Review Article

A Meta-Analysis of the Effect of Selective Serotonin Reuptake Inhibitors on Pain in Fibromyalgia

Abstract: (1) Background: Fibromyalgia is a clinical condition that causes widespread severe pain, sleep problems, fatigue, and often emotional and mental distress. Patients with fibromyalgia may be more sensitive to pain than others. (2)Aim: The aim of this study is to screen and evaluate the efficacy and safety of selective serotonin reuptake inhibitors (SSRIs) in the management of pain in patients with fibromyalgia.(3)Methods: This systematic review and meta-analysis gathered all studies related to selective serotonin inhibitors in the treatment of pain in fibromyalgia, using the databases of PubMed, the Cochrane Library and Google Scholar. All articles using a visual analogue scale (VAS) were included in the review. All duplicates and non-eligible or unavailable full-text studies were excluded. The primary outcome was defined as pain reduction by VAS score. Secondary outcomes were the assessment of the occurrence of adverse effects at any time in the study or premature withdrawal. (4)Results: The five studies included in the meta-analysis for pain management have moderate heterogeneity. This is shown by the test of heterogeneity with a p-value greater than 0.05 and an I2 value less than 50%. If the I2 value is more than 50% and the p-value is significant, this results in differing study results. The result of this meta-analysis shows that the SSRI group had a statistically significant reduction in pain ($Z = 2.37$, $p = 0.02$).(5)Conclusion Based on the results of the meta-analysis, SSRIs may be considered for pain management for a short-term duration, preferably in female patients aged over 45 years old, in the absence of other health problems except for fibromyalgia. However, close monitoring of the potential withdrawal effects is necessary.

Keywords: Serotonin reuptake inhibitors – SSRI – fluoxetine – paroxetine – citalopram – pain Fibromyalgia

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1. Introduction

The introduction should briefly place the study in a broad context and highlight why it is important. It should define the purpose of the work and its significance. The current state of the research field should be carefully reviewed and key publications cited. Please highlight controversial and diverging hypotheses when necessary. Finally, briefly mention the main aim of the work and highlight the principal conclusions. As far as possible, please keep the introduction comprehensible to scientists outside your particular field of research. References should be numbered in order of appearance and indicated by a numeral or numerals in square brackets—e.g., [1] or [2,3], or [4–6]. See the end of the document for further details on references.

Fibromyalgia is a prevalent medical condition characterised by widespread chronic pain, sleep disorders, fatigue, and cognitive difficulties (1). The prevalence of fibromyalgia ranges between 2% and 4% in the general population and occurs in human populations all over the world (1). There are controversies concerning its definition, pathogenesis, and treatment, and some scholars have even contested the existence of this disorder (1). In 1990, the American College of Rheumatology (ACR) defined classification criteria for fibromyalgia that included multiple areas of tenderness occurring in muscles and muscletendon junctions along with widespread chronic pain (1). The classification criteria were updated in 2010, where the ACR excluded tender points and allowed less extensive pain in the criteria, and the diagnosis was based on patient-reported somatic symptoms, as well as cognitive difficulties (1).

The pathogenesis of fibromyalgia remains unclear; however, a model has been suggested in which the psychological and biological variables of the syndrome interact, which consequently influences factors such as predisposition, trigger and the aggravation of the chronic disease (1). Therefore, diagnosis requires a history of a cluster of symptoms occurring simultaneously as an exclusion of a somatic disease which can otherwise explain the symptoms by medical examination (1). Current evidence-based guidelines emphasize the value of the suggested multimodal treatments, which consist of both nonpharmacological and selected pharmacological treatments designed to treat individual symptoms such as pain, insomnia, fatigue, and mood changes (1). As treatment of fibromyalgia is based on its associated symptoms only, treatment is primarily focused on managing the disorder through pain and other associated symptoms, namely pain management (2). Serotonin reuptake inhibitors (SSRI) are often prescribed to manage pain in fibromyalgia; however, data on the screening and assessment of their effects are still sporadic (2).

