Impact Questionnaire*

Contents

Table Contents

Figure Contents

Abbreviations list

ACR – American College of Rheumatology

AMPA - Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

APJOF – Portuguese Association of Young People with Fibromyalgia

AWMF - Association of the Scientific Medical Societies in Germany

CBT - Cognitive Behavior Therapy

CNS – Central Nervous System

COMT - Catecholamine o-methyl transferase

DGS – *Direção Geral de Saúde*

EEG - Electroencephalograms

EMA - European Medicines Agency

EULAR - European League Against Rheumatism

FDA - Food and Drug Administration

FIBRO - Fibromyalgia Association

FIQ – Fibromyalgia Impact Questionnaire

FM – Fibromyalgia

GH – Growth Hormone

HPA - Hypothalamic-pituitary-adrenal

IGF-1 - Insulin-like growth factor type-1

IMAO - Monoaminoxidase inhibitors

LFESSQ - The London Fibromyalgia Epidemiology Study Screening Questionnaire

MYOS - National Association Against Fibromyalgia and Chronic Fatigue Syndrome

NK-1 - Neurokinin

NMDA - N-methyl-D-aspartic acid

NO – Nitric Oxide

NSAID - Nonsteroidal anti-inflammatory drugs

PTN - Transmission neurons (PTN)

RA - Rheumatoid arthritis

SNRI - Serotonin–Noradrenalin Reuptake Inhibitors

SP – Substance P

SPSS - Statistical Package for the Social Sciences

SS – Symptoms severity

SSRI - Selective serotonin reuptake inhibitors

TCAs - Tricyclic Antidepressants

THC – Tetrahydrocannabinol

TSQM – Treatment Satisfaction Questionnaire for Medication

USA – United States of America

WPI – Widespread pain index

1. Introduction

Fibromyalgia (FM) is a chronic disease characterized by widespread musculoskeletal pain, associated with sleep disorders and fatigue. FM is also following for emotional changes and decreased quality of life (Rosado, et al., 2006; Wiffen Philip et al., 2013).

Fibromyalgia replaced the previous term "fibrositis", in the 1980s after exhaustive efforts to prove the existence of inflammatory or other abnormalities of muscle and connective tissue had failed (Hawkins, 2013).

The pathophysiology of FM is not completely recognized. However, is pathogenesis and etiology are known to be multifactorial (Yunus & İnanici, 2001). The most accepted theory is related to the state of centralized pain, which amplifies the pain creating an abnormal response to different stimuli (Clauw, 2014; Tzellos et al., 2010).

FM diagnosis is based in the criteria of the American College of Rheumatology (ACR) of 2010. Rheumatologists are the indicated to make the diagnosis and prescribe the necessary treatment to the patient (Dymon et al., 2015). The management must be composed by pharmacological and non-pharmacological therapies. Once the FM don't have any cure, the treatment needs to be based on the symptoms.

1.1 Epidemiology

Results from the prevalence of FM between 1990 and 2005, varied from 0,7 to 4,4%. Marques et al, shows, on their literature update, the prevalence between 2005 and 2014 ranged from 0,2 and 6,6% after 39 studies were analyzed (Marques et al., 2017). In 2013, Queiroz mentioned in his paper that the global prevalence of FM, in 26 studies worldwide, is 2,7% (Queiroz, 2013).

A literature review of 2017 shows the lowest results in Venezuela (0,2%) and the highest in United States of America (USA) (6,4%), using the ACR criteria. Meanwhile in Europe the prevalence is 2,5% (Marques et al., 2017; Queiroz, 2013). A prevalence study of 2010, made in five different countries of Europe (France, Italy, Germany, Spain and Portugal), shows a point prevalence of FM in Portugal of 3,6%, using The London Fibromyalgia Epidemiology Study Screening Questionnaire (LFESSQ) (Branco et al., 2010). According to the Portuguese Health Agency – Direção Geral de Saúde (DGS), 1,7% of the Portuguese population is affected with FM (Direção-Geral da Saúde, 2017).

Many surveys show a higher prevalence on the female population. In the review of Marques et al, the prevalence of the disease was between 2,4% and 6,8% (Marques et al., 2017). Queiroz, et al, indicates a 4,2% prevalence in female and 1,4% in male, with a 3:1 ratio (Queiroz, 2013).

Studies also show a higher occurrence of FM in the middle age or after 50 years, low educated individuals, obese women and who live in rural areas (Marques et al., 2017; Queiroz, 2013)

1.2 Etiology and Pathofisiology

Since the first description of FM in 1981 many researches and studies have been published clarifying the etiology and pathophysiology of the disease. FM is heterogeneous and explained by different hypotheses. Is believed that factors as genetic, sleep disorders, infections, stress factors, both physical or emotional can contribute to FM's pathophysiology (Clauw, 2014).

Is known that the pathogenesis of this disease is related to a dysregulation in the reception of nociceptive stimuli by the central nervous system (CNS) (Pillmer et al., 1997).

1.2.1 Central Sensitization

Patients with FM present **hyperalgesia**, an increased response to a painful stimulus as well as **allodynia**, pain caused by a stimulus that normally does not cause pain like touching or rubbing. Studies shown that patients with FM are sensible to any type of stimuli such as heat, cold, electrical stimuli, the brightness of a light or the loudness of tones (Schmidt-Wilcke & Clauw, 2011).

FM is related to **central sensitization** (Clauw, 2014; Yunus & İnanici, 2001). Central sensitization is defined as a hyperexcitability of the CNS neurons in response to a peripheral nociceptive stimulus leading to an exaggerated response to a normal painful stimulus (hyperalgesia) or a normal painless stimulus (allodynia) (Yunus & İnanici, 2001).

When a stimulus is caused in the skin or muscles, the coursing is made till the periphery to the dorsal horn via C-fibers (primary afferent fibers) and to the brain via the spinothalamic tract (Bradley, 2009; Yunus & İnanici, 2001). In the dorsal horn, pain transmission can be modulated by the activation of descending pain inhibitory pathways, which include serotonin and norepinephrine/noradrenaline (Bradley, 2009; Yunus & İnanici, 2001).

In the cortex, primary afferents transmit action potentials to presynaptic terminals where the substance P (SP) and glutamate (excitatory aminoacid) are released, these bind to pain transmission neurons (PTN) such as amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA); N-methyl-D-aspartic acid (NMDA) and neurokinin (NK-1) (Bradley, 2009; Yunus & İnanici, 2001).

In FM patients, the PTN became sensitized when there's an exposure to a painful stimulus. An influx of Ca^{2+} increases nitric oxide (NO) which causes PTNs to be hyperexcitable, who leads to augmented release of SP and excitatory aminoacids. Glia cells are also involved in this mechanism, being activated and releasing substances (e.g., nitric oxide, reactive oxygen species, prostaglandins, proinflammatory cytokines, nerve growth factor) increase presynaptic release and cause post synaptic hyperexcitability (Figure 1) (Bradley, 2009; Yunus & İnanici, 2001)..

Russel et al., indicate that serotonin and noradrenaline, both involved in descending pain inhibitory pathways, are decreased in FM patients. Russel et al. found low levels of these neurotransmitters on blood serum and also low levels of their metabolites on cerebrospinal fluid (Russell et al., 1994).
SP, an important nociceptive transmitter, has also an important role in pain transmission. Studies measure SP in cerebrospinal fluid indicates that is three times higher in FM patients compared to healthy patients (Yunus & İnanici, 2001).
The NMDA, involved in the central sensitization mechanism, in specific their receptors (NMDAR) where the glutamate binds, as an important role in the pathophysiology of the pain. A double-blind placebo controlled test, indicates a reduction of pain intensity when ketamine, a non-competitive NMDAR antagonist, was administrated as compared with a isotonic saline (Yunus & İnanici, 2001).
Cagnie et al., indicated that exists several changes in the brain of individuals of FM, such as decrease in gray matter volume in regions associated to pain processing and stress (Cagnie et al., 2014).

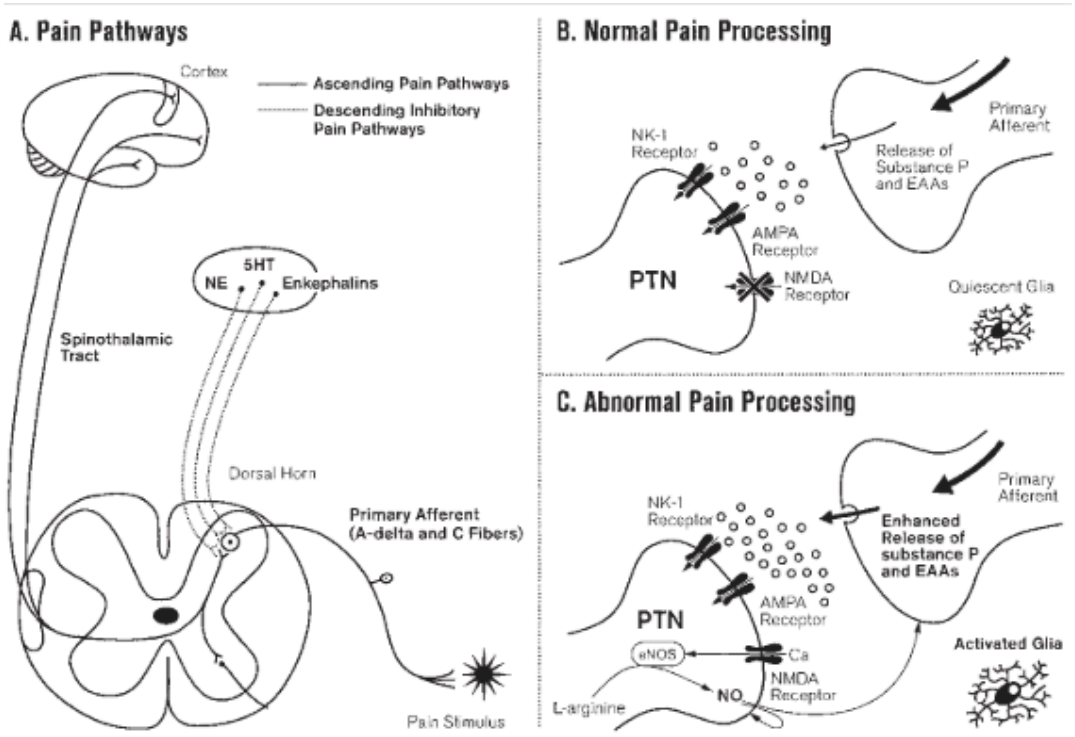


Figure 1 - Pain Perception (Adapted Bradley, 2009)

1.2.2 Genetic

Harte et al, indicates that serotonin 5-HT2A receptor polymorphism T/T phenotype, serotonin transporter, dopamine 4 receptor and catecholamine o-methyl transferase (COMT) polymorphism have a higher frequency in FM patients then controls (Harte, Harris, & Clauw, 2002; Neumann &

Buskila, 2003). There is also a 8,5 bigger probability that first degree relatives develop the disease in comparation to the normal population (Hawkins, 2013).

1.2.3 Sleep disorders

Sleep problems such as insomnia, poor sleep quality or non-restorative sleep are usual in FM. There's evidence that a poor night of sleep can contribute to worsening the symptoms, causing painful days and painful days can cause a poor night of sleep, turning into a vicious cycle (Pillemer et al., 1997).

Polysomnographic studies show the existence of alpha activity during non-REM sleep on electroencephalograms (EEG) of patients with FM. This activity is associated with decreased production of growth hormone (GH) and insulin-like growth factor type-1 (IGF-1), required for physiological repair (Bradley, 2009).

This suggested that treating sleep disorders may be essential to improve FM symptomatology (Pillemer et al., 1997; Yunus & İnanici, 2001).

1.2.4 Psychological Stressors

Depression, anxiety, bipolar, post-traumatic stress, and obsessive-compulsive disorders are common psychiatric syndromes in patients with FM (Hawkins, 2013; Sancassiani et al., 2017; Schmidt-Wilcke & Clauw, 2011).

There is a relationship between pain and distress, who can be a cause or consequence of pain. When presented as a consequence, it may cause problems to the patient which may increase their symptoms leading to isolation, difficulty in coping and decreased activity (Schmidt-Wilcke & Clauw, 2011).

