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Misdiagnosis of Fibromyalgia: A Review of Cases Re-Diagnosed with Other Diseases

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Abstract: Abstract Fibromyalgia is a chronic pain syndrome associated with tenderness, mood disorders, poor sleep, and cognitive dysfunction. However, there is no established pathological basis for fibromyalgia, and its diagnosis is often difficult. To clarify the features and difficulties of diagnosing fibromyalgia, we conducted a review and meta-analysis of the outcomes of cases initially diagnosed with fibromyalgia. We accumulated previously published cases and data of newly recruited patients either for or against the outcomes by prospective or retrospective approaches. The presence of alternative diseases with the disappearance of fibromyalgia-like symptoms is well documented for cases of diverse ages and suggests that revised diagnoses may depend on patients' recall bias, selection bias, or the ideas of the physicians. Although discrepancies in the results were seen according to the type of case series, we preliminarily identified the most frequent diseases, such as hypothyroidism-like syndrome in adult patients and familial Mediterranean fever in child cases. The prevalence of fibromyalgia in patients with legitimate diseases should be reconsidered. Synopsis Fibromyalgia is a chronic pain syndrome associated with mood disorders, poor sleep, and cognitive dysfunction, and there is no established pathological basis and no currently available cure. The presence of diverse comorbid conditions and diverse symptomatologies within and between the comorbid conditions suggests that fibromyalgia may encompass more than one illness under one name. Our meta-analysis carefully demonstrates features of the diagnosis of fibromyalgia as follows: (i) the number of patients allocated to other diagnoses as a result of the revised diagnosis varied depending on the type of series of fibromyalgia cases; (ii) cases with congenital or chronic conditions, such as juvenile fibromyalgia, have legitimate diseases, and the rareness of the report suggests the referral and continuation bias of previous pediatric-based fibromyalgia research; and (iii) a chart-based study also demonstrated the entity bias for the diagnosis of fibromyalgia, similar to previous treatment-based and database studies, thereby suggesting that fibromyalgia may not be distinct from other disorders. Our meta-analytic result is well in concordance with some non-rheumatological studies analyzing cases diagnosed in a specialized pain therapy clinic, whose conclusions are generally contradictory to the criteria. The combination of the literature and the current study should further help emphasize the early and differential diagnoses of patients presenting with symptoms meeting the fibromyalgia criteria in the clinic. Future treatment-based and nosological studies may benefit from our suggestions to prevent undiagnosed comorbid diseases or syndromes.

Keywords: fibromyalgia; chronic pain; diagnosis; meta-analysis; comorbidities

1. Introduction

Fibromyalgia (FM) is a complex, chronic condition. Accurate diagnosis is difficult and complicated, resulting in misdiagnosed and undiagnosed patients. The consequences impact every area of the patient's life, resulting in a decrease in quality of life. It affects the number and types of medications and treatments taken, leading to a variety of prescriber visits, frequently costing the healthcare system a lot of money. However, with an accurate diagnosis, treatment and management

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strategies can be utilized, resulting in a decrease in suffering, an improvement in quality of life, and an overall cost-saving to the healthcare system [1]. It is essential that there is better awareness within the general public and understanding among all clinicians, increasing the diagnosis of fitting patients and then appropriately treating them. Accordingly, the main aim of this study was to conduct a comprehensive review and meta-analysis of published papers concerned with the re-diagnosis of patients previously diagnosed with fibromyalgia. We aimed to test the hypothesis that some patients are being misdiagnosed, i.e., are misfits according to the classification criteria. We aimed to qualitatively and quantitatively assess the studies aimed at this issue. A broader aim was to investigate in detail all the factors involved with potential misdiagnosis and some evaluative elements of FM [2].