Pharmacological Treatments

The 1st new-generation anti-depressant class, which are selective serotonin reuptake inhibitors (SSRI), are reported to have beneficial effects in the management of fibromyalgia symptoms based on pain and brain neuroimaging analysis (3, 4). The family of

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selective serotonin reuptake inhibitors vary greatly in their chemical structure; however, they all work through the inhibition of the neuronal serotonin reuptake mechanism, therefore, providing pain relief (3, 4). All SSRIs also exhibit similar side effects, which are generally associated with their mechanism of action (3). These may include impaired cognition, sexual dysfunction, anxiety, and gastrointestinal disturbances (3), with serotonin syndrome being the most feared complication. Side effects of SSRIs can be of a mild type (characterised by over-responsive reflexes, sweating, and increased heart rate), moderate type (characterised by agitation, hyperthermia, and hypertension), or severe type (characterised by disseminated intravascular, seizures, rhabdomyolysis, arrhythmia, and hypertension) (3). Drugs that belong to the selective serotonin reuptake inhibitor class include fluoxetine, citalopram, paroxetine, sertraline, and fluvoxamine, as well as vilazodone (3). SSRIs can exhibit adverse effects depending on the specific type of drug prescribed and the dosage. It is, therefore, essential that each patient receives a tailored personal treatment plan at an individual level based on their subjective responses (3). There are several examples of variable effects, which include the most common paroxetine and citalopram. Paroxetine is associated with a high incidence of withdrawal because of its high selectivity and ability to inhibit noradrenaline reuptake(5, 6). However, paroxetine has a weak affinity to cholinergic receptors and low uptake of norepinephrine, making it relatively safer for elderly patients, especially when related to adverse cardiovascular effects (3, 7). Citalopram, meanwhile, is known as a very selective inhibitor but lacks activation of sedation properties (3, 8). The bioavailability of citalopram is high due to strong lipophilicity(8). It binds to the human plasma membrane with 80% efficacy, allowing it to be absorbed by the gastrointestinal system, with a prolonged effect, and reaching a peak at about 4 hours (8). When comparing SSRIs against the traditional antidepressants, such as monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants(TCAs), SSRIs have been proven to have higher profiles of efficacy, safety, and tolerance (3, 9). They also report much lower chances of severe adverse events such as cardiovascular side effects (3, 9).A review of studies that reported the effects of the SSRI fluoxetine against a placebo group found that fluoxetine resulted in significant improvement in the control of fibromyalgia-related symptoms of pain and fatigue using a fibromyalgia-related impact questionnaire scoring system (10). Fibromyalgia syndrome (FMS) is now defined as a multisystem disease including allodynia, mechanical pain, hyperalgesia, and hypersensitivity to pain (9). It is distinguished from other types of musculoskeletal pain due to the presence of functional dysautonomia (11). A double-blinded placebo-controlled clinical trial, excluding patients with concurrent mood and anxiety disorders, showed a10 statistically significant effect of paroxetine which was well-tolerated and improved symptoms of fibromyalgia (12). The study employed the Fibromyalgia Impact Questionnaire (FIQ) as an assessment tool which showed more than a 50% reduction of pain and an improved quality of life when compared to the placebo group (p=0.08) (12).Contrary to the belief that SSRIs help with pain, a study of several patients with fibromyalgia who were given 20 mg/day of fluoxetine vs a placebo group showed that the effect of increased wellbeing was only due to a decrease in depression over 3–6 weeks, even though the subjects were not diagnosed previously with depression (13). However, a study showed higher titres of antibodies against serotonin gangliosides in patients with FMS (14). This may explain why a patient with FMS experiences improvement in symptoms after being treated with SSRIs (14). Additionally, a Cochrane study analyzing several studies regarding the efficacy of SSRIs revealed low-quality evidence in pain reduction when compared to placebo groups (2). Therefore, no SSRI has been approved to treat fibromyalgia by any drug agency (2). Studies on this subject are complex since reporting is subjective, and the nature of the disease is chronic (2). Despite low clinical evidence, most clinical practices recommend using SSRIs, either sole use of fluoxetine or in combination with a tricyclic anti-depressant, such as recommended by the American Society of Pain (2).

2. Aims and Objectives

This study aims to determine the efficacy and safety of SSRIs in the pain management of patients with fibromyalgia via the design of a systematic review and meta-analysis of double-blinded, randomized controlled clinical trials. The two objectives are:

1. to quantify the analgesic effect of SSRIs (i.e., citalopram, fluoxetine, and paroxetine) in fibromyalgia, and
2. to assess the frequency of the occurrence of adverse events upon the prescription of an SSRI.