Studies have revealed a prevalence of major depression in 26% of 31 FM patients compared with none of 14 rheumatoid arthritis (RA) patients and onset of depression occurred in 64% after FM diagnosis (Yunus & İnanici, 2001). In a multicenter study was found that FM patients had high levels of major depression and panic disorder. However it's hard to predict who came first due to the difficult of the accuracy of the begging of the symptoms in FM (Epstein et al., 1999).

Childhood abuse is also related to FM, a meta analyses shows that people who suffered abuse or where neglected have more pains symptoms compared to others (Sancassiani et al., 2017). Furthermore, past traumatic events such as car accidents, death of a relative or hospitalizations can also increase the risk of developing generalized pain (Hawkins, 2013; Schmidt-Wilcke & Clauw, 2011).

The hypothalamic-pituitary-adrenal (HPA) axis can also be associated to FM, once emotional and physical stress can activate him (Schmidt-Wilcke & Clauw, 2011).

1.2.5 Infections and other mecanisms

Biological stressors can also be a trigger to the development of FM. It has been shown that 5 -10% of individuals exposed to viral or bacterial infections such as Lyme's disease, Epstein-Barr virus, parvovirus, Q fever, hepatitis B and C can develop generalized pain (Schmidt-Wilcke & Clauw, 2011). Also, autoimmune diseases such as RA, lupus erythematosus or physical trauma may be the cause of central sensitization. Inflammatory states are involved in central sensitization, a theory corroborated for the appearance of FM followed after inflammatory diseases, who proves the inflammation can be the source of central sensitization (Clauw, 2014; Hawkins, 2013; Yunus & İnanici, 2001).

Some studies refer to a deficiency of vitamin D is also related to chronic pain and FM, directing therapy with this vitamin can improve symptoms of the disease. However, these studies are few and inconclusive (Chinn et al., 2016)

1.3 Clinical Condition

The main symptom of FM patients is **pain**: a generalized chronic pain. Symptoms of the disease also include fatigue, depression, sleep disturbance, anxiety, stiffness, headache and cognitive impairment. About 60-70% of patients complain of "hurt all over". The most common locations of this pain are neck, lower back, hands, knees, shoulders, arms, elbows, hips and feet (Yunus & İnanici, 2001).

Stiffness is also common in those patients. Stiffness and pain can be potentiated by weather factors, trauma, noise, poor sleep or stress (Hawkins, 2013).

Extreme fatigue, paresthesia, extremity swelling, headache, irritable bowel syndrome, restless leg syndrome, primary dysmenorrhea, female urethral syndrome, poor balance, sicca symptoms and Raynaud phenomenon are also symptoms present in FM (Yunus & İnanici, 2001).

Physical exams show swollen knees in patients with FM. There is also limitation of movement in the neck and joints due to pain, however they may also be related to the presence of other diseases such as osteoarthritis or RA (Yunus & İnanici, 2001).

1.3.1 Diagnostic Criteria

In 1990, the ACR developed the diagnostic criteria for FM. It defined the disease as a combination of the history of generalized pain for more than 3 months and the presence of at least 11 of the 18 tender points, digitally palpated with a pressure of approximately 4kg (Figure 2) (Gittins et al., 2017; F Wolfe et al., 1990)

1. History of Widespread Pain *Definition*. Pain is considered widespread when all of the following are present: pain in the left side of the body. pain in the right side of the body, pain above the waist. and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition. shoulder and buttock pain is considered as pain for each involved side. "Low back" pain is considered lower segment pain.
2. Pain in 11 of 18 tender point sites on digital palpation *Definition*. Pain, on digital palpation, must be present in at least 11 of the following 18 tender point sites: Occiput: bilateral, at the suboccipital muscle insertions. Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5–C7. Trapezius: bilateral. at the midpoint of the upper border. Supraspinatus: bilateral, at origins, above the scapula spine near the medial border. Second rib: bilateral. at the second costochondral junctions. just lateral to the junctions on upper surfaces. Lateral epicondyle: bilateral, 2 cm distal to the epicondyles. Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle. Greater trochanter: bilateral. posterior to the trochanteric prominence. Knee: bilateral. at the medial fat pad proximal to the joint line. Digital palpation should be performed with an approximate force of 4 kg. For a tender point lo be considered "positive" the subject must state that the palpation was painful "Tender" is not to be considered “painful”.
* For classification purposes. patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.

Figure 2 – The 1990 ACR criteria for the classification of FM* (Wolfe et al.,1990)

However, these criteria show some shortcomings, once fatigue and cognitive problems were not yet relevant. On the other hand, the count of tender points can be influenced by the patient-physician relationship and may also be related to stress (Clauw, 2014; Frederick Wolfe et al., 2010).

Due to these problems, the ACR made new criteria in 2010. These eliminated the need for examination of tender points and included new symptoms such as fatigue, non-restorative sleep and cognitive symptoms (Figure 3) (Frederick Wolfe et al., 2010).

Criteria

A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

1) Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or WPI 3–6 and SS scale score ≥9.

2) Symptoms have been present at a similar level for at least 3 months.

3) The patient does not have a disorder that would otherwise explain the pain.

Shoulder girdle, left	Hip (buttock, trochanter),	Jaw, left	Upper back
Shoulder girdle, right	left	Jaw, right	Lower back
Upper arm, left	Hip (buttock, trochanter),	Chest	Neck
Lower arm, left	right	Upper leg, right	Abdomen
	Upper leg, left	Lower leg, left	Lower arm, right
	Upper arm, right	Lower leg, right	

2) SS scale score:

Fatigue

Waking unrefreshed

Cognitive symptoms

For the each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:

0 = no problem

1 = slight or mild problems, generally mild or intermittent

2 = moderate, considerable problems, often present and/or at a moderate level

3 = severe: pervasive, continuous, life-disturbing problems

Considering somatic symptoms in general, indicate whether the patient has*:

0 = no symptoms

1 = few symptoms

2 = a moderate number of symptoms

3 = a great deal of symptoms

The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.

* Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms.

Figure 3 – The 2010 ACR criteria for FM (Frederick Wolfe et al.,2010)

The new criteria do not replace the old one but add some previously unrelated criteria such as cognitive problems and somatic symptoms. Two variables were added: WPI and SS. WPI is related

to tender points and SS allowing to better identify the patient's symptoms. SS used alone allows measuring the severity of symptoms such as fatigue, waking unrefreshed cognitive symptoms and the somatic symptoms (Frederick Wolfe et al., 2010).

The new criteria do not require a physical examination of tender points and showed to correctly classify 88.1% of the previously cases (Frederick Wolfe et al., 2010).

However, further testing is required to exclude other syndromes that may be mistaken for FM, such as hypothyroidism, inflammation and other myopathies, rheumatic diseases, viral infections, and severe vitamin D deficiency (Hawkins, 2013).

According to the criteria of DGS, the differential diagnosis is composed to complete blood count, sedimentation velocity, C-reactive protein, TSH, creatinine phosphokinase and serum calcium (Direção-Geral da Saúde, 2017).

1.4 Pharmacological Treatment

There is great evidence of anomalies in the mediators of serotonin, norepinephrine, SP, glutamate and other neurotransmitters when talking about FM. Thus, the pharmacological agents used are expected to have as their primary objective a reduction in the activity of neurotransmitters (e.g. glutamate) or increasing the activity of pain inhibitors such as serotonin and norepinephrine (Hawkins, 2013; Schmidt-Wilcke & Clauw, 2011).

To date, the Food and Drug Administration (FDA) has approved three FM drugs in the USA: pregabalin, duloxetine and milnacipran. In Canada, only pregabalin and duloxetine are approved while the European Medicines Agency (EMA) does not have any FM approved drugs. Which means that in the European Union, the prescribed medication for FM is off-label (Chinn et al., 2016).

Given the various symptoms experienced by patients, it is expected that not only one drug is capable of solving the potential symptoms of FM (Hawkins, 2013).

1.4.1 Antidepressants

Tricyclic Antidepressants (TCAs)

Amitriptyline (ADT®) and **cyclobenzaprine** (Flexiban®) are both TCAs with proven effects on FM therapy, both showing a 1A level of evidence in the USA (Schmidt-Wilcke & Clauw, 2011). Amitriptyline is an inhibitor of serotonin and norepinephrine reuptake, increasing the presynaptic concentration of both. According to the European League Against Rheumatism (EULAR) amitriptyline reduces pain in 30%, has also a moderate effect on sleep disorders and some effect on fatigue. According to this source 25mg/day improves the symptoms described in 6 to 8 weeks. 50mg/day does not show any benefits due to large rate of drop out because of adverse effects

(Goldenberg, Burckhardt, & Crofford, 2004; Kia & Choy, 2017; Macfarlane et al., 2017). On the other hand, cyclobenzaprine has a greater effect as a muscle relaxant due to is action mechanism that decreases noradrenergic function (Goldenberg et al., 2004; Schmidt-Wilcke & Clauw, 2011).

Serotonin–Noradrenalin Reuptake Inhibitors (SNRI)

Serotonin and norepinephrine are involved in descending pain inhibitory pathways and therefore linked to the pathophysiology of FM. In these patients, the concentration of serotonin and tryptophan (serotonin precursor) is in low concentrations both in serum and cerebrospinal fluid (Kia & Choy, 2017).

Duloxetine (Cymbalta®) has a greater effect on serotonin, involved in anxiety, depression and sleep. EULAR shows that 60mg/day of duloxetine improves depression, anxiety and quality of life, not showing substantial effect in lower doses. Duloxetine is both approved by the FDA and Health Canada (Calandre et al., 2015).

Milnacipran (Ixel®) has a greater effect on noradrenaline, being the analgesia is main effect, increasing inhibitory neurotransmission in brain pain modulating mechanisms, with concentrations between 100 to 200mg/day. This is one of the three drugs approved for the FDA (Macfarlane et al., 2017; Matthey et al., 2013).

Venlafaxine (Efexor®), shows to be helpful in FM patients, regarding to their depression symptoms (Epstein et al., 1999).

Selective serotonin reuptake inhibitors (SSRI)

Drugs such as **escitalopram, paroxetine, fluoxetine** (Prozac®) or **sertraline** show a moderate effect on pain and sleep but no effect on fatigue. A Cochrane review found that there is no benefit compared to placebo in the treatment of symptoms but may be beneficial for treating depression in patients with FM. Despite being well tolerated, SSRIs do not show superior efficacy (Kia & Choy, 2017; Macfarlane et al., 2017).

1.4.2 Anticonvulsants

Anticonvulsant drugs, **pregabalin** (Lyrica®) and **gabapentin** (Neurontin®), act by binding to the calcium (Ca^{2+}) channels in CNS, inhibiting the release of neurotransmitters such as glutamate and SP in pain pathways, causing an analgesic effect (Kia & Choy, 2017).

Unlike pregabalin, whose use is approved by the FDA and recommended in guidelines, gabapentin presents only one study where it has a beneficial effect on pain (Tzellos et al., 2010).

Pregabalin was the first FDA approved drug in 2007 for the treatment of FM. Several studies confirm its effectiveness in improving pain and sleep, also demonstrating positive results in

decreasing the Fibromyalgia Impact Questionnaire (FIQ) score (Kia & Choy, 2017; Macfarlane et al., 2017; Tzellos et al., 2010).

The combination of pregabalin with milnacipran has shown beneficial effects on pain, fatigue and increased quality of life when compared to placebo. (Tzellos et al., 2010)

1.4.3 Analgesic Treatments

Opioid drugs are not recommended for pain management as they may worsen FM symptoms such as fatigue and cognition. Although **tramadol** (Tramal®) has been shown to be beneficial in relieving pain, is use should be considered due to adverse effects and potential abuse (Dymon et al., 2015).

Nonsteroidal anti-inflammatory drugs (NSAID) do not show a relevant effect on pain given their peripheral action (Dymon et al., 2015).

1.4.4 Cannabinoids

Cannabinoid drugs have analgesic and beneficial properties in sleep disorders due to their receptors on peripheral and central nerves. Moreover, they are related to the regulation of pain perception, mood, appetite and memory (Calandre et al., 2015; Kia & Choy, 2017).

