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Efficacy and Safety of Duloxetine in the Treatment of Fibromyalgia: A Systematic Review

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ABSTRACT

Background: Fibromyalgia (FM) is a pain syndrome with manifestations of chronic musculoskeletal pain of non-articular were spread widely without being discovered abnormalities in the musculoskeletal system. In addition to widespread pain, patients with FM often experience other troublesome symptoms, such as fatigue, sleep disorders, and cognitive disorders; other specific pain conditions such as chronic headache. Frequently used therapies for treating FM are duloxetine, milnacipran, and pregabalin. Duloxetine is an antidepressant drug that belongs to the SNRI (serotonin norepinephrine reuptake inhibitors) class of drugs. The analgesic effect of duloxetine is believed to be the result of increased serotonin (5-HT) and noradrenaline (NA) activity in the central nervous system (CNS), by increasing the inhibition of pain pathways in the CNS and spinal cord.

Methods: We conducted a system-based, computer-based literature search on 8 January 2020. We looked for literature relating to the effectiveness of duloxetine on pain management on FM, using keywords, fibromyalgia, pain, painful, management, therapy, treatment, duloxetine and SNRI.

Results: Of the 5 papers that can be used in this review article, the sample population was 732 with FM and was treated with duloxetine. All studies show duloxetine can reduce pain scores and have a side effect that is mostly nausea and headache.

Conclusion: Duloxetine can be used to reduce the pain suffered by FM patients and should also be prepared for other treatments to deal with the effects of arising.

Keywords: Pain, Fibromyalgia, Duloxetine, effects.

INTRODUCTION

Pain is most common complaint faced by patients, which leads them to seek for treatment. Fibromyalgia (FM) is a painful syndrome with manifestation of non-articular chronic musculoskeletal pain (at least for 3 months) that is widespread (chronic widespread pain) without any abnormalities in the musculoskeletal system. Widespread pain includes axial pain, pain on the left and right sides of the body, as well as pain in the upper and lower segments of the body.[1] In Japan, nearly 1.7% of the 2 million people suffer from FM is almost the same as in the US itself where the figure reaches 2.0%.[2] Ratio between men and women who suffer from FM ranges from 1: 4.8 and the average age is 51.5 years.[3]

In addition to widespread pain, patients with FM often experience other troublesome symptoms, such as fatigue, sleep disorders, and cognitive disorders; other specific pain conditions such as chronic headache, temporomandibular disorders, irritable bowel syndrome and psychological disorders, including anxiety, depression. In addition, FM often has a negative effect on personal relationships, career, and daily activities.[4] There are three main symptoms, namely fatigue, not fresh when you wake up and cognitive symptoms. Other symptoms that can accompany are such as muscle pain,

irritable bowel syndrome, fatigue, impaired thinking or memory, muscle weakness, headache, abdominal pain or cramps, pins and needles, dizziness. There are 18 tender points in FM patients which were found by palpating with a finger, and applying a pressure of approximately 4 kg, which is equivalent to the force needed to make the examiner's finger pale.[5]

Treatment for FM remain becomes a major challenge, starting from a non-pharmacological approach and more than 40 pharmacological compounds have become the subject of research and clinical practice for the treatment of FM throughout the world.[6] Frequently used therapies for treating FM are duloxetine, milnacipran, and pregabalin. Duloxetine is an antidepressant drug that belongs to the SNRI (serotonin nor epinephrine reuptake inhibitors) class of drugs. Duloxetine is a selective inhibitor of 5-HT (serotonin) and NA (noradrenaline) reuptake in the central nervous system (CNS). The analgesic effect of duloxetine is believed to be the result of increased 5-HT and NA activity in the CNS, by increasing the inhibition of pain pathways in the CNS and spinal cord.[7]

METHODS

We conducted a system-based, computer-based literature search on 8 January 2020, data was taken from the PubMed database with articles published between 2015 and 2020. We searched for literature relating to the effectiveness of Duloxetine on pain management in FM, using keywords (1) " Fibromyalgia "; (2) "pain", "painful"; (3) "management ", "therapy", "treatment"; (4) "duloxetine", "SNRI" . We are also looking for literature related to this article on Google Scholar.