3. Materials and Methods

The Materials and Methods should be described with sufficient details to allow others to replicate and build on the published results. Please note that the publication of your manuscript implicates that you must make all materials, data, computer code, and protocols associated with the publication available to readers. Please disclose at the submission stage any restrictions on the availability of materials or information. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited.

Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

Interventionary studies involving animals or humans, and other studies that require ethical approval, must list the authority that provided approval and the corresponding ethical approval code.

Search Strategy

This systematic review employs a meta-analysis upon gathering all relevant studies related to selective serotonin inhibitors in the treatment of pain in fibromyalgia. The titles and abstracts which were generated by the search strategy were reviewed in terms of quality and relevance. From this review, papers were refined and selected for inclusion in the meta-analysis. The keywords used to gather the reviews are serotonin reuptake inhibitors – SSRI – fluoxetine – paroxetine – citalopram – pain – fibromyalgia (see Fig-

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ure1) using the databases PubMed, Cochrane Library, and Google Scholar. This research will include all published articles written in the English language, and all other languages will not be considered.

Eligibility and Exclusion

Selected studies in this paper are double-blind placebo-randomised control trials composed of adult patients between the ages of eighteen and seventy years old diagnosed with fibromyalgia. The intervention of choice was selective serotonin reuptake inhibitors, mainly citalopram, fluoxetine, and paroxetine. Only trials greater than six weeks long will be included, and patients should have no medical history of any other chronic disease and should not be using any medications or anti-depressants except for paracetamol (acetaminophen) which was permitted. If the study did not meet the eligibility criteria or the full text could not be obtained, this also merited removal from analysis(Figure 1).

Selection of Studies

All articles related to the utilisation of selective serotonin reuptake inhibitors, mainly citalopram, fluoxetine, and paroxetine, for the assessment of pain improvement in fibromyalgia using a Visual Analogue Scale (VAS) for pain will be identified through database searching and followed by the removal of duplicates and exclusion of noneligible and unavailable full-text trials.

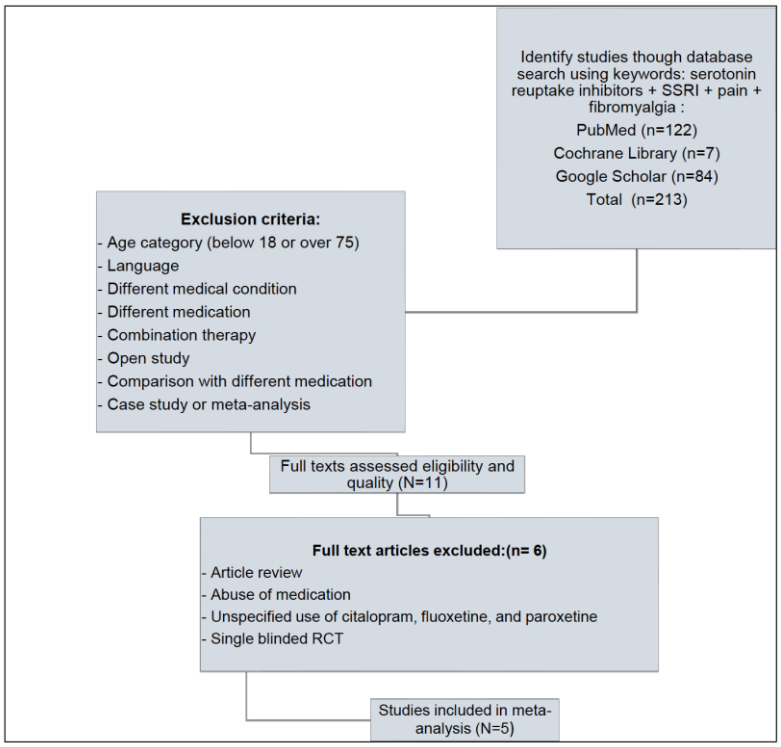

Figure 1: PRISMA flow diagram demonstrating search strategy, n=number.

Quality Assessment Issues Involving Unit Analysis

The evaluation of the study quality was based on the premise of the Jadad scale, which is used to classify quality with a scale from 0-5 where a score of 0-3 indicates a poo rquality study and a score of 4-5 indicates a good quality study (15). The Jadad scale is highly reliable and appropriate for this study, as a meta-analysis study carried out by Häuser et al. on the same topic using the Jadad scale, supporting its efficacy and reliability (24). Therefore, the scale has been used previously in a similar study (10) which provided the confidence to use it in this study. Two questions were also formulated for inclusion in the analysis: Q1: Does the study contain randomisation and blinding, and Q2:Does it also have cases of withdrawal or leakage? As a result, five studies were suitable for critical evaluation and were included in this study (see Appendix 1).