Nabilone, a synthetic cannabinoid that mimics tetrahydrocannabinol (THC), has been studied for pain management, showing improvement in FIQ score, anxiety and sleep. However, many individuals have dropped out of studies due to adverse effects (Calandre et al., 2015; Chinn et al., 2016; Kia & Choy, 2017). At the moment, any synthetic cannabinoid is approved in Portugal for the management of FM symptoms.

1.4.5 Others

Anxiolytic drugs, like alprazolam and other benzodiazepines show positive effects in sleep disturbances, however because of their potential dependence is not recommended in long term treatments. Also, zolpidem was shown positive effects on sleep and day time energy, but not in pain relief (Goldenberg et al., 2004).

Pramipexole, a dopamine agonist, has been shown to be effective in reducing pain and is recommended by EULAR and the Spanish guidelines (Calandre et al., 2015).

Growth hormone therapy has shown positive effects in some studies, however there is some concern about is safety, therefore is not recommended for the treatment of FM (Macfarlane et al., 2017).

Studies with narcolepsy-approved, sodium oxybote, have positive effects on pain, sleep and fatigue, however, the EMA and FDA do not approve is use due to safety issues. Monoaminoxidase inhibitors

(IMAOs), such as pirlindole (Implementor®) have also been studied an showed positive effects, yet their interactions are life-threatening (Calandre et al., 2015; Macfarlane et al., 2017).

1.5 Non-Pharmacological Treatments

Non-pharmacological therapies can be beneficial in improving quality of life, reducing the severity of symptoms or even coping with the disease (Mansoor M. et al 2018; Sim & Adams, 1999).

The practice of physical exercise has shown to improve the quality of life and also pain. Aerobic exercise is shown to have better results, but also flexibility and strength training are beneficial for the patient (Chinn et al., 2016; Dymon et al., 2015).

Cognitive Behavior Therapy (CBT) consists in combination of therapy that helps understand, recognize and identify inappropriate behaviors and thoughts with behavioral therapy for a disease adaptation (Dymon et al., 2015; Mansoor M. et al., 2018). Patients with FM often show personality profiles with high levels of pain and catastrophizing, which further exacerbate pain. CBT develops methods such as relaxation, distraction or writing, helping the FM patients create behavioral patterns (Mansoor M. et al., 2018).

Several reviews indicate that practicing *yoga, tai chi* or *qigong* can be positive in symptoms such sleep and fatigue (Macfarlane et al., 2017).

Also, mindfulness seems to be useful in developing coping mechanisms. Studies show improvement in sleep and symptom severity (Mansoor M. et al., 2018).

Acupuncture, a traditional Chinese medicine technique, consists in the allocation of thin needles on defined body sites, has effect reducing the pain and inflammation, release endorphins and create a calmer mind (Mansoor M. et al., 2018). Acupuncture has shown effects on pain, sleep and fatigue (Macfarlane et al., 2017).

1.6 Fibromyalgia and life quality

Several studies exploring the life quality in FM patients, conclude that the disease conditions lead to a drastic decrease in quality of life compared to other groups (Bernard et al., 2000).

Disorders involving chronic pain drag to disability in daily life due to both pain and psychological problems. The decrease in social support can lead to isolation of the individual that can, in the future, interfere with individual, family and social well-being. Restrictions on daily activities such as going to work due to FM symptoms may also trigger depression and other mental hilliness in these patients (Bernard et al., 2000; Verbunt et al., 2008).

FM affects physical, psychological, social function and social relationships. Most patients cannot fulfil family and work responsibilities and perform daily activities not only due to pain, but also due to fatigue, cognitive impairment and others (Galvez-Sánchez et al., 2019). Martins et al., showed that

the main influencers of life quality are advanced age, living alone, low level of academic skills and no practice of physical exercise. In their sample, 50% of study participants indicate FM as very disabling and 45,7% as moderately disabling and FIQ score is 63,76 points, which means reduced quality of life (Martins et al., n.d.).

The life quality of people around is also affected. Social support is compromised, most patients report that others cannot understand their disease, thinking they exaggerate their symptoms. Also love relationships seem to be compromised: Bernard et al, show in their study that, of the divorced participants with FM, 93,9% reported that the cause was disease related (Bernard et al., 2000).

With regard to sexual health, FM patients have lack of sexual desire, sexual aversion, orgasm disorder, vaginismus and dyspareunia which can be related to FM symptoms but also to medication side effects or psychological problems. This is an important aspect to solve, because poor sexual life can lead to problems in relationships and breakup (Galvez-Sánchez et al., 2019).

Problems at work are also a reality that patients live due to non-restorative sleep, stress due to work and other disease symptoms. Is necessary to readjust the work: since the understanding of colleagues, workload and tasks given (Bernard et al., 2000; Galvez-Sánchez et al., 2019). Studies show that most patients stopped working after diagnosis and those still working had to cut back on their work (Bernard et al., 2000). It was found that when the work schedules were adapted to the perception of the abilities of each patient, the patients had shown less exhausted, being able to enjoy periods of leisure and greater satisfaction in daily activities (Rosado et al., 2006).

Emotions such as sadness, fear, anger and guilt are associated with FM patients. Many sufferers develop depression, anxiety and other psychological comorbidities that affect the patient's daily life, including enhance symptoms of FM (Galvez-Sánchez et al., 2019).

Personality disorders are also related to FM, including obsessive compulsive disorder, borderline disorder, avoidance disorder. Also, perfectionism, neuroticism and psychoticism are associated with FM. The origin is related to psychological stress and readjustment to chronic disease (Galvez-Sánchez et al., 2019).

Self-esteem also appears to be affected in patients with FM. It may be linked to low cognitive performance in terms of attention or memory. Self-image, the perception, feelings and thoughts about the body, are also affected in patients with FM who find their image affected because the diagnose (Bernard et al., 2000; Galvez-Sánchez et al., 2019).

Given the impact of this disease on patient's quality life, is crucial to evaluate the true influence of the pharmacological approaches on FM outcome.

1.7 Aims of the study

The main objective of this study relies on characterizing the pharmacotherapeutic profile and impact of FM in a sample of Portuguese patients.

The specific objectives are:

1) To characterize the pharmacotherapy of the patient with FM;
    a. Identify the main classes of drugs used to treat FM and related it with the therapeutic guidelines;
2) To analyze patient's perception about the efficacy, tolerance, convenience and global satisfaction of the used medication;
    a. Relate the efficacy, tolerance, convenience and global satisfaction with the different drugs used to treat FM, the number of used drugs and the diagnosis time.
3) To understand the health condition and functional capacity of the individual with FM.
    a. Analyze the impact of the disease in different daily life situations;
    b. Relate the impact of FM with age, time of diagnosis and experience of the medication

2. Methodology

This chapter intends to describe the methodology used during the investigation, including population and study sample, instruments, statistical analysis and ethical concerns.

2.1 Study design

This study was an observational (non-experimental) study, since the investigator collected available information from patients without any type of intervention, with a cross-sectional design, since information was collected at a certain point in time, non-defined in the individual's life (Kumar, 2014).

2.2 Population and study sample

Sample was recruited in Portuguese associations who accompany patients with the fibromyalgia in Portugal: National Association Against Fibromyalgia and Chronic Fatigue Syndrome (MYOS), Portuguese Association of Young People with Fibromyalgia (APJOF) and Fibromyalgia Association (FIBRO) (Attachment 1).

For the participation in the study, the individuals must had been diagnosed with fibromyalgia, had more than 18 years, with Portuguese nationality, be able to read and write, and had access to a computer or smartphone with internet connection.

All the participants were invited to fill an online questionnaire in a voluntarily and anonymously way, after reading the informed consent.

2.3 Instrument of study

The method for collecting the necessary information was by an online questionnaire helped to divulge by MYOS, APJOF and FIBRO. The questionnaire was able online between July 26 and August 21.

The used questionnaire was composed by four different parts:

Socio-demographic Characterization

The first part was about the socio-demographic characterization of the population (Attachment 2). The socio-demographic questionnaire was applied with the purpose of knowing the age, sex, civil status, academic degree, work situation and age of the disease diagnosis.

Fibromyalgia Impact Questionnaire

In the second part of the questionnaire the Portuguese version of the FIQ was applied (Attachment 3) (Rosado et al., 2006). The FIQ-P is valid for the Portuguese language and proved to be an effective instrument used for health professionals (Rosado et al., 2006).

The purpose of FIQ is to determine the impact of the disease in the daily life and the incapacity resultant. The higher the score the patient obtains in the FIQ, the greater the impact of the disease in the person. The average fibromyalgia patient scores about 50 (Burckhardt, C.S., Clark, S.R, & Bennett, 1991).

The questionnaire is composed for 10 items, when the first item is composed for 11 sub-items. The first 11 sub-items measure the functional capacity of the individual or the *physical impairment*. Each item is classified to 4 points, where 0 means "never" and 3 means "always", so the highest score is 33 (3x11). Because some patients don't execute all the tasks, they can delete them of the score. For a valid summed score, the items the patient has rated are summed and divided by the number of items rated (i.e. if the patient completed 8 items at a score of 3 for each, the final score would be 3x8/8=3) (Burckhardt, C.S., Clark, S.R, & Bennett, 1991).

The next item, who measure how the patient *feels* (item 12), is scored inversely: the higher number means impairment (i.e., 0=7, 1=6, 2=5, 3=4, 4=3, 5=2, 6=1 and 7=0). The item number 13, who measure the *missed work* days, is scored directly (i.e. 7=7 and 0=0) (Burckhardt, C.S., Clark, S.R, & Bennett, 1991).

For the last items (14 to 20), each are scored in 10 increments, so the range is 0 to 10. Those items measure the *capacity of do work, the pain, the fatigue, the stiffness, anxiety* and *depression.*

Once the score is done, is necessary to do a normalization procedure so all the scores are expressed in the same units. The range of normalized scores is 0 to 10 with 0 indicating no impairment and 10 indicating maximum impairment. The figure below shows how to normalize the scores of the 10 items.

Scale	Item #	Recode	Score Range	Normalization
Physical impairment	1	No	0 -3	S X 3.33
Feel good	2	Yes	0-7	S X 1.43
Work missed	3	No	0-7	S X 1.43
Do work	4	No	0 - 10	None
Pain	5	No	0 - 10	None
Fatigue	6	No	0 - 10	None
Rested	7	No	0 - 10	None
Stiffness	8	No	0 - 10	None
Anxiety	9	No	0 - 10	None
Depression	10	No	0 - 10	None

Figure 4 – FIQ scores normalization (Burckhardt, C.S., Clark, S.R, & Bennett, 1991)

To obtain a score of 100 it necessary to employ the "equalization calculation". If the patient doesn't answer to all the 10 items the final summative scores needs to be multiplied by 10/x, when x is the number of questions missed (e.g if one question is missed: 10/9) (Burckhardt, C.S., Clark, S.R, & Bennett, 1991).

Pharmacotherapeutic Characterization

The third part of the questionnaire correspond to the pharmacotherapeutic characterization. In this part of the questionnaire, the patient informs about the medication used in present and past (if any), the reason for discontinuation of a previous treatment and who did the prescription (Attachment 4).

Treatment Satisfaction Questionnaire

Four and last part of the questionnaire is applied the Treatment Satisfaction Questionnaire for Medication (TSQM) version 1.4 (Attachment 5). Was applied the translated Portuguese TSQM provided by IQVIA (Attachment 6).This questionnaire is a valid instrument to assess patient satisfaction with the medication in four ways: side effects, effectiveness, convenience and global satisfaction (IQVIA, 2018)

The TSQM 1.4 consists in 14 items, who corresponds to domains referred above. For each domain is necessary a specific calculation to obtain a score range between 0 and 100. The specific calculation is presented below:

Global Satisfaction

([(Sum(Item 12 to Item 14)) – 3] divided by 14) * 100

If Item 12 or 13 is missing

[(Sum(the two completed items)) – 2] divided by 10) * 100

If Item 14 is missing

([(Sum(Item 12 and Item 13)) – 2] divided by 8) * 100

Effectiveness

([(Item 1 + Item 2 + Item 3) – 3] divided by 18) * 100

If one item is missing

([Sum(the two completed items)) – 2] divided by 12) * 100

Side Effects

If Question 4 is answered 'No' then score = 100

or

([Sum(Item 5 to Item 8) – 4] divided by 16) * 100

If one item is missing

([(Sum(the three completed items)) – 3] divided by 12) * 100

Convenience

([Sum(Item 9 to Item 11) – 3] divided by 18) * 100

If one item is missing

([(Sum(the two completed items)) – 2] divided by 12) * 100 (IQVIA, 2018)

2.4 Statistical Analysis

For the data's edition and treatment was used the Statistical Package for the Social Sciences (SPSS) version 25 for MacOS.