Articles used in this review are included if they meet the inclusion criteria, such as: articles must be included in a randomized controlled trial study, age is determined more than 13 years, reference research articles are in English, articles are less than 5 years old, in the research results listed the improvement of pain and effectual conditions. The exclusion criteria in this article are: we do not use journals with review articles, case reports, letters to the editors, and text books.

Data collected from the journal and selected with the following characteristics: (1) patient demographics (sex, age), (2) characteristics of the study (type of research, year of study, country of study), (3) intervention (comparison / comparison , the dose of duloxetine used, duration of therapeutic intervention, (4) Outcomes (reduced pain, with standard deviations and resulting effects).

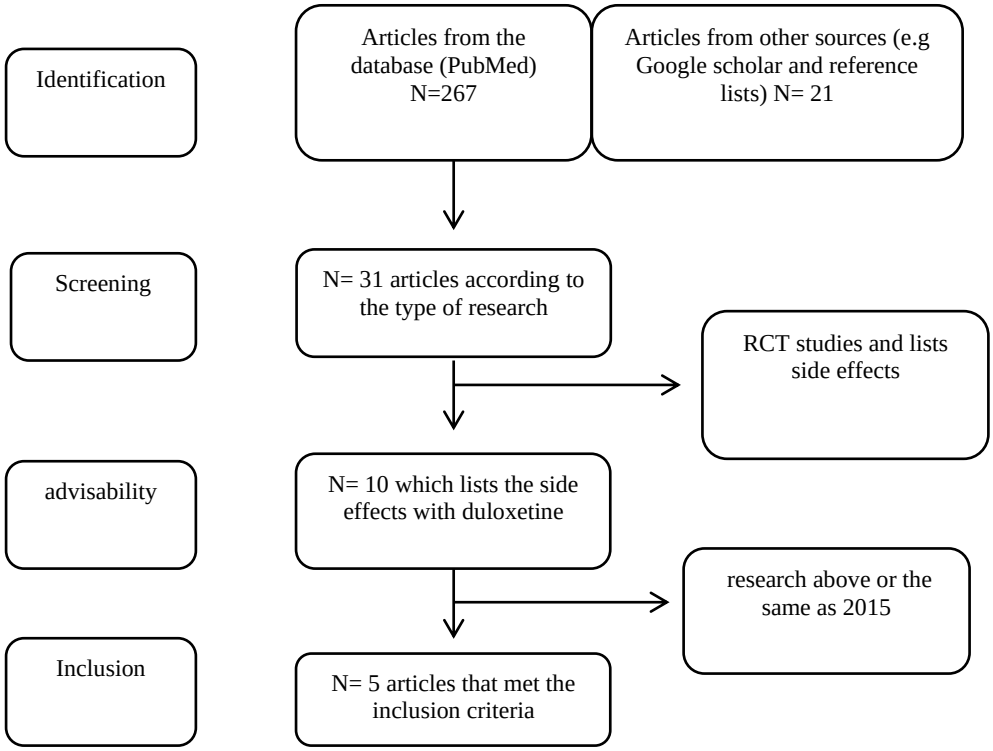
Analysis focused on changes in pain intensity in patients and incidence as well as the severity of side effects of treatment. The number of patients who experience an adverse effect is the result of interviews and also observations for certain side effects, such as nausea and vomiting.

RESULTS

Review of the research being tested

Identification of 267 articles from PubMed and 21 articles from other sources (e.g Google Scholar and reference list), where 31 articles are in accordance with article selection criteria, then selected based on inclusion criteria, 5 papers can be used in this review article. All selected articles selected are published between 2015-2020. The selection process is shown in the table below.