Data Extraction and Analysis

A meta-analysis method was used to pool the results of these independent studies.Statistical analyses will be performed to pool outcome data for trials that compare the same intervention with the same comparator before inputting them into RevMan5, which is a software application used to facilitate the review professionally, run statistical analysis, show the risks of bias, and manage references (16). Also, it is available on the university's website in the Student Centre and with a video explanation, and it can be downloaded straightforwardly. The isolated information was that of sample size, length of treatment, intervention, and

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outcome measure (16). The primary outcome was defined as pain reduction, and secondary outcomes assessed major adverse effects at any time of the study and premature withdrawal.

The pain improvement score was tested by the Visual Analogue Scale (VAS),which is a random-effects model applied to incorporate between-study variability. The data were analysed through the generation of standard stander deviation of the mean with a confidence interval of 95%. The standard stander deviation of the mean of the affected size was calculated by dividing the mean difference in change of the effect size measures by the stander deviation. Forest plots were created from the inputted data to provide a graphical representation of the pooled information, which provided an estimate of the overall treatment effect.

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Issues Involving Unit-of-Analysis

Some issues were faced when reviewing the literature as, firstly, several studies reported the baseline value of the outcome of pain as a mean and standard deviation; however, this value was not reported in the same format after the intervention. In fact, the study by Norregaard provides the mean change value and the standard deviation after the final intervention (17). Some studies also reported values from the start and change, while some reported mean values at baseline and follow-up and did not report a change in mean score, as can be seen in Wolfe's study (13). An issue in Norregaard's study included a problem in the unit of analysis (17) as the objective was to evaluate the change in pain following SSRI therapy, so the change scores were used.

To do this, the result from studies that reported baseline and follow-up mean scores were extracted by calculating the change score. This was done by subtracting the mean VAS pain score at the final time point from its baseline value. Thus, the result was altered, and the change in the mean score was calculated by subtracting the mean VAS pain score at the final time point from its baseline value. The baseline means pain VAS score minus the final time point mean pain VAS score equals the change in the mean pain VAS score. The change number was used to make all the units in the studies uniform.

A rough guide to the interpretation in the context of the meta-analysis of randomised trials is as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity, and 75% to 100% may represent considerable heterogeneity. I2 shows the heterogeneity of results, which identifies the difference or variance of the results of the studies used in the analysis. Whilst a good heterogeneity is desirable, as it shows that the meta-analysis included diverse studies, it should not be too high as it contradicts the meta-analysis by showing a higher variance in results extracted from the studies (18).

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4. Results

Description of Studies

The three databases, PubMed, Cochrane Library and Google Scholar, were searched using the abovementioned keywords, and 213 studies were generated. A total of 202 papers were excluded as they did not meet the inclusion criteria based on the premise of different conditions, age category (below 18 or over 75), language, different medical conditions, different medication combination therapy, open study, comparison with different medication, and case study or meta-analysis. 11 full-text articles were obtained; however, 6 of these studies were excluded at this stage due to abuse of medication, unspecified use of the type of SSRI or using a single-blinded RCT. This left a total of five studies included for analysis.

Characteristics of Studies Included

A total of 243 patients were included in this meta-analysis. The majority of participants in the studies were females and were in ages > 45 years. All studies used the American College of Rheumatology (ACR) 1990 diagnostic criteria for confirmation of fibromyalgia. With regards to the location of the study venues, three studies were conducted in the US, and two studies were conducted in European countries. In terms of the length of the studies, they ranged between 6 and 16 weeks. With regards to the comparison of intervention, fluoxetine, paroxetine, and citalopram were compared with placebo. All studies use a parallel study design. All studies involved one intervention against a placebo and provided the primary outcome for pain. However, four from five studies provided the data for the secondary outcome: adverse effects at any time of the study and premature withdrawal. The details of the studies selected for pain are provided in table 1.