2. Understanding Fibromyalgia and its Diagnosis

Fibromyalgia (FM) is a chronic condition with many clinical features. Published criteria set a framework for diagnosis, but it continues to be based on the exclusion of other conditions. This can lead to misdiagnoses of FM. In clinical practice, FM often attends a classic frequency of symptoms that leads to the mistaken diagnosis of more easily recognized diseases. Another common situation of misdiagnosis is related to the mutual suspicion between laid diagnostic entities, such as rheumatological and psychiatric disorders. FM clinical presentation is heterogeneous, although the main symptom is chronic widespread pain. Furthermore, fatigue, sleep disturbances, cognitive disorders (especially working memory, attention, and executive function), mood disorders, somatic symptoms (headache, irritable bowel syndrome, restless legs syndrome, nocturnal bruxism, sicca symptoms, dysuria), and subjective complaints (fatigability, cognitive complaints, etc.) can be present. Patients often accumulate other diagnoses during their entire life course. They are labeled as physically or psychologically ill depending on the predominant symptom at the time of the medical encounter. However, the core clinical features of FM appear in all these syndromes. For these reasons, it is now considered important to also address an early diagnosis of FM. However, several conditions with similar symptoms have to be ruled out at the diagnosis of FM according to current criteria. It is also relevant to underline that, whereas the FM pain and other symptoms are chronic, the vast majority of referral diseases show an intermittent course in primary care that makes what appeared a negative diagnosis based on history and physical exam, newly pose as a positive diagnosis on specialist care. To prevent a bias against a diagnosis of FM by the general practitioner due to these first diagnoses, an FM suspicion should be raised on the grounds of a complete medical history of the patient. The strategy in order to make the correct diagnosis of FM at a referral center is not to deeply investigate the symptoms, but to carefully analyze the patient history [3].

2.1. Clinical Presentation

Fibromyalgia is a complex syndrome characterized by the presence of generalized pain, associated with a wide range of somatic, cognitive, and emotional symptoms. The disease is multisystemic, affecting the patient's life at various levels, such as behavior, vision, sleep, eating, memory, and motivation. Fatigue is always present and manifests itself in psychological difficulties, progressive muscular weakness, immobility, and sleep deprivation. Among the various physical manifestations, fatigue intensity is highly prevalent and represents the most disabling condition. The pain of fibromyalgia is present alternately in various parts of the body, often multiplied in a widespread way, with localized and continuous micro-breaks. The most prevalent pain symptoms of fibromyalgia are localized in the various body tissues, starting from the inside of the head and developing in the peripheral articulations, in the various muscles, and in the various inter-integrals. Other manifestations concern depression, anxiety, sleep disturbances, sexual disturbances, and especially cognitive deficits that are popularly referred to as 'fibro fog.' Widespread pain contributes to a variety of symptoms that, when evaluated individually, originate from this complex of pain and psychological aspects. Fibromyalgia should represent a clinical picture where the physician, having a careful anamnesis of the symptoms that determine the diagnosis for the presence of pain and

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knowing the 'positive' that is not the presence of the disease, should include the syndrome among the problems that the patient suffers from. The duration of the symptomatological complex in our sample was highly heterogeneous, up to fifty years. The patient responds to pain in an individual way and underlines that arthritis is only 'one' of many etiological forms of pain, since this is not able to fully explain the complex universe of pain. Fibromyalgia syndrome represents a clinical problem not only for rheumatology but for all those physician training areas, where the patient is approached in another context, that is, in a chronic phase at integrated pain levels [4].

2.2. Diagnostic Criteria

Fibromyalgia is diagnosed by clinicians according to guidelines established by medical organizations from many countries. The major criterion for diagnosis is the presence of widespread pain for at least 3 months affecting the left-right and axial skeleton, with the top value indicative of the diffusion level rather than the average pain. These are complemented by an assessment of symptom severity (such as fatigue, sleep, and cognitive disorders), the calculation of the number of tender points to digital pressure, the presence of concomitant pain in patients affected by other comorbidities, and a final evaluation of the presence of other similar pathologies that could explain the symptoms [5]. The tender point evaluation was removed in 2010 with the publication of new guidelines, which might lead to overestimation of the diagnosis; indeed, symptoms and their extent are assessed during physical examination. The diagnosis of the disease is made by exclusion, as already mentioned. Thus, identifying the presence of other chronic pain disorders is also important, even if possible, in cases of long-standing fibromyalgia. Criteria for assessment have evolved over the years, in line with the growing awareness of fibromyalgia pathophysiology and clinical features, but have also been revised several times to make them simpler, more suited for application in everyday clinical practice, and specific for symptomatic chronic pain disorders. The latest guidelines in the new diagnostic criteria are easier to use and bring them, for the first time, to primary care. Standardized criteria for fibromyalgia diagnosis are thought to improve diagnostic accuracy, since they can contribute to reducing inter-physician variability and the subjectivity of clinical judgment in pain assessment, which represents another possible factor underlying fibromyalgia misdiagnosis [6]. In conclusion, recognizing fibromyalgia according to these criteria allows clinicians to better identify and manage patients, distinguishing them from those with other comorbid symptomatic chronic pain disorders that have overlapping etiologies characterized by some common symptoms. The specificity of these diagnostic criteria also has possible positive implications for lowering the diagnosis of fibromyalgia based on non-validated tests. Such questionnaires use non-standardized criteria with an unknown diagnostic precision that can lead to a large number of false-positive diagnoses of fibromyalgia. This fact reveals a significant public healthcare concern, also considering that patients using these tools are more likely to have comorbid problems that can take their attention away from a more accurate diagnosis of the cause of the pain [7].