Figure 1. The process of selecting literature from the PubMed database and additions sources that then go through the process of screening and eligibility



Five papers that met the inclusion criteria.[8-12] Total sample population 732 with FM and treated with duloxetine. Table 1 shows the demographic characteristics of these patients. The age of patients included in this study ranged from 13 to 75 years. One study used patients with young age who were vulnerable between the ages of 13-17 for their research. There are three studies comparing placebo with duloxetine.[9,10,12] Two studies compare with pregabalin.[10,11] One study also compared *Saffron (Crocus sativus L).*[11] Doses between 30-120 mg, in three studies the initial dose was used 30 mg which was then increased to 60 mg.[8,11,12] and two studies used a 60 mg dose.[9,10] One study increased the dose periodically from 20 mg in the first week followed by 40 mg in week 2 and 60 in week 4-14.[10] Duration therapy in this research varies from 4 weeks to 14 weeks.[8-12] Of the 5 studies, 4 used BPI to assess the main outcome of pain.[8,9,10,12] besides BPI (Brief Pain Inventory) and FIQ (Fibromyalgia Impact Questionnaire) are also used to assess the severity of FM suffered , [10] while CGI-I (Clinical Global Impression – Improvement) and SF-36 (Short Form-36) scale are widely used to assess the effects of suffering on patients.[13] As well as all the studies tested included side effects experienced during the study.[8-12]

Primary Output

The Masato M, et al.[8] study divided into 2 groups, placebo group (n = 197) and duloxetine group (n = 196), after an analysis showed that changes in mean pain scores were significantly greater in the duloxetine group (both p = 0.0132) compared in the placebo group. Patients with a decrease in pain threshold of about ≥30% (p = 0.0130) or ≥50% (p = 0.0318) and sustained response rate (p = 0.0139), pain reduction was significantly greater in the duloxetine group than in the placebo based on the mean BPI score. Duloxetine therapy was also associated with improvement in the quality of life (QoL) of patients as measured by BPI, FIQ score, and SF-36 score. Improvements in QoL were also found to be significant in the total WPI

(Widespread Pain Index) and SS (Symptom Severity) scores of -1.64 (95% CI , −2.74, −0.54; p = 0.0037).

In a study conducted by Gilron I, et al.[10], the mean pain of patients in the MTD score was as follows: placebo = 5.1 ± 0.3; pregabalin = 5.0 ± 0.3; duloxetine = 4.1 ± 0.3; combination = 3.7 ± 0.3. With combination therapy, the patient's pain threshold decreased lower than that of placebo with (p = 0.001) and pregabalin (p = 0.001). The pain scores of patients with duloxetine were also lower than in patients with placebo (p = 0.001) and pregabalin (p = 0.003). BPI scores also experienced significant differences (p <0.05 for the combination with pregabalin and with placebo; and p <0.05 for duloxetine vs pregabalin and vs placebo). Whereas for the order of therapy administration, the analysis revealed that there was no significant effect of the sequence of therapy administration, but the effect of the therapy administration period was significant (p = 0.0003).

Bidari A, et al.[11] on their study found that the mean score was significantly higher in the pregabalin group compared to the duloxetine for FIQ-R (The Revised Fibromyalgia Impact Questionnaire) with (p = 0.037), only on the WPI the duloxetine score had a significant effect (-2.32, 95% CI, -4.46 - 0.18; p = 0.034; Cohen's d 0.53 95% CI, 0.04 - 1.02). No significant difference was detected for BDI-II (Beck Depression Inventory), FIQ-R, or SF-12 between the two treatment.

Similar results were obtained in the Upadhyaya HP, et al.[12] study. At week 39, the average change in BPI pain score was statistically significant in patients taking placebo during the double-blind treatment period and switching to duloxetine in the extension phase (placebo /duloxetine: -1.11 [0.259]; p <0.001). Similar results were also observed in duloxetine/ duloxetine patients (-0.57 [0.217]; p = 0.01). In addition, the mean BPI pain score was statistically significant in the treatment group during the initial and extension phases in all duloxetine patients (week 0–39) (-1.63 [0.297]; p <.001).