Variables can be divided into dependent and independent variables. Independent variables present in the socio demographic questionnaire were age, sex, education, residence area, professional and civil status and years of diagnosis. Also, the drug-related variables present in the questionnaire of pharmacotherapeutic characterization are independent. The study dependent variables were FIQ and TSQM.

To describe the results a descriptive analysis of the nominal and ordinal variables was performed, such as the described in the socio demographic questionnaire (e.g., sex, civil and employment status) to obtain their frequency and percentage. In contrast, to describe the quantitative variables (e.g. age, age of diagnosis, FIQ and TSQM scores), the mean, standard deviation, minimum and maximum were obtained.

To perform associations between variables, the ANOVA test was used to associate dependent and independent variables. The Pearson correlation was also used to correlate depended variables. A significance value of 5% ($p < 0,05$) was always used.

2.5 Ethic Concerns

To certify the quality and integrity of the study and respect the confidentiality of the participants it was necessary to ensure that the study meet all ethical guidelines. The participant anonymity was taken into account and data were used only to statistical purposes. Before filling the questionnaire, the participant declares if wants to participate or not, with the filling of the informed consent.

The Ethical committee of Escola Superior de Saúde approved the study, whose authorization is present in Attachment 7.

3. Results

3.1 Part I – Socio-demographic characterization

The sample was initially composed of a total of 187 individuals recruited through MYOS, FIBRO and APJOF associates. Out of 187, one of the individuals was excluded for not accepting to answer the questionnaire and another 9 were excluded for not having Portuguese nationality. The final sample was composed by 177 individuals. The socio-demographic characterization is described in the table below (table 1).

The obtained sample was mostly female, with a percentage of 96,6% (n=171), while male participants represented only 3,4% of the sample (n = 6).

The average age of the participants was 47,26±10.60 years, and regarding civil status, mostly were married (66,7%).

Most of the participants were living in Portugal mainland (96,6%), without major differences between the three main regions: north, center and south, with only 6 individuals living in the islands: Azores or Madeira.

Regarding academic education, most of the sample had a higher education degree (54,8%). And regarding employment status, the majority (75,1%) was working at the moment of the study enrolment.

Table 1 – Socio demographic characterization: age, civil status, residence area, education and employment status *

Variable	Frequency (n)	Percentage (%)
Age		
20-29 years	10	5,6
30-39 years	28	15,8
40-49 years	68	38,4
50-59 years	45	25,4
60-69 years	23	13,0
+ 70 years	2	1,1
Civil Status		
Married	118	66,7
Divorced	20	11,3
Single	37	20,9
Widower	2	1,1
Residence Area		
Azores or Madeira	6	3,4

Centre	63	35,6
North	50	28,2
South	58	32,8
Education		
4th Grade	9	5,1
6th Grade	3	1,7
9th Grade	17	9,6
High School	51	28,8
University	97	54,8
Employment Status		
Not working	23	13,0
Employed	133	75,1
Student	1	0,6
Retired	20	11,3

*note that an individual did not respond to his age.

One of the questions answered in the first part of the questionnaire was about the time of FM diagnosis. The table below (Table 2) describes the time diagnosis was made, note that most respondents were diagnosed with FM less than 5 years ago (55,4%). Participants received diagnosis of FM at a mean age of 45,43± 10,10 years (note that an individual did not respond to his age).

Table 2 – Time of FM diagnosis

Variable	Frequency (n)	Percentage (%)
Time of diagnosis		
< 5 years	98	55,4
6–10 years	34	19,2
11–15 years	26	14,7
15–20 years	16	9,0
+20 years	3	1,7

3.2 Part II – Fibromyalgia Impact Questionnaire (FIQ)

Regarding the FIQ, the Portuguese version was applied to the studied sample (Rosado et al, 2006). This questionnaire, which allows us to understand the impact of FM on the quality of life of their patients, is divided into several sections, which allow do evaluate the impact of FM into different variables: depression, anxiety, stiffness, rested, fatigue, pain, do work, work missed, feel good and physical impairment. This score allows considering the impact of FM on a scale from 0 to 10. The different variables and their averages are described in the table 6 (Rosado et al., 2006).

Table 3 – Average values of the different FIQ variables

FIQ VARIABLES	MEAN (SD)
PHYSICAL IMPAIRMENT	4,12 (1,75)
FEEL GOOD	7,20 (2,39)
WORK MISSED	3,64 (3,45)
DO WORK	6,75 (2,52)
PAIN	6,78 (2,08)
FATIGUE	7,99 (1,19)
RESTED	7,89 (2,17)
STIFFNESS	7,55 (2,14)
ANXIETY	6,74 (2,68)
DEPRESSION	6,23 (2,95)

The table above presents the average values of the different variables found in FIQ. It was observed that there is a greater impact of the disease on fatigue, rest, stiffness and feeling good (7,99; 7,89; 7,55 and 7,20, respectively). In contrast, the smallest values are found in work missed and physical impairment (3,64 and 4,12).

However, the essential value of FIQ is obtained through a final formula that takes into account all the variables and allows to reach a value from 0 to 100. The average score obtained by a person with FM is 50, and a person where the disease has a major impact has a score around 70 (Rosado et al., 2006). The average score obtained was 64,89 ± 15,92 (10-96).

Regarding the relationship between the FIQ score and the number of drugs the individual takes and the time of diagnosis there is no statistically significant. However, there was a statistically significant association between age and FIQ value (p = 0,039), that means, this score increases with

age. Also, FIQ and the residence zone shows to be statically significant (p= 0,047), the value of FIQ are increased in individuals who live in Portugal mainland (Table 4).

Table 4 – Association between FIQ and age, number of drugs, time of diagnosis and residence zone

Variable	Frequency (n)	FIQ mean	p value
Age			
20–29	10	54,64	0,039
30–39	28	67,77	
40–49	68	65,21	
50–59	45	62,62	
60–69	23	66,84	
+70	2	90,60	
Number of Drugs			
1	28	65,15	0,571
2	55	61,32	
3	47	66,64	
4	24	65,84	
5	13	68,92	
6	6	69,73	
7	4	65,57	
Time of Diagnose			
< 5	99	62,97	0,367
6–10	33	65,72	
11–15	26	68,34	
15–20	16	69,80	
+20	3	63,03	
Residence Zone			
North	50	60,53	0,047
Centre	63	67,74	
South	58	66,41	
Azores/Madeira	6	56,63	

3.3 Part III- Pharmacotherapeutic Characterization

In this section of the questionnaire, subjects were asked about the medication used for FM treatment.

In this study, the average number of drugs used to manage FM is **2,85 (1-7).**

Regarding the medication used in FM, of 504 responses, the most common drugs were NSAIDs (17,7%), anxiolytic/benzodiazepines (16,9%) and cyclobenzaprine (Flexiban®) (15,5%). The less used drugs were milnacipran (Ixel®) and bupropion (Elontril®/Wellbutrin®), also anyone respond pirlindole (Implementor®). The table below described the medication and respective frequencies.

Table 5 - Described frequency and percentage of the drugs used to FM treatment*

DRUGS	Frequency (n)	Percentage (%)
NSAIDS (e.g. ibuprofen, naproxen, piroxicam)	89	17,7
Anxiolytics/Benzodiazepines (e.g.lorazepam, alprazolam, clonazepam)	85	16,9
Cyclobenzaprine (Flexiban®)	78	15,5
Tramadol (Tramal®)	59	11,7
Duloxetine (Cymbalta®)	48	9,5
Pregabalin (Lyrica®)	42	8,3
Fluoxetine (Prozac®)	31	6,2
Amitriptyline (ADT®)	25	5,0
Gabapentin (Neurontin®)	21	4,2
Venlafaxine (Efexor®)	20	4,0
Bupropion (Elontril®, Wellbutrin®)	4	0,8
Milnacipran (Ixel®)	2	0,4

* note that no one respond pirlindole (implementor®)

When asked about this being their first treatment, most respondents have already tried other medication: 67,2% (n=119). Regarding the reasons associated with the drug modification they included: lack of efficacy (45,4%), adverse reactions or others.

The rheumatologist (n=113), followed by the family doctor(n=24), mainly prescribed FM drugs.

3.4 Part IV- TSQM 1.4

Concerning to TSQM, this questionnaire allows to understand the satisfaction with the medication currently using, in this case, to FM.

With the TSQM is possible to find the individual opinion about the medication in four different ways: effectiveness, convenience, adverse effects and global satisfaction. The score ranges from 0 to 100, where higher scores indicate greater satisfaction (IQVIA, 2018). The means of each variable is described on table 6. It's possible to observe a minor mean in the variable "effectiveness" and "global satisfaction".

Table 6 – Means of the TSQM variables: convenience, adverse effects, effectiveness and global satisfaction.

TSQM variables	**Mean (SD)**
Convenience	67,07 (19,66)
Adverse effects	67,59 (30,12)
Effectiveness	45,01 (19,52)
Global satisfaction	46,25 (22,23)

Using Pearson's correlation coefficient, to relate de FIQ score and the four TSQM variables it's possible to observed that the variable "convenience" and "adverse effects" had an inverse correlation with the FIQ score (r=-0,165, p=0,029 and r=-0,167, p=0,027, respectively), that means individuals with lower score on FIQ had a highest score on TSQM (table 7).

Table 7 – Pearson's correlation between FIQ and TSQM

	FIQ	
	Pearson Correlation (r)	p value
Convenience	-0,165	0,029
Adverse Effects	-0,167	0,027
Effectiveness	-0,098	0,196
Global Satisfaction	-0,093	0,212

When observe the association between the TSQM values and the diagnosis time, it is possible to notice the variable "global satisfaction" was associated with diagnosis time (p = 0,025). Individuals

diagnosed longer (+20 years) have a lower score then the other groups. On other hand, adverse effects, effectiveness and convenience didn't show to be statistically associated.

When associate the number of drugs taken with the TSQM, only the variable adverse effects show a significant *p* value ($p = 0{,}012$). This means that individuals taking a larger number of drugs have a lower score on the adverse effect's variable. The other TSQM variables were not statistically correlated. The table with the discriminated values can be found on the attachments (table 8 and 9 on attachment 8).

Regarding the association among the groups who are treated (yes) or not (no) with the drugs presented on the questionnaire and the mean scores of the TSQM variables, only the values of "global satisfaction" in duloxetine and fluoxetine are significant ($p = 0{,}028$ and $p = 0{,}027$). Individuals who take duloxetine present a higher score in global satisfaction, while individuals who take fluoxetine presents a lower value on global satisfaction. In addition, the variable "adverse effects" was statistically associated with the use of NSAIDs and tramadol ($p = 0{,}025$ and $p = 0{,}003$). In fact, individuals who take both drugs present a lower score on adverse effects. The described values can be observed on the attachment, table 10 (attachment 8).

4. Discussion

Socio-demographic characterization

This study intends to characterize the pharmacotherapeutic profile and impact of FM in a sample of Portuguese patients. In the study there was a clear prevalence of female patients (96,6%) compared to male (3,4%). Epidemiological studies in several countries around the world also show a higher prevalence of FM among females in relation to males (Branco et al., 2010; Marques et al., 2017; Neumann & Buskila, 2003). This result may be related to the fact that chronic pain and depression is closely related to the female gender, and possibly modulated by estrogens. Pamuk et al., suggests a relationship between sex hormones and female prevalence; on their study, menopause women present more FM symptoms than premenopausal women (Maurer, Lissounov, Knezevic, Candido, & Knezevic, 2016; Pamuk & Çakir, 2005). In addition, Munce at al., indicates a bidirectional association with pain and depression: a vicious cycle that can be explained for low norepinephrine and serotonin, both related to depression and perception of pain (Munce & Stewart, 2007).