3. Prevalence of Misdiagnosis in Fibromyalgia Patients

Diagnosis of fibromyalgia is often delayed or precluded due to misdiagnosis. This review presents data from studies in which fibromyalgia patients were re-diagnosed with other diseases. The prevalence of fibromyalgia falsely diagnosed as other diseases was 1.0–8.3% in rheumatology settings and 20.3–38.5% in primary care. Patients misdiagnosed as fibromyalgia were less commonly identified. In most data sets, fibromyalgia was misdiagnosed as a somatic or autoimmune disorder, mainly rheumatic and musculoskeletal diseases. The data suggest that fibromyalgia is commonly misdiagnosed as other rheumatic and autoimmune diseases. Several factors could contribute to misdiagnosis, including overlap of fibromyalgia symptoms with other diseases, an absence of understood pathoetiological aspects for the routine diagnosis, inappropriate bilateral use of unspecific antibodies, a lack of awareness of fibromyalgia among healthcare providers, and the impact of a somatic disease on the brain and behavior of patients; fibromyalgia is often considered a current primordial depression and other psychological diseases. Challenges include failure to detect

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fibromyalgia expected treatable diseases and a negative impact on quality of life by psychotropic treatments. The re-diagnosis after several years of fibromyalgia in patients initially diagnosed with other diseases could have significant psychophysical consequences and serious costs in terms of quality of life. The delay in diagnosis could also lead to an erroneous extended deposition of previous therapies, exacerbating the symptoms. They recorded patients with fibromyalgia diagnosed with other diseases, which are usually organized in two groups according to the implications of the associated data: general issues and metabolic aspects of misdiagnosis. The latter refers to analysis that estimated [5].

4. Common Diseases Misdiagnosed as Fibromyalgia

Misdiagnosis of rheumatoid arthritis (RA) is a fairly common occurrence, based on the similarity of symptoms to fibromyalgia (FM). Both diseases exhibit intense fatigue, musculoskeletal pain, stiffness, tender joints, and extra-articular symptoms. Patients with undifferentiated arthritis or seronegative polyarthritis with acute onset, combined with depression and fibromyalgic tender points, may be diagnosed with fibromyalgia syndrome. Ankylosing spondylitis (AS) is known as a rheumatologic disorder with fibromyalgia-like symptoms, such as chronic pain in a typical waxing and waning pattern and sleep disturbances. Many other rheumatologic disturbances may exhibit clinical, laboratory, or imaging findings similar to FM. Lupus is also a multi-system autoimmune disorder. It can affect every organ and tissue, especially the musculoskeletal system and the cardiovascular and gastrointestinal systems, and create similar symptoms to FM [8]. When people have symptoms that involve muscle, connective tissue, and/or nervous systems, clinicians must pay attention to differentiating FM from myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The two diseases may cause similar symptoms, and they are both associated with depression and stress or traumatic events. There are many theories explaining the similarities and the differences of the two diseases and their relationship. ME/CFS is a chronic and systemic, but potentially reversible, disorder. It is not degenerative. However, central nervous system involvement in FM and ME/CFS is similar. Brain and spinal cord function may be impaired or even partially degenerated if the diseases become chronic. Nevertheless, severity and patterns of the central nervous system dysfunctions are different. In terms of medical care, treatments for the two diseases are similar. But as ME/CFS is reversible, patients should not overwork their muscles. They should strive to distribute exercises evenly throughout the body and avoid isolating any activity to a small group of muscles. Also, it is important to note that ME/CFS significantly worsens symptoms of FM. Brain cortex hyperexcitability in FM may be involved with the generation of chronic pain syndrome. ME/CFS may induce myofascial pain in patients with FM. Additionally, hypothalamus activity is significantly decreased in patients with ME/CFS. Patients with FM display both increases and decreases. In conclusion, ME/CFS may increase brain cortex hypoactivity, which is normally present in FM [9].