While in Shakiba M et al.'s study there was no significant difference in baseline scores between the two treatment groups for either scale (e.g. HRSD (Hamilton Rating Scale for Depression), FIQ, BPI, VAS (Visual Analogue Score), GFI (Groningen Frailty Index) or HADS (Hospital Anxiety and Depression Scale). The scale of all scores decreased in both groups during the trial in response to treatment (change in mean score: -4.26 to 2.37; p: 0.182-0.900) or in terms of time and treatment interactions (p-value: 0.209-0.964). In previous studies, *Saffron* showed comparable efficacy to imipramine, citalopram, and fluoxetine in mild to moderate depression disorder[14], for fluoxetine in mild to moderate depression after percutaneous coronary intervention and for fluoxetine in post-partum depression.[9]

Secondary output (Side effects)

Most of the side effects occur during the first and second weeks of therapy, some things to note from the use of duloxetine-related side effects are that duloxetine cannot be used together with other serotonin reuptake inhibitors because there is a possibility that it can increase the risk of serotonin syndrome.[15]

In Japan alone, side effects were almost the same in the two groups studied, somnolence (placebo, 10.7% vs duloxetine, 26.3%), nausea (4.6% vs 21.6%), constipation (4.1% vs 14.9%), decreased appetite (0.5% vs 6.7%), and dizziness (1.0% vs 5.7%) were significantly more frequent in the duloxetine group than in the placebo group.[9] Most of the side effects were mild, and patients recovered quickly or after discontinuation of treatment. No distinct changes caused by duloxetine were observed in laboratory test results, blood pressure and pulse, body weight, or electrocardiogram (ECG). None of the patients had application of the risk of parental suicide according to C-SSRS (Columbia-Suicide Severity Rating Scale).[9]

Several side effects were self-reported during dose titration. During titration, side effects of dizziness were more frequently felt with combination therapy (35.1%) than with placebo (7.5%, p = 0.004); insomnia with combination therapy (18.9%) versus placebo (50%, p = 0.008); insomnia was less common with pregabalin (20%) and with placebo (50%, p = 0.009). Nausea was less common with pregabalin (5%) than with placebo (22.5%, p = 0.05). While somnolence was more frequently seen in combination therapy (26.5%) compared to duloxetine (5.3%, p = 0.02), insomnia was significantly more frequent with placebo (34.2%) than with combination (11.8%, p = 0.03) and also compared with pregabalin (7.9%, p = 0.01). During the drug dose reduction study, headache was more common with the combination (29.4%) than with placebo (10%, p = 0.04).[10]

The overall incidence of nausea was significantly higher in the duloxetine group compared with pregabalin. Although we noted a higher incidence of constipation, dry mouth, headache, insomnia, and rash on the duloxetine arm, no statistical significance was detected. On the other hand, dizziness, lightheadedness, and drowsiness were seen in patients in the pregabalin group. Other side effects such as palpitations, tremors, decreased sexual desire, and flatulence were rare and mainly reported in the duloxetine group.[11] During the duloxetine treatment period, the most frequent reported side effects when compared with placebo were nausea (25.27% vs 15.05%), headache (14.29% vs 10.75%), vomiting (15.38% vs 5.38%), and decreased appetite (15.38% vs 3.23%) of the total sample.[12]

Table 1. Summary of research characteristics

	Year	Types of research	Country	Total Population sample	Duration	Comparation	Result	Side effects
Shakiba M, et al.	2018	RCT	Iran	54	28 week	*Saffron (Crocus sativus L.)*	Scoring: HRSD, FIQ, BPI, VAS	Yes
Masato M, et al.	2015	RCT	Japan	393	14 week	Placebo	Scoring: BPI, PGI-I, CGI-I, FIQ, SF-36, BDI II, WPI	Yes
Gilron I, et al.	2016	RCT	Canada	41	24 week	Pregabalin	Scoring: BPI, BDI-II, SF-36	Yes
Bidari A, et al.	2019	RCT	Iran	60	4 week	Pregabalin	Scoring: WPI, BDI-II, FIQ-R, SF-12	Yes
Upadhyaya HP, et al.	2019	RCT	USA	184	13 week	Placebo	Scoring: BPI, CGI-I, FIQ, BDI II, WPI, FDI	Yes