FM can be developed at any age, however, is uncommon in young ages: only 10 participants presents an age less than 30 years. In mostly surveys the peak is around the middle age (30-50 years) or after the 50's. A study of Branco et al, shows that Portugal is the country with the youngest population (mean: 41 years), in the same study, the mean age in five European countries (France, Germany, Italy, Portugal, and Spain), is about 56 years old (Branco et al., 2010; Clauw, 2014; Queiroz, 2013). The mean age of the participants in the present study was 47,26 years, which is in agreement with the existing literature (Branco et al., 2010; Clauw, 2014; Queiroz, 2013).

Regarding to others social demographic aspects, the population was mainly married or single (66,7% and 20,9%, respectively). The literature is not clear about the marital status, with different authors finding higher frequency in widowed, divorced or married people (Queiroz, 2013). Opposing to existing literature, who relates the FM with low education (Bannwarth et al., 2009; Branco et al., 2010; Mas et al., 2008), the majority of the sample of the present study had a college degree or completed high school (54,8% and 28,8%, respectively). Mas et al., reports a lower prevalence of active work in FM patients. However, in this sample it's possible to observe that 75,5% of the patients are currently working, who corresponds to a great majority of the sample (table 4) (Mas et al., 2008). Concerning the residence area, the literature is clear about the prevalence of FM in rural areas, however it's not possible to demonstrate in the present study, since the questionnaire only refers to the different areas of Portugal, and there was no question addressing if it was a rural or urban area (Queiroz, 2013).

Considering the diagnosis time, it was possible to observe that the bigger part of the sample was diagnosed less than five years (table 2), what gives a mean age of diagnosis of 45,43 years. Although FM was recognized as a rheumatic disease in 1992 by the World Health Organization, only

in 2016 the DGS recognized officially FM as a disease (Direção-Geral da Saúde, 2017). The relationship between this recent diagnosis time (<5 years) can be explained by the recent recognition of FM in Portugal. It must be noted that the year of the onset of symptoms was not asked, that means the individuals could already have the symptoms and have not yet been diagnosed.

Fibromyalgia Impact Questionnaire (FIQ)

The literature agrees that FM is one of the most disabling disease. Mas et al., report that FM affects more quality of life than other rheumatic disease such as lupus erythematosus, RA, or ankylosing spondylitis (Mas et al., 2008). Verbunt et al., also points out that patients with FM have a lower quality of life than the general population. This decrease in quality life is related to the disability that patients feel in various aspects of daily life, such as functional capacity, professional life, quality of sleep or psychiatric disorders (Martinez et al., 1998; Mas et al., 2008; Verbunt et al., 2008). The FIQ, who was validated in 2006 for the Portuguese language, can help health professionals to study the functional capacity of a patient with FM and further help to manage the disease with the pharmacological and non-pharmacological treatment. In the present study, the mean of the 10 items who made the FIQ was analyzed (table 3): fatigue, rested and stiffness are the points with more impact in the participants, comparatively to work missed and physical impairment who presents the lowest mean score. Green et al., also indicates stiffens, pain muscle and awakening tired the symptoms more reported by FM patients (Green et al., 2005). The mean of the FIQ was 64,89, which indicates a relevant impact in quality life, once the score is above 50, and nearest 70, who indicates a severe impact. Martins et al., presents on his survey, also with Portuguese population, a mean score of 63,76 and also indicates a less score in missed work, as in the present study (Martins et al., n.d.) In the survey of Ruiz-Montero et al., the FIQ was applied in the three areas of Europe (North, South and Center). The south area corresponds to Spain where the FIQ presents the higher score: 64,80, comparatively to the north area (62,85) and center area (60,87). In all three areas, the missed work dimension was the one with the lowest score. Is also observed that the population of the northern zone has less depression and anxiety prevalence (Ruiz-Montero et al., 2019).

About the association between the FIQ score and some demographic variables (table 4), it can be concluded that age can be associated with the FIQ score. Older individuals have a higher FIQ score, this may be related to the fact that older people have more comorbidities, as other illnesses and greater pain sensitivity. Although, Green et al, didn't report any relation between age and the FIQ score (p> 0,673) (Green et al., 2005).

Regarding the area of residence, individuals living in the islands (Azores and Madeira) have a lowest FIQ score, this relationship may be associated with the more isolation who leads to less stress

(Clauw, 2014). However, the frequency of participants living in the islands is much smaller compared to those residing on the continent.

Pharmacotherapeutic Characterization

Given the substantial number of symptoms present in a patient with FM, it was not expected that only one drug will be effective in improving symptoms. Combination therapy is extremely common in these individuals and drugs are commonly prescribed according to patient's needs. Robinson et al., state that over 75% of the FM population takes two or more drugs to treat the disease (Robinson et al., 2013). The mean of drugs used to manage FM in this sample was 2,85; with a maximum of seven drugs and a minimum of one.

Considering the treatment to manage FM, is important to highlight that there's no drug approved to FM in Portugal or any country of the Europe, all the prescribed drugs are off-label (Chinn et al., 2016). As also said before, FDA approves three drugs: pregabalin, duloxetine and milnacipran, however TCA drugs are also prescribed and in many cases as a first line therapy (Robinson et al., 2013). In the present study it's possible to observe that NSAIDs and anxiolytic drugs are the most common drugs used for FM patients (table 5). Regarding to NSAIDs, several studies discourage the use of these drugs due to its peripheral action, and chronic use who can lead to harmful adverse effects. However, the high frequency of their use in this study can be explained by the easy access, since some of them are over the counter drugs (Green et al., 2005; Kia & Choy, 2017; Macfarlane et al., 2017; Robinson et al., 2013; Schmidt-Wilcke & Clauw, 2011). Anxiolytic drugs are the second most used drugs in the study; however, this group is not clearly associated with an improvement in pain. In fact, its use might be correlated with the effect in sleep disorders, one of the most common symptoms in FM. Like NSAIDS, this group in not recommended to manage FM for EULAR and Scientific Medical Societies in Germany (AWMF), due to his addiction effect (Kia & Choy, 2017; Schmidt-Wilcke & Clauw, 2011)Tramadol (Tramal®), an opioid drug, but also a reuptake inhibitor of serotonin, also presents a high frequency use in this study (11,7%). However, tramadol use in FM is controverse: while EULAR and Canada guideline recommend is use, AWMF don't recommend is use due to lack of solid data (Kia & Choy, 2017).

Cyclobenzaprine (Flexiban®), one of the drug in the ATC group, is also one the most used drugs to manage FM (15,5%), is not only efficient in improvement pain but also in fatigue and sleep disturbance due to his muscle relaxant action, and it's recommend by EULAR (Kia & Choy, 2017; Schmidt-Wilcke & Clauw, 2011). Amitriptyline (ADT®), is also recommend by AWMF for first line therapy, and in low doses by EULAR; however only presents a 5% of response in the study (Kia & Choy, 2017).

Regarding the drugs approved by FDA, Pregabalin (Lyrica®) and Duloxetine (Cymbalta ®), present a considerable frequency (n=42 and n=48, respectively) comparatively with the study of Green et al (Green et al., 2005). Pregabalin is recommended by EULAR and AWMF, when the treatment with amitriptyline (ADT®) is not efficient (Kia & Choy, 2017). Duloxetine (Cymbalta ®), has a higher frequency of responses in the study (n=48): the AWMF recommend this drug when a depression disorder his associate to FM due to his effect on serotonin (Kia & Choy, 2017; Macfarlane et al., 2017), and this comorbidity might explain is elevated prescription. In contrast, only two individuals actually take milnacipran (Ixel®) for FM management, a drug also approved by FDA. Although pirlindole (Implementor ®) shows better results comparatively to placebo, there was no reference to is use in the study. This result can be explained for the fact that IMAO drugs have harmful effects when interacts with other medication such as SSRI (Macfarlane et al., 2017).

Patients with FM report high rates of change increase or discontinuation of therapy associated with lack of efficacy or adverse effects, which are not well tolerated by patients. In this study, a large part of the sample (67,2%) have already been treated with other drugs, being the most pointed reason for the change the lack of effectiveness. This result is in agreement with the study of Robinson et al. (Robinson et al., 2013).

TSQM

The TSQM is a tool which allows to evaluate patient's experience and satisfaction with the medication they take. This tool score from 0 to 100, where higher scores indicate a better satisfaction. In the present study is possible to observe that the effectiveness and global satisfaction present a lower score (45,01 and 46,25). The low effectiveness score can be supported for the diagnosis time (the major part of the sample was diagnosed under 5 years), which means the complete control of the disease was not accomplish yet. In the survey of Lauche et al., it's possible to observe that people who have been diagnosed longer has higher satisfaction in general, who contraries the results found in this study. However, the large percentage of the sample in the study of Lauche et al. shows a low to moderate satisfaction to the treatment (Lauche et al., 2013).

Regarding the relation between FIQ and TSQM, the convenience and the adverse effects appeared to be statistically related. These two variables present an inverse correlation: individuals with a lower score of FIQ present a higher score in TSQM. Individuals who have a lowest FIQ score are more satisfied with the adverse effects (don't have significant adverse effects) and with the convenient (it's easy to take the medication). A lower FIQ score, means that the disease has a minor impact in the life of a FM patient: the medication is effective, has no adverse effects and is convenient to take (Lauche et al., 2013).

Nöller et al., state that people diagnosed longer have a higher satisfaction with treatment, which may be related to a mental adjustment made to the disease, in contrast, when observed the relationship between the TSQM and the time of diagnosis, in this study, is possible to observe that the individuals diagnosed longer present the lowest TSQM value on the global satisfaction dimension, which translates into non-satisfaction of the treatment (Nöller & Sprott, 2003). In other hand, when observed the association between the TSQM and number of drugs, patients who take more drugs had a lower score in adverse effects dimension of TSQM. The reason for this result may be related to the fact that the patient experienced adverse effects, possibly related to drug interactions (Clauw, 2014).

When compared the score of TSQM with the different drugs, it can be noted that the group taking NSAIDs and Tramadol (Tramal ®) has a lower adverse effects score, which may be related to the side effects experienced when NSAIDs when used chronically, such as gastrointestinal problems and in tramadol's case, tolerance and withdrawal symptoms (Clauw, 2014). Other significant value was observed in the dimensions global satisfaction of the TSQM and individuals that take fluoxetine (yes) present a lower score, in other hand, individuals who take duloxetine (yes) had a higher score in global satisfaction. One explanation for these results could be that NRIS, such as duloxetine, have an improved effect on pain as they are not only serotonin inhibitors such as fluoxetine, an SSRI, but also norepinephrine, both involved not only in depression but also in pain inhibition (Clauw, 2014).

4.1 Limitations

However, despite the promising results reported here, some points should be highlighted. One limitation of the study was the asymmetry of the sample regarding gender. Although the prevalence of FM is higher in women, men are also affected and are not representative in the sample, which does not allow to have in-depth knowledge about the male reality. Also, the fact that the questionnaire was autofill, leads each individual to interpret certain questions in their own way. Additionally, non-pharmacological treatment, the existence of other diseases, the age of onset of symptoms, or if lives in a rural or urban area where not inquired to the patients. It is also noteworthy that the perception of the impact of the disease and the treatment performed may change over time, which could be solved with a longitudinal study. Another limitation of the study is not being clear which criteria was used to diagnose the disease.

5. Conclusion and future perspectives

In this study, it was possible to observe that FM had a negative impact on life of a sample of Portuguese patients. This impact can range from getting out of bed to work. The disease can affect patient's functional capacity, not only physically but also psychologically. This influence can probably be due to is correlation with disorders like depression and anxiety. In our sample, the impact of FM was associated with age, likely due to the presence of other comorbidities.

Drug treatment was found to have a positive impact on patient's life. In fact, it was observed that the correct treatment is essential to improve the symptoms, with a consequent improvement in health conditions and functional capacity. FM patients tend to take two or more drugs, and the most used in the sample were NSAIDs and anxiolytics. However, and accordingly to different guidelines, they are not the most indicated drugs for FM treatment. The referenced medication to treat FM, such as depressants (TCA, SSIR and SNIR) and anticonvulsants were found to have a lower frequency in this sample.

Treatment satisfaction is essential in FM patient. The two most important factors affecting treatment satisfaction were the presence of adverse effects and drug efficacy, which are also correlated with the drug class.