Results of Outcomes

Primary Outcome: Pain

The primary outcome, the intensity of pain, was assessed in each study using the Visual Analogue Scale (VAS). This scale is a measuring tool that attempts to quantify a feature or attitude that is thought to vary over a continuum of values but is difficult to measure directly. The VAS score is calculated by measuring in millimetres from the line's left end to the point where the patient makes a mark (19). Three studies, Anderberg, Norregaard, and Arnold, used VAS 1 – 10mm (10, 17, 20). Patkar's study utilised VAS 1 – 100mm, and Wolfe's study used VAS 0 – 3mm (13). A total of 5 studies were analysed, with 120 participants in the SSRI group and 123 participants in the placebo group. The details of the data are presented in table 1 below:

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Table 1: Primary Outcomes (Pain)

Studies	SSRI Group			Placebo Group			Total	Std mean differences
	Std. Mean Difference VAS pain score at study endpoint	SD	Total participants	Std. Mean VAS pain score at study endpoint	SD	Total participants	The trial population at the endpoint	Effect size
Wolfe 1994	-0.1	0.79	15	-0.2	0.79	9	24	0.12
Norregaard 1995	-1	2.1	21	-0.7	1.1	21	42	-0.18
Anderberg 2000	-1	1.86	21	0	2.47	19	40	-0.45
Arnold 2002	-1.8	2.4	25	0.4	2.4	26	51	-0.90
Patkar 2007	-12.2	18.5	38	-8.8	16.6	48	86	-0.19

Study Result Summary

Following, the data was entered in Revman5, and the confidence intervals revealed thin horizontal lines emerging from the box indicating the magnitude of the confidence interval. In addition, horizontal lines in the forest 21 plot were seen for all studies except Arnold's, which crossed the zero line; this shows no effect in any group in Figure 2. The zero line shows no significance, and the results did not favour any side. The effect of the study is shown by the small squares; for instance, a study with a small number of participants will show a small square. However, the random effect model used in this study has been selected to manage the effect demonstrated by the small and large squares together and not to consider small squares as a lesser contribution to the study and large squares as a greater contribution like in a fixed-effects model. Furthermore, random effects were used to take into consideration all potential differences between the studies and the small sample size of each. All studies displayed in Figure 2 favoured the use of SSRI except Wolfe's, which used a small number of participants in the placebo group. The weight column in the forest plot figure shows how much each study contributed in total, and using the random-effects model does not impact the study results according to participant sample size. The diamond shown in black shows the total effect result; the top side of the diamond is the result, and the sides are 95% confidence intervals. The standard mean difference (SMD) method was selected in Revman5 as the VAS score for pain in studies showed a continuous variable. The studies included in the meta-analysis for pain management show moderate heterogeneity. This is also shown by the test of heterogeneity with a p-value greater than 0.05 and an I2 value less than 50%. If the I2 value is more than 50% and the p-value is significant, then the study results differ from each other. The overall result of this meta-analysis demonstrates that the SSRI group 22 demonstrated a statistically significant reduction in pain (Z = 2.15, p-value =0.03), as shown in the overall effect of the forest plot.

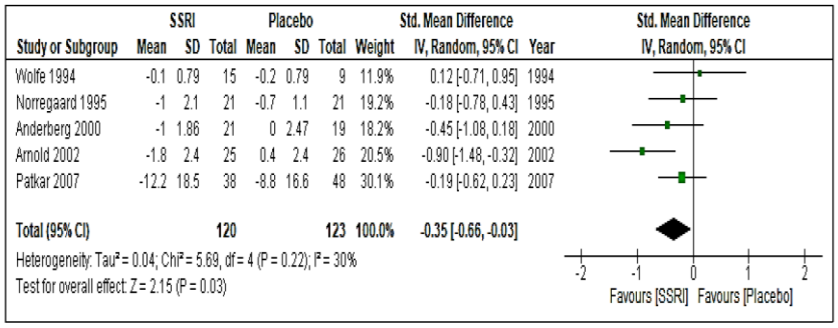

Figure 2: Forest plot of SMD and 95% CI related to SSRI vs Placebo for pain

Secondary Outcome: Main Side Effects of SSRI

Whilst the studies showed that there were several side effects, including dry mouth and sexual dysfunction, the main side effect of SSRI treatment which will be discussed, was nausea. As shown in Figure 3, nausea was the most reported side effect in the included studies reported by four of the five included. The total effect size (occurrence of nausea) seems to favour the SSRI groups versus the placebo groups. However, the confidence interval crosses the middle line, which points out that there was no significant difference between the intervention and the placebo groups. A fixed-effect model performs well in this meta-analysis due to the small heterogeneity between groups as I2=8%, and the test of heterogeneity was not significant (p= 0.350). Moreover, the use of the random-effect model resulted in similar meta-analysis results as the risk 23 ratio was used as an effect-size measure because the outcome (occurrence of nausea) is dichotomous.