**Patient Global Impression of Improvement (PGI-I), Clinical Global Impressions Global Improvement (CGI-I), Fibromyalgia Impact Questionnaire (FIQ), Short-Form Survey (SF-36), Beck Depression Inventory II (BDI-II), Brief Pain Inventory (BPI), Widespread pain index (WPI), Short Form Survey (SF-12), Pediatric Pain Questionnaire (PPQ), Functional Disability Inventory-child version scale (FDI-child), Functional Disability Inventory-parent version scale (FDI-parent)*

Table 2. Summary of research results

	Total sample	Age	Sex Male/ Female	Duloxetine Dosage	Comparison	Duration	Primary output	Secondary Output
Shakiba M,et al.	Total: 46 Group A. *Saffron*: 23 Grup B. Duloxetine: 23	18-60 A: 42 (mean) B: 41 (mean)	Total 12/34 A: 5/18 B: 7/16	30 mg	*Saffron (Crocus sativus L.)*	28 Week	-Decrease in pain scale is, (Mean score changes: -4.26 to 2.37; *P*-values: 0.182-0.900)	-Abdominal pain (43.3%) -Nausea (17.3%) -Decresed of appetite (13.4%) -Headache (8.7%)
Masato M, et al.	Total:393 Grup A. Placebo: 197	20-75 A: 49 (mean) B:48	Total 65/321 A: 31/164	Week 1: 20 mg, Week 2: 40 mg, Week	Placebo	14 Week	-Decrease in pain scale, moderate pain score at week 14 -Reduction pain	-Somnolen (26%) -Nausea (21%)

	Grup B. Duloxetine: 196	(mean)	B: 34/157	3-14: 60 mg			in Duloxetine (*P* = 0.0132) -Duloxetine therapy increases QoL and BPI interference, FIQ score, and SF-36 of -1.64 (95% CI, -2.74 - 0.54; *P* = 0.0037	-Constipation (14%) -Dizziness (5%) -Headache (4.6%) - Decresed of appetite (6.7%)
Gilron I, et al.	Total: 41 A: Placebo B: Pregabalin C: Duloxetine D: Pregabalin + duloxetine	18-70 56 (mean)	Total 5/36	60-120 mg	Pregabalin, placebo	24 Week	-Pain in combination therapy was lower compared to placebo (*P* = 0.001) and pregabalin (*P* = 0.001). -Pain score on duloxetine was lower on placebo (*P* = 0.001) and pregabalin (*P* = 0.003).	- Nausea (15%) - Constipation (2.6%) -Dizzines (10.5%) -Headache (25.6%) - Decresed of appetite (5.1%) -Dry mouth (10.3%)
Bidari A, et al.	Total: 66 A: Duloxetine : 35 B: Pregabalin: 31	18-65 A: 41 (mean) B: 43 (mean)	Total: -/66	30-60 mg	Pregabalin	4 Week	-Pregabalin compared to duloxetine FIQR (*P* = 0.037), intensity of symptoms (*P* = 0.011). -WPI score duloxetine (Mean difference in score change - 2.32, 95% CI, −4.46 to -0.18; *P* = 0.034; Cohen's d 0.53 95% CI, 0.04 to 1.02).	-Insomnia (17%) -Nausea (34.2%) -Vomiting (2.6%) -Constipation (21.6%) -Dizziness (17.5%) -Headache (22.8%) - Decresed of appetite (8.5%) -Dry mouth (17.3%)
Upadhyaya HP, et al.	Total: 184 A. Duloxetine: 91 B. Placebo: 93	13-17 A.16 (mean) B.15 (mean)	Total: 46/138 A.18/73 B.28/65	30-60 mg	Placebo	13 Week	-BPI scores on Duloxetine significantly decreased at week 13 compared with placebo (placebo / duloxetine: - 1.11 [0.259]; *P* <.001)	-Nausea (25.2%) -Vomiting (3.6%) -Headache (14.2%) - Decresed of appetite (15.3%)