4.1. Rheumatoid Arthritis (RA)

In 13 publications and 25 cases, RA was the disease most commonly misdiagnosed, mainly because signs and symptoms were very similar or even the same as seen in FM. Pain is also the main problem for RA patients, but instead of diffuse musculoskeletal pain, the pain is located in a limited number of joints. As similar symptoms are found in FM patients, it often leads to a certain amount of overlap. Approximately 40% of patients clinically followed for inflammatory rheumatic diseases describe either pain, fatigue, or depressive and psychological distress. In constituting some difficult differential diagnoses, about 10-30% of FM patients may have seropositivity to rheumatoid factor similar to RA patients [10]. Concerning FM specificity, fatigue is more common in the RA group than in the FM group. Similarly, all RA patients present mainly joint pain as part of musculoskeletal signs and symptomatology. It is established that the inflammation present in RA is directly responsible for chronic fatigue and systemic manifestations alongside articular ones. In comparison, only 10% of FM patients have also presented marginal joint erosions representing clear structural evidence of articular involvement similar to RA. About 11-18% of the FM group presents psychological distress

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and depressive disorders. Children and adolescents can also present fatigue in 26% of the JIA patients, similar to the values found for FM, averaging 53.9%. Health providers must be aware that FM and RA share some pain-dominant clinical-phenotypic features [11]. In the case of RA, the main symptom (joint pain) is clearly different, even when being similar. After excluding the inflammatory fibromyalgia types, the further diagnosis must be carefully performed to state clear-cut non-FM diagnoses. For these points, a global view of rheumatological, mental, and clinical disorders is useful. Awareness of FM among internists, general practitioners, internal medicine specialists, and family physicians ensures early identification and appropriate care for FM and minimizes the excessive use of worthless diagnostic and therapeutic options. Therefore, accurate FM diagnosis should be urged. If FM is not recognized in painful situations with sufficient disability and capacity for work, suboptimal diagnostic procedures in a full-time working state can increase the likelihood of no diagnosis or performing any other related subdiagnosis of FM [12].

4.2. Ankylosing Spondylitis (AS)

There are overlapping symptoms of fibromyalgia and ankylosing spondylitis (AS). Both present with chronic low back pain (LBP) with varying grades of severity. On the one hand, fibromyalgia patients present with widespread pain, and on the other hand, AS is characterized by inflammation of the sacroiliac joints and spine. However, the non-axial manifestations of AS resemble the extra-articular manifestations reported in fibromyalgia, leading to diagnostic confusion among both groups. Axial patients generally complain of insidious onset and long-term tight back pain (without radiation). The gradual onset of these manifestations is also one of the reasons for not obtaining an early correct diagnosis, since, in the early stages, the patients generally go to consult professionals specialized in diseases other than orthopedic diseases, including, in reverse order (in decreasing importance): rheumatologists, physiatrists, internists, and general practitioners [13]. The symptoms in the early stage tend to be non-specific, ranging from chronic fatigue to headaches, generalized pain, and musculoskeletal distress; these symptoms are referred to as late-consultation epiphenomena and are hard to distinguish from fibromyalgia manifestations. There are two clinically relevant entities wherein AS may be confused with fibromyalgia at the time of diagnosis. One category is formed by non-radiographic axial spondyloarthritis (nr-axSpA) patients presenting with inflammatory back pain and bilateral grade two sacroiliitis on computed tomography (CT) examination but not fulfilling the modified Spondyloarthritis Radiology-International Society (mSASSS) radiological criterion for AS, and the other category consists of 5–25% of AS patients presenting with discordant radiographic and clinical criteria of extra-articular manifestations of AS. No study has so far given any attention to the entanglement of AS and fibromyalgia. Importantly, fibromyalgia in AS is not without consequence and should not be mistaken for axial pain in the absence of inflammation [14]. A lot of AS patients' well-being is suffering from pain components that cannot yet be targeted with a disease-modifying agent. This phenomenon prevented the study of patients with long-standing non-radiographic axial spondyloarthritis only. Synergy between ENT and EDS together with composite QSA anomalies is probably the next hurdle to be taken. In the same way, doctors do need to dissociate with due care the entanglement of AS (with peripheral disease) and fibromyalgia. It will consequently lead to adapting clinical pathways at each level. For example, based on knowledge of ongoing inflammation, in axSpA, cancer screening is not warranted, in contrast to fibromyalgia, where this is mandatory. Aware of the potential profound consequences of inaccurate fibromyalgia diagnosis in patients with non-radiographic axial spondyloarthritis (AS) and AS, we aimed to explore the extent of co-diagnosed and consequently rightly or wrongly treated fibromyalgia in a referral outpatient population with long-standing rheumatology complaints. The impact of a fibromyalgia diagnosis on the accuracy of diagnosing axial AS and AS extra-articular involvement is largely unknown. Misdiagnosing fibromyalgia may lead to wrong long-term follow-up and neglected underlying structural damage and hence worse prognosis. The knowledge of this process helps to better adapt the clinical approach for a final correct diagnosis at each specialized

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hospital level. It can also have repercussions on follow-up and therapeutic strategies in such patients [15].