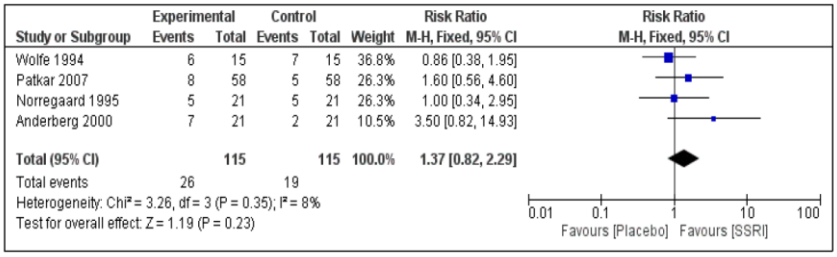

Figure 3: Forest plot of RR with 95% CI of SSRI vs placebo for at least one adverse effect

Study Quality

The studies analyses show varying levels of quality, with Wolfe and Arnold's studies showing the highest scores on the Jadad scale with a total of 5 points, followed by Norreggard and Anderberg and Patkar's studies which each received 4 points. It is important to mention that all studies included in the analysis received good scores of 4-5 points in total, showing high levels of quality (15) (see Appendix 1). The following discusses a breakdown of how the points were awarded for each study.

Woolfe's study received 2 points for randomisation and 2 points for blinding, which is an effective and appropriate method, as well as 1 point for the data of patients mentioned in the paper. Arnold's study received 2 points for randomisation, 2 points for the blinding methods used and 1 point for providing the patients' data. The studies by Norreggard and Anderberg, and Patkar all received a total of 4 points. Norreggard's study received 1 point for randomisation as one point was deducted due to incomplete randomisation. Methods including a blinded process were used, which resulted in the study being awarded 2 points and another 1 point for providing patients' data. Whilst Anderberg's received 2 points for randomisation, 1 point for randomisation as the process was not clear and 1 point for providing patients' data. Patkar's study obtained 2 points for randomisation; the use of a blinding method allowed the study 1 point; however, the method was inappropriate, and finally, another 1 point for providing the patients' data.

Risk of Bias

The risk of bias was assessed by Revman5. The studies included were Wolfe's, Norregaard's, Anderberg's, Arnold's, and Patkar's, which will be discussed in detail below. The study by Wolfe described how a random sequence was generated and mentioned; therefore, it showed low risk in this aspect (13). However, the study provided no information for allocation concealment or the blinding process of participants, and outcomes suggesting an unclear risk (13).

The study also reports incomplete data and reported some analysis based on intention-to-treat analysis and some on completer analysis, which showed high risk. No information for selective reporting was provided; hence the risk is not clear for this study (13). The study by Norregaard describes no information for random sequence generation, allocation concealment, and the blinding of outcome assessments, suggesting that the risk is not clear (17). The blinding of participants was clearly described; therefore, the risk is low for this aspect(17). However, the study reports incomplete data and reported some analysis 25 based on intention-to-treat analysis and some on completed analysis, showing a high risk (17). Furthermore, there was no information for selective reporting,so the risk is not clear for this study (17).The study by Anderberg described the random sequence generation process and allocation concealment, showing low risk in these areas (20). No information was included for blinding of participants and outcomes and selective reporting; therefore, the risk is not clear (20). The study reports incomplete data and reported some analysis based on intention-to-treat analysis and some on completed analysis, showing a high risk (20). Arnold's study only provides information on the blinding of tablets for participants, revealing a low risk (10). All other information is not present; therefore, the risk is not clear (10). The study by Patkar describes the random sequence generation by computer, allocation concealment from staff, and tablets being blinded, showing a low risk in these areas (12). However, the study gives no information about the blinding of the outcome, in-

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complete outcome data, and selective reporting; therefore, the risk is not clear (12). Figure 4 and Figure 5 demonstrate these results are included below (see Appendices 5, 7, 9, 11 and13).