The request for social support and adaptation in a professional and familiar life must also be addressed, not only to improve the well-being of FM patients, but also the ones around them. Further research is needed to unravel effective therapies that can ameliorating the various symptoms of FM, with minimal adverse effects, in order to ensure treatment adherence and further improve patient's quality of life.

6. References

Bannwarth, B., Blotman, F., Roué-Le Lay, K., Caubère, J. P., André, E., & Taïeb, C. (2009). Fibromyalgia syndrome in the general population of France: A prevalence study. *Joint Bone Spine*, *76*(2), 184–187. https://doi.org/10.1016/j.jbspin.2008.06.002

Bernard, A. L., Prince, A., & Edsall, P. (2000). Quality of life issues for fibromyalgia patients. *Arthritis & Rheumatism*, *13*(1), 42–50. https://doi.org/10.1002/1529-0131(200002)13:1<42::aid-art7>3.3.co;2-i

Bradley, L. A. (2009). Pathophysiology of Fibromyalgia. *American Journal of Medicine*, *122*(12 SUPPL.), S22–S30. https://doi.org/10.1016/j.amjmed.2009.09.008

Branco, J. C., Bannwarth, B., Failde, I., Abello Carbonell, J., Blotman, F., Spaeth, M., … Matucci-Cerinic, M. (2010a). Prevalence of fibromyalgia: A survey in five European countries. *Seminars in Arthritis and Rheumatism*, *39*(6), 448–453. https://doi.org/10.1016/j.semarthrit.2008.12.003

Branco, J. C., Bannwarth, B., Failde, I., Abello Carbonell, J., Blotman, F., Spaeth, M., … Matucci-Cerinic, M. (2010b). Prevalence of fibromyalgia: A survey in five European countries. *Seminars in Arthritis and Rheumatism*. Elsevier Inc. https://doi.org/10.1016/j.semarthrit.2008.12.003

Burckhardt, C.S., Clark, S.R, & Bennett, R. (1991). The Fibromyalgia Impact Questionnaire: Development and validation. *Journal of Reumathology*, *18*, 728–734.

Cagnie, B., Coppieters, I., Denecker, S., Six, J., Danneels, L., & Meeus, M. (2014). Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI. *Seminars in Arthritis and Rheumatism*, *44*(1), 68–75. https://doi.org/10.1016/j.semarthrit.2014.01.001

Calandre, E. P., Rico-Villademoros, F., & Slim, M. (2015). An update on pharmacotherapy for the treatment of fibromyalgia. *Expert Opinion on Pharmacotherapy*, *16*(9), 1347–1368. https://doi.org/10.1517/14656566.2015.1047343

Chinn, S., Caldwell, W., & Gritsenko, K. (2016). Fibromyalgia Pathogenesis and Treatment Options Update. *Current Pain and Headache Reports*. https://doi.org/10.1007/s11916-016-0556-x

Clauw, D. J. (2014). Fibromyalgia: A clinical review. *JAMA - Journal of the American Medical Association*, *311*(15), 1547–1555. https://doi.org/10.1001/jama.2014.3266

Direção-Geral da Saúde. (2010). Programa Nacional de Controlo da Dor - Relatório de Actividades de Janeiro a Julho de 2010. Retrieved from https://www.dgs.pt/paginas-de-sistema/saude-de-a-a-z/programa-nacional-de-controlo-da-dor.aspx

Direção-Geral da Saúde. (2017). *Abordagem Diagnóstica da Fibromialgia*. *Serviço Nacional de Saúde*.

Dymon, B. T. E., Pharm, D., Rogers, S. J., Pharm, D., Hunsinger-norris, D. M., Pharm, D., & Aq-

cardiology, B. (2015). Fibromyalgia, 5–18.

Epstein, S. A., Kay, G., Clauw, D., Heaton, R., Klein, D., Krupp, L., … Zisook, S. (1999). Psychiatric disorders in patients with fibromyalgia: A multicenter investigation. *Psychosomatics*, *40*(1), 57–63. https://doi.org/10.1016/S0033-3182(99)71272-7

Galvez-Sánchez, C. M., Duschek, S., & Del Paso, G. A. R. (2019). Psychological impact of fibromyalgia: Current perspectives. *Psychology Research and Behavior Management*, *12*, 117–127. https://doi.org/10.2147/PRBM.S178240

Gittins, R., Howard, M., Ghodke, A., Ives, T. J., & Chelminski, P. (2017). The Accuracy of a Fibromyalgia Diagnosis in General Practice. *Pain Medicine*, 1–8. https://doi.org/10.1093/pm/pnx155

Goldenberg, D. L., Burckhardt, C., & Crofford, L. (2004). Management of fibromyalgia syndrome. *Journal of the American Medical Association*, *292*(19), 2388–2395. https://doi.org/10.1001/jama.292.19.2388

Green, M. J., Peterson, S. K., Baker, M. W., Friedman, C., Harper, G. R., Rubinstein, W. S., … Mauger, D. T. (2005). Characterization of Fibromyalgia Symptoms in Patients 55 to 95 Years Old: a Longitudinal Study Showing Symptom Persistence with Suboptimal Treatment, *7*(4), 221–229. https://doi.org/10.1016/j.molcel.2009.10.020.The

Harte, S. E., Harris, R. E., & Clauw, D. J. (2002). The neurobiology of central sensitization. *Journal of Musculoskeletal Pain*, *10*(1–2), 23–33. https://doi.org/10.1300/J094v10n01_03

Hawkins, R. (2013). Fibromyalgia: A Clinical Update. *The Journal of the American Osteopathic Association*, *113*(9), 680–689. https://doi.org/10.7556/jaoa.2013.034

IQVIA. (2018). User Manual for the Treatment Satisfaction Questionnaire for Medication (TSQM), (October), 1–40.

Kia, S., & Choy, E. (2017). Update on treatment guideline in fibromyalgia syndrome with focus on pharmacology. *Biomedicines*, *5*(2), 1–24. https://doi.org/10.3390/biomedicines5020020

Kumar, R. (2014). *Research Methodology: A Step-by-Step Guide for Begginers* (second edi). London: SAGE Publications.

Lauche, R., Häuser, W., Jung, E., Erbslöh-Möller, B., Gesmann, M., Kühn-Becker, H., … Langhorst, J. (2013). Patient-related predictors of treatment satisfaction of patients with fibromyalgia syndrome: Results of a cross-sectional survey. *Clinical and Experimental Rheumatology*, *31*(SUPPL.79), 34–40.

Macfarlane, G. J., Kronisch, C., Dean, L. E., Atzeni, F., Häuser, W., Flub, E., … Jones, G. T. (2017). EULAR revised recommendations for the management of fibromyalgia. *Annals of the Rheumatic Diseases*, *76*(2), 318–328. https://doi.org/10.1136/annrheumdis-2016-209724

Mansoor M., A., R., J. Y., Alan D., K., & Richard D., U. (2018). Evidence-Based Non-Pharmacological Therapies for Fibromyalgia. *Current Pain and Headache Reports*, *22*(5), 1–5.

https://doi.org/10.1007/s11916-018-0688-2 LK - http://hy8fy9jj4b.search.serialssolutions.com/?sid=EMBASE&sid=EMBASE&issn=15343081&id=doi:10.1007%2Fs11916-018-0688-2&atitle=Evidence-Based+Non-Pharmacological+Therapies+for+Fibromyalgia&stitle=Curr.+Pain+Headache+Rep.&title=Current+Pain+and+Headache+Reports&volume=22&issue=5&spage=&epage=&aulast=Aman&aufirst=Mansoor+M.&auinit=M.M.&aufull=Aman+M.M.&coden=CPHRG&isbn=&pages=-&date=2018&auinit1=M&auinitm=M.

Marques, A. P., Santo, A. de S. do E., Berssaneti, A. A., Matsutani, L. A., & Yuan, S. L. K. (2017). A prevalência de fibromialgia: atualização da revisão de literatura. *Revista Brasileira de Reumatologia*, *57*(4), 356–363. https://doi.org/10.1016/j.rbr.2016.10.004

Martinez, J. E., Barauna Filho, I. S., Kubokawa, K., Pedreira, I. S., Machado, L. A., & Cevasco, G. (1998). Análise crítica de parâmetros de qualidade de vida de pacientes com fibromialgia. *Acta Fisiátrica*, *5*(2). https://doi.org/10.5935/0104-7795.19980001

Martins, R., Henriques, A., Andrade, A., Moreira, H., Albuquerque, C., Cunha, M., … Martins, L. (n.d.). Impacto da Fibromialgia na Qualidade de vida dos Doentes.

Mas, A. J., Carmona, L., Valverde, M., Ribas, B., Navarro, F., Ortiz, A. M., … Yelin, E. (2008a). Prevalence and impact of fibromyalgia on function and quality of life in individuals from the general population: Results from a natiowide study in Spain. *Clinical and Experimental Rheumatology*, *26*(4), 519–526.

Mas, A. J., Carmona, L., Valverde, M., Ribas, B., Navarro, F., Ortiz, A. M., … Yelin, E. (2008b). Prevalence and impact of fibromyalgia on function and quality of life in individuals from the general population: Results from a natiowide study in Spain. *Clinical and Experimental Rheumatology*, *26*(4), 519–526.

Matthey, A., Cedraschi, C., Piguet, V., Besson, M., Chabert, J., Daali, Y., … Desmeules, J. (2013). Dual reuptake inhibitor milnacipran and spinal pain pathways in fibromyalgia patients: A randomized, double-blind, placebo-controlled trial. *Pain Physician*, *16*(5), 553–562. https://doi.org/10.1016/j.clinthera.2013.07.026

Maurer, A. J., Lissounov, A., Knezevic, I., Candido, K. D., & Knezevic, N. N. (2016). Pain and sex hormones: a review of current understanding. *Pain Management*, *6*(3), 285–296. https://doi.org/10.2217/pmt-2015-0002

Munce, S. E. P., & Stewart, D. E. (2007). Gender differences in depression and chronic pain conditions in a national epidemiologic survey. *Psychosomatics*, *48*(5), 394–399. https://doi.org/10.1176/appi.psy.48.5.394

Neumann, L., & Buskila, D. (2003). Epidemiology of fibromyalgia. *Current Pain and Headache Reports*. https://doi.org/10.1007/s11916-003-0035-z

Nöller, V., & Sprott, H. (2003). Prospective epidemiological observations on the course of the disease in fibromyalgia patients. *Journal of Negative Results in BioMedicine*, *2*, 1–6. https://doi.org/10.1186/1477-5751-2-1

Pamuk, Ö.¨N., & Çakir, N. (2005). The variation in chronic widespread pain and other symptoms in fibromyalgia patients. The effects of menses and menopause. *Clinical and Experimental Rheumatology*, *23*(6), 778–782.

Pillemer, S. R., Bradley, L. A., Crofford, L. J., Moldofsky, H., & Chrousos, G. P. (1997). The neuroscience and endocrinology of fibromyalgia. In *Arthritis and Rheumatism* (Vol. 40, pp. 1928–1939). https://doi.org/10.1002/art.1780401103

Queiroz, L. P. (2013). Worldwide epidemiology of fibromyalgia. *Current Pain and Headache Reports*, *17*(8). https://doi.org/10.1007/s11916-013-0356-5

Robinson, R. L., Kroenke, K., Williams, D. A., Mease, P., Chen, Y., Faries, D., … Mccarberg, B. (2013). Longitudinal observation of treatment patterns and outcomes for patients with Fibromyalgia: 12-month findings from the REFLECTIONS study. *Pain Medicine (United States)*, *14*(9), 1400–1415. https://doi.org/10.1111/pme.12168

Rosado, L., Pedro, J., & Branco, J. C. (2006). Adaptação Cultural e Validação do «fibromyalgia impact questionnaire» – versão portuguesa. *Orgão Oficial Da Sociedade Portuguesa de Reumatologia*.