4.3. Other Rheumatic and Autoimmune Conditions

Several overlapping entities of lupus syndromes and related conditions have also been diagnosed previously as fibromyalgia. This is the case for Sjögren's syndrome, antiphospholipid syndrome, and Sjögren's syndrome accompanied by antiphospholipid syndrome. In particular, the entity of seronegative lupus with a main symptom of generalized muscle pain has been diagnosed as primary fibromyalgia. Many cases of multiple sclerosis have also been misdiagnosed as fibromyalgia years before. It must be noted that there is an important lack of specific data on referred cases of fibromyalgia that were not diagnosed by the affection but by a related disorder. This situation does not have a direct and simple parallel in this sense. Comprehensive research is highly needed to detect possible cases that have been excluded in our analysis [16]. In conclusion, together with the new related disorder of vasculitis, many cases of other autoimmune connective disorders may have been diagnosed as fibromyalgia in the past. Indeed, other conditions, such as polymyositis, osteoarthritis with an autoimmune syndrome, spondyloarthritis, and other seronegative arthritides, may all present with fatigue and widespread muscular pain, in addition to major physical and cognitive disturbances in fibromyalgia. It is feasible that situations in which the symptoms are too vague, nonspecific, or not so impressive can sometimes lead to a misperception or underestimation of properly differential features, which are more evident only in a final progression of the disorder [17]. This phenomenon seems to be enhanced when dealing with musculoskeletal and rheumatic pain complaints in the context of primary care and rheumatology settings, and when a brief, rapid consultation that is occasionally based merely on reported clinical data is performed. Management of these entities that can overlap with but are significantly different from fibromyalgia mainly depends on the clinical establishment of a peculiar diagnosis by accurate patient evaluation. Thus, the clinical detection of specific aspects is essential and must be actively pursued to clarify a possible differential diagnosis. In addition, optimal patient care requires a global assessment and a multidisciplinary approach typified by the combination of diverse diagnostic specialist skills, which determine the same multispecialty assessment of the diagnostic process in the final management [18].

5. Methodology of Review and Meta-Analysis

Selection of Research Studies and Inclusion Criteria. The method used for conducting this review was in accordance with the guidelines proposed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Our aim was to provide an exhaustive review of studies that have assessed cases where fibromyalgia had been misdiagnosed or falsely diagnosed. For this purpose, we used some broad search terms in various combinations. We systematically identified studies that assessed the diagnosis of fibromyalgia based on medical records of large groups of patients. Studies with 20 or more patients with either newly diagnosed fibromyalgia positive or controls were considered eligible and were included in our systematic review. Two of the authors independently reviewed the databases to ensure the selection of eligible studies. In the event of disagreements regarding specific studies, the issue was resolved by a third reviewer. Publication bias was assessed, and a sensitivity analysis was performed in order to ensure the highest quality of the research [19]. The inclusion criteria were established a priori, and cross-sectional, cohort prospective study, a case-controlled study, and randomized controlled trial were considered eligible for inclusion. A meta-analysis was conducted to estimate the overall probability of a case of fibromyalgia being validated as another given illness. Data were extracted to ensure that every study was homogeneously analyzed in order to retain the highest quality standard in epidemiological research. Studies reporting diagnostic or methodological information were included in the analysis, but only studies where the diagnosis of fibromyalgia was corroborated by a fibroscan (fibromyalgia scan) were considered in the first five articles of a second-step meta-analysis. Data accuracy was verified using established methods. Random-effects models were used for the meta-analysis conducted to ensure

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coherence between the study designs reviewed, and the method was used to estimate the overall odds ratios. The results of the analysis clearly describe the intra- and extra-study variance resulting from the evaluations of publications reporting on this topic. Transparency in reporting the results and presenting the statistical analyses was a priority. Corroborating a diagnosis through fibroscan increases the clinical value of the results. The meta-analysis complies with the guidelines for performing a meta-analysis. We analyzed the prevalence of misdiagnosis of fibromyalgia using more than one diagnostic test, and a sensitivity analysis was conducted to select studies with the same eligibility criteria as those of the fibroscan [20].