Risk of Bias Summary

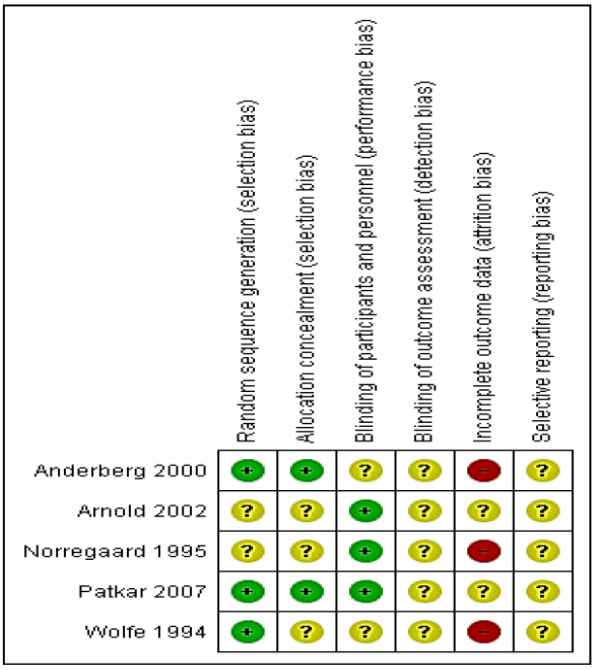

Figure 4: Review of author's judgement on each risk of bias item for each study included (see Appendices 5, 7, 9, 11 and 13).

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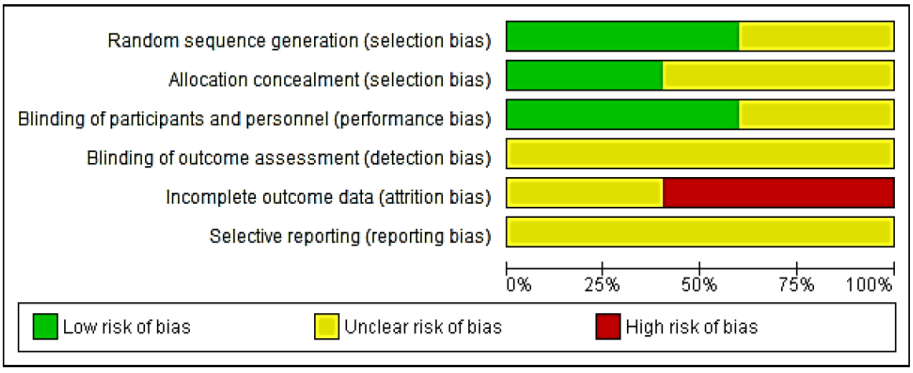

Figure 5: Risk of bias graph showing author's judgements on each risk of bias item presented as percentages across all included studies (see Appendices 5, 7, 9, 11 and 13).

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5. Discussion

Authors should discuss the results and how they can be interpreted from the perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

In this research project, a meta-analysis of five randomized placebo-controlled studies was carried out to establish the efficacy of SSRIs as pain management in patients with fibromyalgia compared to a placebo. The main aim of this study was to screen the effect of SSRIs on the pain experienced by patients with fibromyalgia. Assessing the potential inhibitory effects of SSRIs on the pain sensation felt by this patient group is important for two important reasons. First, fibromyalgia is a critical cause of widespread severe pain and secondly, as it is a common treatment as illustrated by a German study that found 16% of patients who have fibromyalgia were prescribed SSRIs (21) however, under researched. Therefore, this work aims to provide scientific guidance to prescribers and patients regarding the benefits of SSRIs.

The currently available literature is conflicting, as several studies reported positive results, and there are other studies that report negative results. One study found that there is no significant difference between the effect that fluoxetine and a placebo have on pain levels (13). This latter study also had a few limitations: for example, the duration of the trial was short, and the amount of patient withdrawal was high in the placebo group (13). Another study, which was conducted by Goldenberg concludes that fluoxetine is effective (22), yet another trial of fluoxetine reports a better score for pain, and a trial of citalopram found no significant reduction in pain in the citalopram group (17). On the other hand, a study by Anderberg shows significant pain reduction (20).28 These results show that SSRIs have a very small advantage in reducing pain in patients with fibromyalgia. The studies were evaluated using the Jadad scale and clearly showed good quality with scores of 4 and 5. The Jadad scale was used because the studies included in this project were published before the release of the CONSORT 2010 data reporting guidelines (23). Thus, this reporting guideline would not have been used, and other newer scales may review a study based on this guideline.