Ruiz-Montero, P. J., Segura-Jimenez, V., Alvarez-Gallardo, I. C., Nijs, J., Mannerkorpi, K., Delgado-Fernandez, M., & van Wilgen, C. P. (2019). Fibromyalgia Impact Score in Women with Fibromyalgia Across Southern, Central, and Northern Areas of Europe. *Pain Physician*, *22*(5), E511–E516. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/31561664

Russell, I. J., Orr, M. D., Littman, B., Vipraio, G. A., Alboukrek, D., Michalek, J. E., … MacKillip, F. (1994). Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. *Arthritis & Rheumatism.*, *37*(11), 1593–1601. https://doi.org/10.1002/art.1780371106

Sancassiani, F., Machado, S., Ruggiero, V., Cacace, E., Carmassi, C., Gesi, C., … Carta, M. G. (2017). The management of fibromyalgia from a psychosomatic perspective: an overview. *International Review of Psychiatry*, *29*(5), 473–488. https://doi.org/10.1080/09540261.2017.1320982

Schmidt-Wilcke, T., & Clauw, D. J. (2011). Fibromyalgia: From pathophysiology to therapy. *Nature Reviews Rheumatology*. Nature Publishing Group. https://doi.org/10.1038/nrrheum.2011.98

Sim, J., & Adams, N. (1999). Systematic Review of Randomized Controlled Trials of Nonpharmacological Interventions for Fibromyalgia. *Bailliere's Best Practice and Research in Clinical Rheumatology*, *13*(3), 507–523. https://doi.org/10.1053/berh.1999.0041

Tzellos, T. G., Toulis, K. A., Goulis, D. G., Papazisis, G., Zampeli, V. A., Vakfari, A., & Kouvelas, D. (2010).

Gabapentin and pregabalin in the treatment of fibromyalgia: A systematic review and a meta-analysis. *Journal of Clinical Pharmacy and Therapeutics*, *35*(6), 639–656. https://doi.org/10.1111/j.1365-2710.2009.01144.x

Verbunt, J. A., Pernot, D. H. F. M., & Smeets, R. J. E. M. (2008). Disability and quality of life in patients with fibromyalgia. *Health and Quality of Life Outcomes*, *6*, 1–8. https://doi.org/10.1186/1477-7525-6-8

Wiffen Philip, J., Derry, S., Moore, R. A., Aldington, D., Cole, P., Rice Andrew, S. C., … Kalso Eija, A. (2013). Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews*, (11). https://doi.org/10.1002/14651858.CD010567.pub2

Wolfe, F, Smythe, H. A., Yunus, M. B., Bennett, R. M., Bombardier, C., Goldenberg, D. L., … Clark, P. (1990). The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis and Rheumatism*, *33*(2), 160–172. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/2306288

Wolfe, Frederick, Clauw, D. J., Fitzcharles, M. A., Goldenberg, D. L., Katz, R. S., Mease, P., … Yunus, M. B. (2010). The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care and Research*, *62*(5), 600–610. https://doi.org/10.1002/acr.20140

Yunus, M. B., & İnanici, F. (2001). Chapter 16 - Clinical characteristics and biopathophysiological mechanisms of fibromyalgia syndrome. *Myofascial Pain and Fibromyalgia Syndromes*, 351–377. https://doi.org/https://doi.org/10.1016/B978-0-443-07003-7.50021-9

7. Attachments

Attachment 1 – Autorizations MYOS and APJOF

APJOF - Associação Portuguesa de Jovens com Fibromialgia 19:21

Re: Pedido de colaboração

Para: Joana Pereira

Boa tarde Joana,

Teremos todos o gosto em ajudar!
Envie-nos o link do inquérito que iremos partilhar nas nossas redes sociais e contactos

Cumprimentos
Joana Vicente

APJOF - Associação Portuguesa de Jovens com Fibromialgia

Apartado 000019 EC
2460-997 São Martinho do Porto

Site

Facebook | Instagram | Twitter | YouTube

Joana Pereira <joanapereiraip@gmail.com> escreveu no dia segunda, 22/07/2019 à(s) 17:14:

Ver mais de Joana Pereira

Attachment 2 – Socio-demographic characterization

1º Parte - Questionário Sociodemográfico

Instruções: Deverá assinalar com um (X) a resposta correspondente à sua situação.

Sexo: Feminino ____ Masculino ____

Idade: _____

Estado Civil:

Solteiro/a _____

Casado/a _____

Divorciado/a _____

Viúvo/a _____

Zona de residência:

Região Norte _____

Região Centro _____

Região Sul _____

Açores/Madeira_____

Habilitações Literárias:

4º ano _____

6º ano_____

9º ano _____

12º ano _____

Ensino Superior _____

Situação Profissional:

Empregado/a: _____

Desempregado/a: _____

Reformado/a: _____

Estudante: _____

Há quanto tempo foi diagnosticado com a doença?

_____ ano/s.

Attachment 3 – Fibromyalgia Impact Questionnaire Portuguese Version (FIQ-P)

2ª Parte - *Fibromyalgia Impact Questionnaire* (versão portuguesa) - FIQ-P

INSTRUÇÕES: Nas perguntas 1 a 11 por favor faça um círculo no número que, em relação à última semana, melhor descreve a maneira como, em geral, foi capaz de executar as tarefas indicadas. Se habitualmente não faz uma dessas tarefas risque essa pergunta.

Foi capaz de:	Sempre	Quase sempre	Quase nunca	Nunca
1. Ir às compras**?**	0	1	2	3
2. Tratar da roupa na máquina de lavar/secar?	0	1	2	3
3. Cozinhar?	0	1	2	3
4. Lavar louça à mão?	0	1	2	3
5. Aspirar a casa?	0	1	2	3
6. Fazer as camas?	0	1	2	3
7. Andar vários quarteirões (200 a 500 metros)?	0	1	2	3
8. Visitar a família ou os amigos?	0	1	2	3
9. Tratar das plantas ou praticar o seu passatempo?	0	1	2	3

10. Se deslocar, no seu próprio carro ou em transportes públicos? 0 1 2 3

11. Subir as escadas? 0 1 2 3

12. Na última semana, em quantos dias se sentiu bem?

0 1 2 3 4 5 6 7

13. Na última semana, quantos dias faltou ao trabalho e/ou não realizou as tarefas domésticas, devido à fibromialgia?

0 1 2 3 4 5 6 7

INSTRUÇÕES: Nas perguntas que se seguem, assinale um ponto na linha que melhor indica o modo como, em geral, se sentiu na **última semana.**

14. Nos dias que trabalhou, quanto é que a sua doença – Fibromialgia - interferiu no seu trabalho?

Trabalhei sem problemas • ___|___|___|___|___|___|___|___|___|___|___|___• Tive grande dificuldade no trabalho

15. Que intensidade teve a sua dor?

Não tive dor • ___|___|___|___|___|___|___|___|___|___|___|___• Tive dor intensa

16. Que cansaço sentiu?

Não senti cansaço • ___|___|___|___|___|___|___|___|___|___|___|___• Senti um cansaço enorme

17. Como se sentiu quando se levantava de manhã?

Acordei bem disposta • ___|___|___|___|___|___|___|___|___|___|___|___• Acordei muito cansada

18. Que rigidez sentiu?

Não tive rigidez • ___ |___ | ___ | ___ | ___ |___ | ___ | ___ | ___ | ___ | ___ • Senti muita rigidez

19. Sentiu-se nervosa ou ansiosa?

Não tive ansiedade • ___ | ___ | ___ | ___ | ___ |___ | ___ | ___ | ___ | ___ | ___ • Senti-me muito ansiosa

20. Sentiu-se triste ou deprimida?

Não me senti deprimida • ___ | ___ | ___ | ___ | ___ |___ | ___ | ___ | ___ | ___ | ___ • Senti-me muito deprimida

Attachment 4 – Pharmacotherapeutic characterization

3ª parte – Caracterização farmacoterapêutica

Instruções: Deverá assinalar com um (X) a resposta correspondente à sua situação.

1. Assinale qual ou quais o/os medicamento/os que está a tomar, para o tratamento da **fibromialgia** (pode assinalar mais que uma opção).

   Amitriptilina (ADT®)_____

   Ciclobenzapirina (Flexiban®)_____

   Fluoxetina (Prozac®)_____

   Duloxetina (Cymbalta®)_____

   Milnaciprano (Ixel®)_____

   Gabapentina (Neurontin®)_____

   Pregabalina (Lyrica®)_____

   Tramadol (Tramal®)_____

   Pirlindole (Implementor®)_____

   Venlafaxina (Efexor®)_____

   Bupropiom (Elontril®, Wellbutrin®)_____

   Anti-inflamatórios não esteroides (ibuprofeno, naproxeno, piroxicam) _____

   Ansiolíticos (lorazepam, alprazolam, clonazepam) _____

   Outros (indique qual/quais) _____

   _____.

2. É o primeiro tratamento que realiza para a terapêutica da doença?

   Sim_____ (Passe diretamente para a pergunta **5)**

   Não_____

3. Indique quais os medicamentos que tomou no **passado**, para o tratamento da fibromialgia.

   _____

   _____

4. Qual o motivo que levou à alteração da medicação?

   Efeitos adversos_____

   Falta de eficácia_____

   Outro _____ Qual? _____

5. Quem foi o prescritor do/s medicamento/s que toma **atualmente** para a fibromialgia?

   Médico de família_____

   Serviço de Urgências_____

   Reumatologista_____

   Outro _____ Qual? _____

Attachment 5 – TSQM V 1.4 Portuguese

TSQM *(versão 1.4)*

Questionário sobre Satisfação com o Medicamento (versão portuguesa do TSQM)

Instruções: Por favor dedique algum tempo a pensar sobre o seu nível de satisfação ou insatisfação com o medicamento que se encontra a tomar neste ensaio clínico. Estamos interessados na sua avaliação da eficácia, dos efeitos secundários e da conveniência do medicamento *durante as últimas duas ou três semanas ou desde a última vez que usou o medicamento*. Para cada questão, marque somente a resposta que melhor corresponde à sua experiência.

1. Até que ponto está satisfeito ou insatisfeito com a eficácia do medicamento usado em evitar ou tratar a sua doença?

☐1 Extremamente insatisfeito
☐2 Muito insatisfeito
☐3 Insatisfeito
☐4 Mais ou menos satisfeito
☐5 Satisfeito
☐6 Muito satisfeito
☐7 Extremamente satisfeito

2. Até que ponto está satisfeito ou insatisfeito com a maneira como o medicamento alivia os seus sintomas?

☐1 Extremamente insatisfeito
☐2 Muito insatisfeito
☐3 Insatisfeito
☐4 Mais ou menos satisfeito
☐5 Satisfeito
☐6 Muito satisfeito
☐7 Extremamente satisfeito

3. Até que ponto está satisfeito ou insatisfeito com o tempo que o medicamento demora até começar a fazer efeito?

☐1 Extremamente insatisfeito
☐2 Muito insatisfeito
☐3 Insatisfeito
☐4 Mais ou menos satisfeito
☐5 Satisfeito
☐6 Muito satisfeito
☐7 Extremamente satisfeito

4. Sente algum efeito secundário (colateral) causado por este medicamento?

☐1 Sim
☐0 Não (Neste caso, passe para a Pergunta 9.)

5. Até que ponto são incómodos os efeitos secundários do medicamento que se encontra a tomar para tratar a sua doença?

☐1 Extremamente incómodos
☐2 Muito incómodos
☐3 Mais ou menos incómodos
☐4 Um pouco incómodos
☐5 Não são incómodos

6. Até que ponto os efeitos secundários interferem com a sua saúde física e a sua capacidade de viver uma vida normal (isto é, força, nível de energia, etc.)?

☐1 Muitíssimo
☐2 Muito
☐3 Mais ou menos
☐4 Muito pouco
☐5 Nada

7. Até que ponto os efeitos secundários interferem com as suas funções mentais (por exemplo, capacidade de pensar com clareza, permanecer acordado, etc.)?