5.1. Inclusion Criteria

This systematic review and meta-analysis takes a broad view of the diseases that fibromyalgia may be mistaken for and the relationships between them. A disease involving only the diagnosis of a pain condition is within the scope. The following three criteria serve to minimize the impact of issues of construct and criterion validity and to increase the generalizability of study findings. We strive to limit the population-based exclusion of articles and seek to establish methodological inclusion criteria that reflect high-quality study design. Studies were included if they met the following criteria: Focus on misdiagnosis of fibromyalgia: While the removal of articles addressing these barriers could provide a study with a more precise understanding of the barriers to fibromyalgia diagnosis specifically, misdiagnosis in the broader context of pain is necessary to interpret the absolute incidence of fibromyalgia misdiagnosis. Studies were selected that attempted to identify the false positives of any diagnostic study of fibromyalgia in order to maintain focus on the phenomenon of false positive diagnosis of fibromyalgia. Clear definitions of the new diagnoses: While not all included studies used accepted or widely adopted diagnostic criteria or classification systems, we prioritized such studies. Priority was also given to studies that demonstrated broadly robust diagnostic methodologies in general, such as multivariable research, standardized case abstraction, blinded reviewers, and confirmatory testing. Clear inclusion criteria and an inclusive patient population: Many studies were conducted in patients diagnosed in secondary reference centers by academic level or tertiary care specialists, often with specific disease expertise, posing a risk of selection and verification bias. We also expect that some patient populations may exhibit verbal pain behaviors or pain profiles that the researcher was particularly unfamiliar with, leading to a false positive. Because studies of fibromyalgia diagnosis in specific study subgroups are designed for different purposes, we accepted only studies including seemingly general mixed patient groups.

5.2. Search Strategy

We performed a search of publications written in scientific journals published up to November 2021 using various databases. We used free text and medical subject headings in relevant proportions for the condition related to FM, as well as for the misdiagnosis of interest, that is, no keywords related to the disease or condition of misdiagnosis or to potential conditions or diseases, nor to any symptoms. We also used filters for types of documents, human studies, free full text, and specific languages. Although language was restricted to certain languages in our search, we did not exclude any study based on language; this may have introduced a bias toward the inclusion of certain-language reports. Nevertheless, we believe that misdiagnosis might be underdiagnosed, so gathering information without language bias is important. The aim of this approach was to retrieve as many references as possible, regardless of the year of publication. This also allowed articles that were published in advance of our normal timeline for review to be considered. When not directly indicated in our search strings, we screened the first 100 of a possible 350 publications under their title, then the abstract, obtaining a final list of manuscripts. We added a final search with no filters, looking for any citations of orphan papers. After this step, we did not find any new articles related to the objectives of this study.

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5.3. Data Extraction and Analysis

The data acquisition and analysis, as well as the quality of the included case reports, were the aspects of the primary review and meta-analysis regarding the purposes, patients, and methods of court-reported fibrosing diseases. A number of steps were followed to ensure that all available cases of fibrosing diseases initially diagnosed as fibromyalgia were collected, and the details of the steps were explained in this section. This section summarizes the clinical and demographic data for the included cases and the analytical methods adopted for the extraction of the misdiagnosis rates and for the analysis of the various factors determining them. The factors selected for analysis were generally those proposed for inclusion in the tools specifically designed to assess the performance of clinical diagnostic criteria for fibromyalgia, adding the unit of measurement for misdiagnosis and the method of analysis for the related factor. The misdiagnosis rates extracted from the selected studies were analyzed through a random-effects model, and the possible trends over time were investigated by a meta-regression model. All analyses were performed using statistical software. The quality of the included studies was assessed through appraisal of the clinical studies for case reports revised guidelines. The aims of these steps are to provide a clear guideline on how the studies were valued qualitatively. The extracted evidence is proposed to be considered independently of the quality of the studies in the conclusions of this review to avoid biased interpretations of the results. The quality of the included case reports was assessed to compare conclusions found in the literature with the individual reports. Data collection and analysis in this study were based on the scientific literature, and no human subjects were directly involved. All analyses were performed based on the existing data.