This study's result indicates that studies of acceptable quality (those with a Jadad scale score ≥ 4) show that SSRIs provide some benefit in reducing the pain experienced by patients with fibromyalgia when compared with a placebo.

The benefit of this work is that it serves as evidence that informs health agencies to consider allowing doctors to prescribe SSRIs to patients with fibromyalgia for pain relief. The results of this work are similar to that of other meta-analyses on the same topic, with these other meta-analyses also finding that SSRIs, for example, fluoxetine, paroxetine and citalopram, are slightly more beneficial when compared to a placebo in reducing pain and depression caused by fibromyalgia (10, 12, 25). A positive outcome from this review of randomized controlled trials (RCTs) is that no study reported any major adverse effects of the SSRIs used in the trials, and no unexpected number of patients dropping out was recorded, suggesting that SSRIs are well tolerated by patients(12).

The most common adverse effects reported by the studies were nausea, dry mouth, and sexual dysfunction (11). There is evidence published in the literature that drugs that are in the SSRI group may cause these problems (26). During the review, it was noticed that one study by Patkar et al. reported more 29adverse effects in both groups, but the number of patients in the SSRI group was higher due to the number of patients withdrawing from this group increasing (12). Several clinical practice guidelines around the world support this project's results. For example, the EULAR guidelines support the use of fluoxetine for fibromyalgia (27), and the American Society of Pain also indicates fluoxetine for pain relief for this disease (28). Thus, it can be said that these results are in line with the recommendations in clinical practice guidelines.

Limitations of Study

Some limitations should be acknowledged as the studies included in this metaanalysis comprise patients with fibromyalgia who do not have other health comorbidities. Therefore, it is unknown if this work's results can be applied to patients with fibromyalgia who have additional health problems. In addition, most studies only comprised females, making it difficult to apply the results to male patients (although fibromyalgia is uncommon in this patient group).

Further, the studies used for this project carried out their research on SSRIs for a limited time, for instance, between 6 and 12 weeks, and no information about follow-ups after the trials ended is provided. It is reported in the published literature that SSRIs also have withdrawal effects (29); however, no evidence of withdrawal effects is reported in these studies. Moreover, no study confirmed that patient adherence to the drug treatment was good. Additionally, it is not known from these trials if SSRIs will work in the long term. The average age of the patients in the studies included in this project was over 45 years old, so it is difficult to apply the results to young patients with this disease. Furthermore, no data on other medications used by the patients wasm30 provided. Currently, no SSRI has been approved for use for fibromyalgia, and the American food and drug agency (FDA) has ordered a black box warning message be used for SSRIs as according to the FDA, the use of SSRIs can increase the tendency of patients to commit suicide (30). Therefore, the benefit of this work is limited as this warning reduces the likelihood of physicians prescribing SSRIs for pain caused by fibromyalgia.

Study Recommendations

In future studies, patients in other age groups and the male gender should be included as well as studies of a longer duration. It is also recommended that future trials include the use of SSRIs in fibromyalgia by comparing their effectiveness with the use of other anti-depressants, such as selective serotonin-norepinephrine inhibitors (SNRIs) and tricyclic anti-depressants (TCAs), to observe the effect this has on the pain experienced by patients with fibromyalgia. It is also important to consider other pain relief options such as cognitive-behavioural therapy (CBT) that may provide pain relief, as shown by previous studies to decrease the side effects of SSRI (31) and aerobic exercise, which has also been proven to provide pain relief (32).

6. Conclusion and Implications for Practice

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The results of this study have shown clear evidence that SSRIs are effective in providing pain management for patients with fibromyalgia. Also, preferably in female patients aged over 45 years old, in the absence of other health problems except for fibromyalgia. In addition, the treatment also not caused a severe of side-effects, some of which warranted pre-mature withdrawal from trials. However, SSRIs can only be considered for pain management in patients with fibromyalgia for a short duration as a longer duration of SSRI use is not recommended due to the risk of increased tendency to commit suicide, according to the FDA. Moreover, the close monitoring of the potential withdrawal effects is necessary. This study has also shown that the use of SSRIs as a mono therapy only provides a limited reduction in pain in patients with fibromyalgia; therefore, other pain management options should be considered.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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