☐1 Muitíssimo
☐2 Muito
☐3 Mais ou menos
☐4 Muito pouco
☐5 Nada

8. Até que ponto os efeitos secundários do medicamento têm afectado a sua satisfação geral com o medicamento?

☐1 Muitíssimo
☐2 Muito
☐3 Mais ou menos
☐4 Muito pouco
☐5 Nada

9. Qual é o grau de facilidade ou dificuldade em utilizar o medicamento na sua forma actual de administração?

☐1 Extremamente difícil
☐2 Muito difícil
☐3 Difícil
☐4 Mais ou menos fácil
☐5 Fácil
☐6 Muito fácil
☐7 Extremamente fácil

10. Qual é o grau de facilidade ou dificuldade em planear cada uso do medicamento?

☐1 Extremamente difícil
☐2 Muito difícil
☐3 Difícil
☐4 Mais ou menos fácil
☐5 Fácil
☐6 Muito fácil
☐7 Extremamente fácil

11. Até que ponto é conveniente ou inconveniente tomar o medicamento segundo as instruções?

☐1 Extremamente inconveniente
☐2 Muito inconveniente
☐3 Inconveniente
☐4 Mais ou menos conveniente
☐5 Conveniente
☐6 Muito conveniente
☐7 Extremamente conveniente

12. De modo geral, até que ponto está confiante de que tomar este medicamento é bom para si?

☐1 Nada confiante
☐2 Um pouco confiante
☐3 Mais ou menos confiante
☐4 Muito confiante
☐5 Extremamente confiante

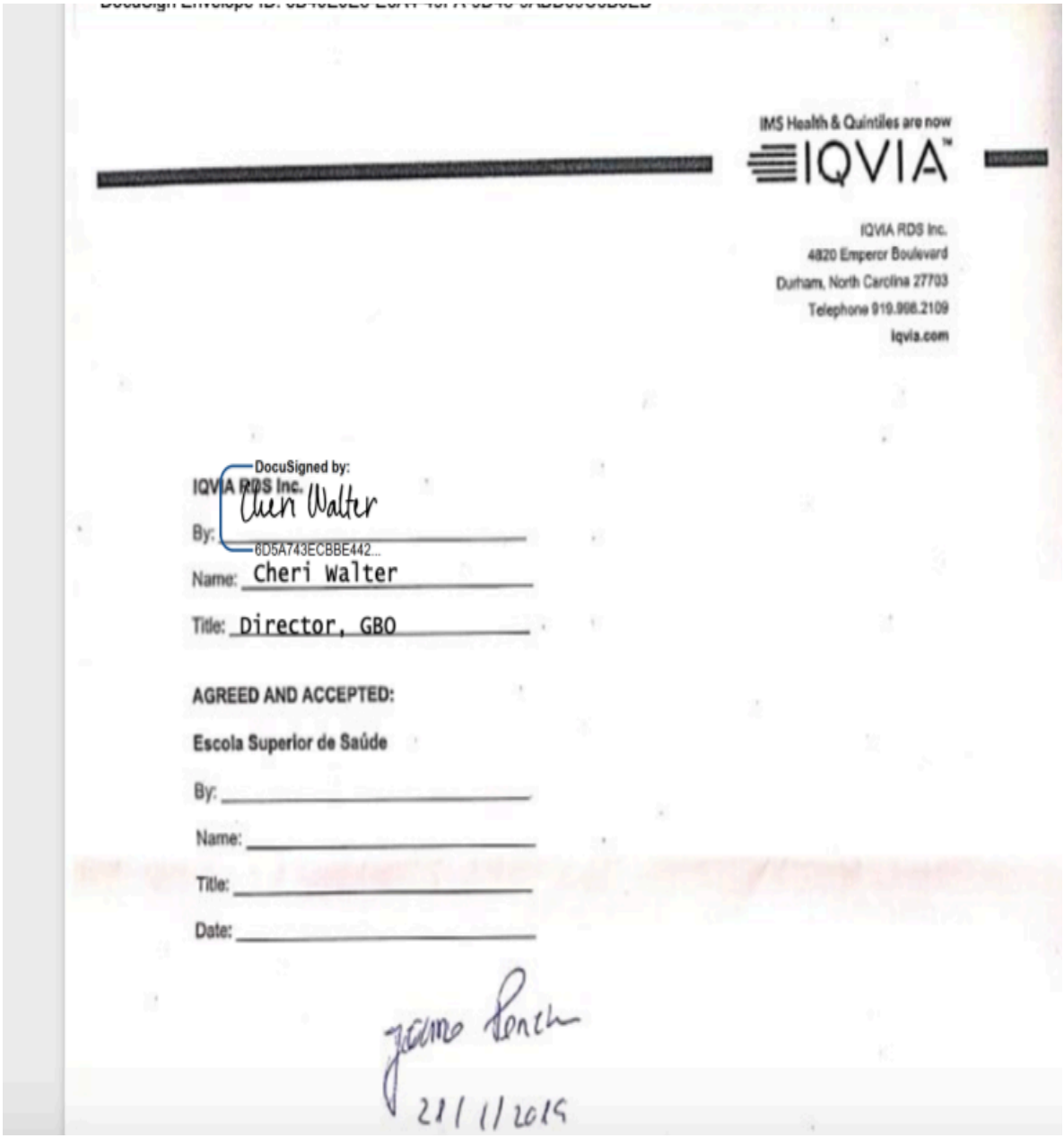
13. Até que ponto está convencido de que os pontos positivos do seu medicamento compensam os pontos negativos?

☐1 Nada convencido
☐2 Um pouco convencido
☐3 Mais ou menos convencido
☐4 Muito convencido
☐5 Extremamente convencido

14. Levando tudo em conta, até que ponto se sente satisfeito ou insatisfeito com este medicamento?

☐1 Extremamente insatisfeito
☐2 Muito insatisfeito
☐3 Insatisfeito
☐4 Mais ou menos satisfeito
☐5 Satisfeito
☐6 Muito satisfeito
☐7 Extremamente satisfeito

Attachment 6 – IQVIA authorization



IMS Health & Quintiles are now

IQVIA™

IQVIA RDS Inc.
4820 Emperor Boulevard
Durham, North Carolina 27703
Telephone 919.998.2109
iqvia.com

DocuSigned by:

IQVIA RDS Inc.

By: Cheri Walter
6D5A743EC8BE442...

Name: Cheri Walter

Title: Director, GBO

AGREED AND ACCEPTED:

Escola Superior de Saúde

By: _____

Name: _____

Title: _____

Date: _____

21/1/2019

Attachment 7- Ethics Reponse

E-ESS/EXP-1942/2019-DATA: 21-06-2019

P.PORTO

ESCOLA SUPERIOR DE SAÚDE
POLITÉCNICO DO PORTO

PARECER DA COMISSÃO DE ÉTICA

1535

Número de Registo da Comissão de Ética

20/05/2019

Data receção do Documento

Não

Existência de entradas anteriores

TÍTULO DO TRABALHO

Fibromialgia : Farmacologia e Qualidade de Vida

INVESTIGADOR RESPONSÁVEL

Joana Preira

DATA PREVISTA PARA A REALIZAÇÃO DO TRABALHO

Início: maio de 2019 | Fim: junho 2019

RESUMO DO ESTUDO

OBJETIVOS

Nada a referir.

AMOSTRA

Adultos com Fibromialgia

FORMULÁRIO DE DADOS A RECOLHER

Foram referido os questionários/escalas a usar foram anexados

MATERIAL

Vêm descritos os processos de aplicação e recolha de dados

MÉTODOS

Está referido o tipo de estudo

RISCOS

Atendendo ao tipo de estudo não há riscos a referir

CONSENTIMENTO INFORMADO

Está incluído e cumpre os requisitos.

AUTORIZAÇÃO PELOS RESPONSÁVEIS LOCAIS

Dos documentos entregues, verifica-se que tem termo de responsabilidade dos orientadores. Existe autorização por parte dos coordenadores de ATC da ESS . Os questionários para recolha de dados constam em anexo e garantem anonimato dos participantes Apresentou pedido/resposta das Instituições onde irá decorrer o estudo

APRECIAÇÃO DA COMISSÃO DE ÉTICA

Após reanálise do processo verificou-se que foram apresentados os dados solicitados.

PARECER FINAL DA COMISSÃO DE ÉTICA

"De acordo com os dados analisados, o parecer é favorável desde que cumpridas todas as diretrizes submetidas a esta Comissão, recomendando-se que a decisão seja suspensa caso haja algum incumprimento grave. "

DATA:19/06/2019

ASSINATURAS

Attachment 8 – Results

Table 8 – Association TSQM variables and time of diagnosis

	Time of diagnosis	Mean	*p* value
Global Satisfaction	< 5 years	44,3723	0,025
	6–10 years	52,5974	
	11–15 years	45,0549	
	16–20 years	52,6786	
	+ 20 years	14,2857	
Effectiveness	< 5 years	43,6027	0,351
	6–10 years	49,4949	
	11–15 years	43,8034	
	16–20 years	48,9583	
	+ 20 years	31,4815	
Adverse Effects	<5 years	69,9705	0,641
	6–10 years	64,0783	
	11–15 years	62,1795	
	16–20 years	71,0938	
	+ 20 years	56,2500	
Convenience	< 5 years	68,5746	0,213
	6–10 years	67,6768	
	11–15 years	64,5299	
	16–20 years	65,2778	
	+ 20 years	42,5926	

Table 9 – Association TSQM variables and number of drugs

	Nr of drugs	Mean	*p* value
Global Satisfaction	1	41,8367	0,300
	2	50,0000	
	3	48,6322	
	4	46,1310	
	5	38,4615	
	6	32,1429	
	7	44,6429	
Effectiveness	1	43,0556	0,666
	2	48,7879	
	3	44,2080	
	4	44,9074	
	5	38,8889	
	6	39,8148	
	7	44,4444	
Adverse Effects	1	70,4613	0,012
	2	75,2652	
	3	66,4007	
	4	69,5313	
	5	46,1538	
	6	51,0417	
	7	39,0625	
Convenience	1	62,3016	0,413
	2	70,1010	
	3	69,9764	
	4	63,1944	
	5	66,2393	
	6	62,0370	
	7	58,3333	

Table 10– Association between TSQM variables and medication*

DRUGS		Global Satisfaction		Effectiveness		Adverse Effects		Convenience	
		Mean	*p* value	Mean	*p* value	Mean	*p* value	Mean	*p* value
DULOXETINE (CYMBALTA®)	No	44,020	0,028	43,928	0,228	67,555	0,976	65,848	0,174
	Yes	52,232		47,917		67,708		70,370	
FLUOXETINE (PROZAC®)	No	47,945	0,027	45,358	0,608	68,721	0,282	67,884	0,235
	Yes	38,249		43,370		62,298		63,261	
CYCLOBENZAPRINE (FLEXIBAN®)	No	47,114	0,569	45,061	0,968	68,940	0,506	65,881	0,364
	Yes	45,146		44,943		65,891		65,590	
ANXIOLYTICS (E.G. LORAZEPAM, ALPRAZOLAM, CLONAZEPAM)	No	47,826	0,327	46,496	0,293	68,682	0,619	67,150	0,958
	Yes	44,538		43,399		66,421		66,993	
NSAID (E.G. IBUPROFENO, NAPROXENO, PIROXICAM)	No	48,458	0,189	47,474	0,095	72,680	0,025	68,308	0,408
	Yes	44,061		42,572		62,570		65,855	
BUPROPION (ELONTRIL®/WELLBUTRIN®)	No	46,160	0,743	44,926	0,710	67,245	0,308	67,084	0,967
	Yes	50,000		48,611		82,812		66,666	
VENLAFAXINE (EFEXOR®)	No	45,723	0,770	44,869	0,071	68,033	0,291	66,737	0,408
	Yes	50,357		46,111		64,167		69,722	
GABAPENTIN (NEURONTIN®)	No	46,062	0,764	45,157	0,785	67,161	0,601	66,987	0,872
	Yes	47,619		43,915		70,833		67,725	
TRAMADOL (TRAMAL®)	No	47,820	0,184	45,386	0,718	72,316	0,003	68,927	0,076

	Yes	43,099		44,256		58,167		63,371	
PREGABALIN (LYRICA ®)	No	46,455	0,824	45,720	0,387	69,120	0,229	67,325	0,762
	Yes	45,578		42,724		62,698		66,270	
MILNACIPRAN (IXEL ®)	No	46,244	0,991	45,079	0,657	68,012	0,086	67,079	0,977
	Yes	46,429		38,889		31,250		66,666	
AMITRIPTYLINE (ADT®)	No	46,053	0,775	44,700	0,605	69,133	0,094	67,727	0,278
	Yes	47,429		46,889		58,250		63,111	

*note that no one respond pirlindole (implementor®).