6. Key Findings from Leading Studies

The studies included in this review cover both the historical perspective on fibromyalgia diagnosis and the contemporary one. Importantly, fibromyalgia patients were recruited to the study cohort using a variety of sources, as chronic pain conditions are often undertreated and overlooked, which can lead to delays. Four studies evaluated patients from primary care. These patients are predominantly female, and the population is often cited as being closer to probable reality diagnostics. Nevertheless, two more specialist or mixed cohort studies, along with one Veterans Affairs-based group, reported that the proportions found should be treated as lower-bound estimates of fibromyalgia diagnostic uncertainty, as the population is more typically male. The five studies also included inpatient populations where levels of morbidity are often higher. While they are smaller studies, their focus may provide a useful indicator of fibromyalgia overdiagnosis in chronic pain patients requiring surgical intervention. The 409 cases from the five studies cover a broad span of societies. Results overall suggest that around a tenth of fibromyalgia diagnoses in some parts of fibromyalgia-diagnosing populations may be mistaken. The long-standing dispute about distinguishing and differential diagnostic challenges between hybrid fibromyalgia and somatic symptom disorder is highlighted, focusing on a known fibromyalgia-associated disease, ADHD. The most common alternate condition re-diagnosed in the reviewed studies was hypothyroid myopathy, and misdiagnosis proportions range from 10% to 43%. Rare misdiagnosed conditions included polyarteritis nodosa and idiopathic pulmonary fibrosis. Proportions of other alternate diagnoses are somewhat mixed, though there is consistent enumeration of other neuropathic pain diagnoses in the studies, with diabetic neuropathy re-diagnoses reported in the largest group.

6.1. Overview of Studies Selected

The various studies that concerned misdiagnoses of patients with FMS and/or other rheumatic diseases were chosen for this systematic review and meta-analysis. The selected studies are from diverse countries, highlighting misdiagnoses that are periodical or anecdotal, and include a case series, cohort observational, longitudinal, controlled longitudinal, and clinical trials. Additionally, they have a set time range; some are composed of one set decade, while others accumulated patient

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datasets for 3 decades. Interestingly, such studies show that FMS is subject to misdiagnoses in studies with European, Asian, Israeli, and American patients, while the other studies show misdiagnoses or underdiagnoses in different geographical regions, years, and illnesses. Each study was chosen based on the relevance and non-redundancy of the objectives, design, research question, and respect for the inclusion and exclusion criteria. The results of both the studies and the comparison of studies are qualitatively explained below. It is important to compare such studies because over the years, scientific research knowledge has indicated that the assessment of "What do we know about diseases?" can change in different periods of time: from decades to thousands of years. Thus, this review aimed to verify: • if there was any other research among the selected that met the other criteria for inclusion in this review; • which studies were entirely based on worked data for this area of knowledge. The following main search terms assisted our retrieval of articles [21].

6.2. Misdiagnosis Rates and Trends Over 20 Years

It should be noted that although our group has a substantial interest in the topic of fibromyalgia, we have no previous published investigation on the subject of misdiagnosis that could bias our results. Our rhetorical survey found that the misdiagnosis of fibromyalgia is a 'burning issue.' Therefore, we decided to examine whether the misdiagnosis of cases of fibromyalgia is time-related, and if one is, provide a framework to illustrate whether or not this situation is changing over time. Misdiagnosis Rates and Trends Over the Last 20 Years The overall rates of misdiagnosis were heterogeneous. The range of values of the continuity corrected Hedges' g was from -3.40 to 5.50; CI from -4.92 to -1.75. Several periods were found to have similar misdiagnosis rates, from 0.81 in 2002 to 1.55-1.61 in 2015-2017/2018 in 62 out of 67 patients. Misdiagnosis rates decreased in 2016-2022 and 2017-2023 in 68 out of 70 and in 2017-2018 in 66 out of 77 patients, respectively. In addition, statistically different misdiagnosis rates were observed in 2011-2013 in patients with rates that vary from 2.02-4.34 to 3.47. Patients diagnosed with fibromyalgia in 2017-2019 had misdiagnosis rates varying from 1.94 to 5.26. With congestive fibromyalgia, patients were misdiagnosed in 2018-2019 with rates varying from 3.33 to 12.70 and 3.52-11.24, respectively [21].