**Patient Global Impression of Improvement (PGI-I), Clinical Global Impressions Global Improvement (CGI-I), Fibromyalgia Impact Questionnaire (FIQ), Short-Form Survey (SF-36), Beck Depression Inventory II (BDI-II), Brief Pain Inventory (BPI), Widespread pain index (WPI), Short Form Survey (SF-12), Pediatric Pain Questionnaire (PPQ), Functional Disability Inventory-child version scale (FDI-child), Functional Disability Inventory-parent version scale (FDI-parent)*

DISCUSSION

Fibromyalgia (FM) is characterized by pain that is felt in the body as well as various symptoms that affect overall health status and quality of life. Therefore, PGI-I and CGI-I scores were assessed for a comprehensive evaluation of disease improvement from the initial to the 14th week of treatment. In addition to the BPI pain scale, SF-36 and FIQ also used to assess the overall impact of FM on patients. Because FM is associated with neuropsychiatric symptoms, BDI-II can also be used to assess improvements in these symptoms.[16]

In a study conducted in Japan, the results of a trial showed that 12 weeks of treatment with duloxetine significantly reduced pain scores compared to placebo, starting from the first week of treatment and the reduction in pain scores continued in each subsequent week.[17] FIQ and SF-36 scores showed a significant improvement from baseline to 14 weeks of treatment in the duloxetine group

compared to the placebo group.[8] There have been several previous studies using duloxetine to reduce pain scores in the treatment of neuropathic pain and concluded that compared with placebo, using duloxetine for five weeks showed a decrease in clinical and statistical pain scores. After four weeks of treatment duloxetine showed an average lower VAS, compared with those chances, reduction of average VAS score VAS was statistically significant during duloxetine treatment.[18]

BDI-II and FIQ-R scores patients in the pregabalin group had a higher initial score compared to the duloxetine group and experienced more decreased scores. Also about MCS, patients in group pregabalin has a basic score that is lower initially and increased scores were higher during the trial.[11]

Duloxetine dose mean changes in BPI pain score within the range (-0.49 to -1.23) of duloxetine 60 mg and placebo in adult patients with FM. However, in a study comparing duloxetine 30 mg and placebo, the reduction in BPI scores was not statistically significant between the two groups.[19]

Nausea, headache, vomiting, and decreased appetite were the most frequently reported side effects in this study. Side effects of the use of duloxetine, such as headache, dry lips, constipation and body weakness were less complained of by patients compared to use of pregabalin, but complaints of nausea, anxiety disorders were less in the pregabalin group.[9] The duloxetine group was better at reducing pain than pregabalin, but there was no significant difference in mental health or improvement in QoL between the two treatments. They also reported the superiority of pregabalin to duloxetine in improving the patients' sleep disorders.20

In comparison with Saffron, it was found that changes in average pain scores from the beginning to the end point did not differ significantly and that both the change in mental or physical symptoms of FM was said to be the same as duloxetine. This finding signifies a comparable effect of the two drugs.

CONCLUSION

This study shows that duloxetine treatment can be associated with a reduction in pain associated with FM and an increase in related symptoms. Because of the variety of clinical manifestations of FM, this disease can greatly worsen a patient's QoL. Based on these findings, duloxetine has the potential to improve the QoL of patients and improve depressive symptoms by improving symptoms related to FM. The majority of the side effects of duloxetine are mild and can be well tolerated, but care must be taken when giving duloxetine to the elderly, maybe the dose adjustment should be considered because it can increase the side effects compared to the desired exposure results. There are several limitations about this study, one of which is the study included in this review only 5, because the lack of RCT in this population mainly uses placebo as a comparison than other drugs, resulting in insufficient evidence to evaluate the effect of duloxetine for FM management. Experiments case control which in number of population is more necessary in the future. We can conclude that for FM treatment, duloxetine is a good choice, especially for reducing neuropathic pain.

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