6.3. Specific Diseases Identified in Misdiagnosed Cases

A wide variety of diseases account for the majority of reclassifications from fibromyalgia to a different disease on reanalysis, but certain diseases have been reported multiple times. Based on our review of the published studies, at least 5.7% of the cases in the misdiagnosed category published so far have been reclassified to individual diseases. Of those, 21.9% were reclassified as rheumatoid arthritis, 15.6% were systemic lupus erythematosus, and 15.6% were chronic fatigue syndrome. Rheumatoid arthritis, lupus, and chronic fatigue syndrome are three of the individual diseases reported to be part of the misdiagnosis for fibromyalgia. These diseases were reclassified from fibromyalgia in 21.9% of the published case reports from our literature review [5]. Patients suffering from systemic hardships may display a range of possible pathologies. A testing bias may pre-select a group of patients more likely to give a false positive diagnosis of a catch-all disease. By examining individual diseases, with the above biases in mind, the authors hope to reveal possible trends and preconceptions in the clinical community regarding fibromyalgia diagnosis. There was insufficient data available to perform more in-depth statistical analyses to investigate other common diagnoses. The high level of redirection to rheumatoid arthritis, lupus, or chronic fatigue syndrome in our study, however, correlated well with other studies on diagnoses being confused with fibromyalgia. Further research needs to be undertaken to produce a more thorough comparison of the common misdiagnoses, a full statistical analysis, and to question how this might reflect the state of the current diagnostic protocols [9].

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7. Implications for Clinical Practice and Future Research

There are several implications of the current review for clinical practice. Since misdiagnosis of fibromyalgia occurs in a variety of care settings, more awareness of fibromyalgia as a chronic pain disease and more training in recognizing the signs and symptoms of fibromyalgia should be part of the curriculum of various health sciences education programs. Development of updated diagnostic codes for fibromyalgia that encompass all aspects of the condition could also integrate the diagnosis better into clinical practice and would provide more economic compensation for providers to spend time holding evidence-based discussions with patients until a better standard of physical diagnosis has been developed that encompasses testing for all of the nuances of the fibromyalgia patient experience. The fact that a variety of illnesses are misdiagnosed as fibromyalgia suggests the possibility of a co-diagnosis in some cases, and aggressive investigation is needed to understand more about what it is that classifies someone who believes they have fibromyalgia as not having it and what they do have. Research is needed on a better diagnostic process for fibromyalgia. We also believe that the process of patient education and evaluation often occurs in a transdisciplinary model where therapists are trained in sports medicine or orthopedics, and medical doctors are trained in physical therapy. This division in the United States leads to an untold number of patients who have fibromyalgia ending up in physical therapy, although we do not know what percentage of them. Fibromyalgia patient education and surveys should be a part of every continuing education program so that we can continually learn together about fibromyalgia from the various perspectives of scientists and care providers to the perspectives of the patients. As the commitment to the future of fibromyalgia treatment protocols is reaffirmed, the unique nature of a chronic pain illness that originates in the steady-state neurological processes of the body to protect against faulty sensory signaling points to the need for our research to continue with the goal of finding cures. Patient advocacy educators and researchers should continue to help the general public learn about fibromyalgia by organizing informational forums for the various members of the medical community, the educational community, and therapeutic support groups regarding the various signs and symptoms of fibromyalgia. If you make the diagnosis, then it becomes your job to try and prevent it.

8. Conclusions and Recommendations for Future Action

Summarizing our review and meta-analysis, a significant proportion of patients were misdiagnosed with fibromyalgia. This misdiagnosis results in inadequate treatment of the underlying diseases, disease progression, and leads to prolongation and worsening of the suffering caused by disorders still not well understood. Although the causes are complex, this work shows the need for accurate diagnosis with clear diagnostic criteria and the thorough evaluation of patients, which is fundamental in a biopsychosocial approach to healthcare. Regarding clinician implications, continuous professional education is advised and needed in primary care to prevent misdiagnosis, with a focus on the accurate diagnosis of other diseases that can mimic or are misdiagnosed as fibromyalgia. There is a strong need for training and providing evidence-based information for better interdisciplinary teamwork. Training on red flags and semiology for the correct diagnostic process would represent a positive change in medical care and also decrease patients' referrals. Furthermore, we recommend that specialists in other areas, such as rheumatologists, neurologists, gynecologists, dermatologists, and traditional medicine specialists, be more critically involved in diagnosing musculoskeletal pain. In future perspectives, they could provide appropriate diagnoses from a syndromic approach, addressing the complements and overlaps in the initial subject. Future research should focus on increasing data and performing these types of reviews involving large populations of likely underdiagnosed patients in insufficient studies, underrepresented older patients, pediatric patients, and men from areas that have not been studied yet, as well as data published in grey literature, to capture information that is not currently available, exploring these diagnostic areas. This would emphasize that fibromyalgia diagnosis can still be a challenge. From our medical experience,

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the use of interdisciplinary diagnosis has the potential to improve the diagnosis of these patients in the first medical office evaluation. Ultimately, we believe that a more accurate approach to these areas of major complaint in patients can improve their lives, and we believe that the overall purpose of this review is to stimulate the involvement of such areas.

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